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ABSENCE OF EXCESS BODY FATNESS

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2. CANCER-PREVENTIVE EFFECTS IN HUMANS

2.1 Methodological considerations

Randomized trials addressing body fatness and risk of cancer are rare and are often not feasible. Hence, observational epidemiological studies on various weight parameters are relied on to provide evidence. Body fatness can be a reflection of genetic, metabolic, lifestyle, dietary, environmental, and psychosocial factors. Therefore, it is important that epidemiological studies are designed appropriately to control for the many potential confounders. This section reviews some of the methodological issues in epidemiological studies that must be carefully considered when evaluating the body of evidence on the association between body fatness and risk of cancer.

2.1.1 Bias

(a) Recall bias

Retrospective studies addressing body fatness and risk of cancer may rely on participants' recollections of their past weight or other measures. If there is differential recall between cases and controls, or between overweight people and lean people, this is considered recall bias. This imbalance can have an impact on estimates of effect, particularly in case–control studies.

(b) Selection bias

Non-randomized studies are at risk of selection bias, because subjects are not allocated to groups at random, and instead are generally selected based on their disease or exposure status. Therefore, if cases and controls, or exposed and unexposed individuals, are selected systematically in a different way, estimation of the association between exposure and risk can be affected, depending on the study design.

For example, in case–control studies, those who agree to participate as controls may be more likely to have a history of being at a healthy weight, and may be more likely to engage in other healthy behaviours, than those who do not agree to participate. They may not be representative of the larger population from which they are selected, and this can result in an overestimation or underestimation of the association between body fatness and risk of cancer.

(c) Detection bias

Detection bias refers to systematic differences between groups in the detection of outcomes of interest. Studies of cancers that can be detected by screening are at higher risk of this bias, affecting their estimate of effect. Individuals who are likely to engage in healthy behaviours, such as behaviours that lead to maintaining a healthy weight, may also be more likely to seek the recommended screening tests. They may

therefore be more likely to receive early diagnosis and to have access to early treatment, which can affect their prognosis. If the outcome of interest is mortality, individuals who receive early diagnosis may be less likely to die from the disease, because of earlier treatment. If these individuals are also more likely to have a lower weight, this could result in an overestimation of the impact of these behaviours.

Similarly, individuals who are less likely to engage in healthy behaviours, and may be less likely to be at a healthy weight, may also be less likely to participate in screening and therefore will be less likely to receive early diagnosis and to have access to early treatment. The estimated effect of body fatness on the poorer outcomes in such individuals can be affected by their behaviour. This type of bias is of less concern for cancers that are more likely to be fatal, because early detection or screening may not have as large an effect if the outcome of interest is death.

2.1.2 Confounding

Confounding is the result of an association between exposures, resulting in the conclusion that the effect on the risk of disease is due to one variable rather than another. Although the exposure and the risk of disease are linked, this is due to their joint relationship with the confounding variable, rather than due to a direct relationship.

Potential confounders can be addressed either in the design of studies or in the analysis of the data. In case–control studies, suspected confounders can be controlled for by matching on those variables. Similarly, in cohort studies, unexposed and exposed groups can be selected to be as similar as possible with respect to the potential confounders. In the analysis of the data, stratification or statistical adjustment can be used to control for potential confounders.

Individuals who maintain a healthy weight may be more likely to engage in other healthy behaviours, so these associations should be explored as potential confounders when investigating the association of body fatness with risk of cancer. In high-income countries, people with lower socioeconomic status are more likely to be overweight or obese. Race and other factors may also be related to body fatness and to risk of cancer, and when the results of epidemiological studies are evaluated, it is important to consider whether such confounders have been adjusted for appropriately.

Tobacco use is strongly associated with a higher risk of many cancers. However, smoking is more common among lean individuals than among overweight or obese individuals; one mechanism that could explain this association is that smoking can have an anorectic effect. Smoking must therefore be properly adjusted for to ensure that it is not confounding the relationship between body fatness and risk of cancer. Current smoking modifies weight gain trajectory; therefore, among former smokers, time since quitting must be considered when stratifying by smoking status.

2.1.3 Reverse causation

Reverse causation occurs when the exposure is affected by the outcome, whereas it is usually assumed that the outcome is affected by the exposure. The direction of causality must be considered when evaluating associations between body fatness and risk of cancer. Weight may affect risk of cancer, but preclinical cancer can also cause weight loss. Additional chronic diseases that may affect risk of cancer may also result in weight loss. The timing of measurement must also be considered, because closer to the time of diagnosis, body fatness is more likely to be affected by disease.

2.1.4 Mendelian randomization

In the absence of large-scale and long-term randomized controlled trials (RCTs) on body fatness and risk of cancer, the concept of Mendelian randomization can provide insights into whether observed associations are causal, by leveraging the properties of genetic variation to overcome limitations present in observational epidemiological studies. Mendelian randomization exploits the random allocation of alleles between parents and offspring at conception as the basis of natural experiment to strengthen causal inference within the association between a modifiable exposure and an outcome of interest (Smith & Ebrahim, 2003, 2004; Lawlor et al., 2008).

The method relies on three main assumptions: the genetic variant (i) is a valid instrument, in that it is reliably associated with the exposure of interest, (ii) is not independently associated with the outcome, except through the exposure (known as the exclusion restriction criterion), and (iii) is not associated with any of the confounding factors that would otherwise distort the observational association between the exposure and the outcome. There are several general limitations to this methodology (for reviews, see Smith & Ebrahim, 2003, 2004). Importantly, effects of common genetic variants on the exposure are small and prone to weak instrumentation if used alone, which can bias estimates (Smith & Ebrahim, 2003, 2004). Therefore, using a greater number of variants included within Mendelian randomization analyses increases the variance explained in a given trait and can thus improve the precision of the causal estimate (Locke et al., 2015).

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2.2 Cancer-preventive effects by organ site

2.2.1 Cancer of the colorectum

Colorectal cancer (CRC) accounts for about 10% of all cancer diagnoses and 8.5% of all cancer deaths worldwide (Ferlay et al., 2013). CRC is more common in high-income countries than in low- and middle-income countries and is more prevalent in men than in women. It is well established that the risk of CRC changes within one generation after migration from low-incidence areas to high-incidence areas and thus has a strong environmental component. Cancers of the colon and of the rectum, although similar in many ways, have important differences in their risk factor profiles. Cancers of the rectum seem to be less associated with dietary factors and more associated with consumption of alcohol (particularly beer). Cancers of the colon arise most often from colorectal adenomas, and cancers in the proximal colon tend to have a worse prognosis than cancers in the distal colon.

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that there was *sufficient evidence* for a cancer-preventive effect of avoidance of weight gain for cancer of the colon. The 2007 World Cancer Research Fund (WCRF) review concluded that there was convincing evidence that both body fatness and waist circumference were associated with increased risk of CRC (WCRF/AICR, 2007). The 2007 conclusions were reaffirmed in 2011 (WCRF/AICR, 2011). Results from studies published since 2001 are summarized here and in Table 2.2.1a, Table 2.2.1b, and Table 2.2.1c.

(a) Cohort studies

A total of 39 cohort studies have been published since 2001 (excluding analyses that were later updated and analyses based on fewer than 100 incident cases). Table 2.2.1a summarizes their results for body mass index (BMI) at baseline, with comments on findings according to other measures of body fatness, such as weight change over the life-course and waist circumference.

(i) Body mass index

Although findings vary across studies, there is a general observation of a positive association between BMI and colon cancer risk across most studies, and a much weaker (but still positive) association between BMI and rectal cancer risk. In the studies that included both colon cancer and rectal cancer, the association with BMI for colon cancer was almost always either stronger or of the same magnitude as that for rectal cancer. For both colon cancer and rectal cancer, the association with BMI is stronger in men than in women. The association between BMI and colon cancer is approximately linear with increasing BMI levels. In a meta-analysis of prospective studies (Table 2.2.1c), the relative risk per 5 kg/m^2 increase in BMI was estimated to be 1.24 in men and 1.09 in women for colon cancer, and 1.09 in men and 1.02 in women for rectal cancer (all $P < 0.05$, except for rectal cancer in women, with $P = 0.26$) (Renehan et al., 2008). Another meta-analysis reported a relative risk of CRC for obesity relative to normal weight of 1.53 (95% confidence interval [CI], 1.44–1.62) in men and 1.25 (95% CI, 1.14–1.37) in women, and an overall increase in CRC risk of 18% (95% CI, 14–21%) per 5 kg/m^2 increase in BMI (Ning et al., 2010). The most recent meta-analysis of CRC, by Ma et al. (2013), based on 43 cohorts, estimated the relative risk for obesity relative to normal weight to be 1.33 (95% CI, 1.25–1.42).

In women, an interaction between use of hormone replacement therapy (HRT) and the BMI–CRC association has not been found consistently in the identified cohort studies that have investigated this (Lin et al., 2004; Adams et al., 2007; Wang et al., 2007; Aleksandrova et al., 2013; Kabat et al., 2015). There is not a consistent

set of evidence pointing to a differential of the BMI association for proximal versus distal colon subsites (Lin et al., 2004; Larsson et al., 2006; Bassett et al., 2010; Laake et al., 2010; Oxentenko et al., 2010; Hughes et al., 2011; Matsuo et al., 2012; Kitahara et al., 2013). BMI is also associated with risk of colorectal adenomas (Keum et al., 2015). The BMI–CRC association is observed consistently in diverse parts of the world (Renehan et al., 2008; Ma et al., 2013).

Several investigators have assessed the association between BMI at different ages or weight gain over the life-course and later colon cancer risk and/or rectal cancer risk. BMI at earlier ages seems to also be related to colon cancer risk (see Section 2.3), but BMI closer to the time of diagnosis is more consistently and strongly associated with risk than is BMI earlier in life (Bassett et al., 2010; Hughes et al., 2011). Weight gain since age 18 years has been found to be associated with colon cancer risk in several studies (Thygesen et al., 2008; Bassett et al., 2010; Renehan et al., 2012), but it is difficult to separate the effects of long-term weight gain from those of the resultant excess adiposity.

(ii) Waist circumference

Several cohorts have included measurements of waist circumference. Waist circumference at baseline is about as strongly associated with risk as is BMI in those studies that used identical quantile cut-off points for both measures (Table 2.2.1a). The meta-analysis of CRC and waist circumference by Ma et al. (2013), based on 13 prospective cohort studies, estimated the relative risk for the highest versus lowest categories of waist circumference across studies to be 1.46 (95% CI, 1.33–1.60), and no heterogeneity among studies was found ($P = 0.323$).

(b) Case–control studies

Since 2002, a total of 11 case–control studies, in Australia, Canada, China, Europe, the Republic of Korea, Thailand, and the USA, have reported on the association of BMI with CRC risk (Table 2.2.1b). In most of the studies, BMI was calculated from body height and self-reported body weight for a recent period before cancer diagnosis; in some of the studies, body weight was measured after diagnosis. Most studies showed an increase in risk of cancers of both the colon and the rectum with increasing BMI, and in some studies the association of BMI with risk was stronger for colon cancer than for rectal cancer. Some, but not all, studies showed more pronounced BMI-associated increases in risk in men than in women, although globally the evidence indicated increases in risk in both sexes. A meta-analysis of 12 case–control studies (Ning et al., 2010) found a relative risk of 1.23 for colon and rectal cancers combined, per 5 kg/m^2 increase in BMI.

The frequent observation of stronger associations of BMI with colon cancer risk in men than in women has led to the hypothesis that high blood levels of estrogens might confer protection against colon cancer. To address this issue, a few studies provided results in women stratified by estrogen status (determined by menopausal status and use of HRT). In a study in Germany in postmenopausal women only, a stratified analysis by users and non-users of postmenopausal HRT showed a strong association between BMI and CRC risk in the non-users only (odds ratio [OR], 3.30; 95% CI, 1.25–8.72 for BMI ≥ 30 kg/m^2 compared with BMI < 23 kg/m^2, based on 31 cases in the highest BMI category) and no association in the ever-users (OR, 0.89; 95% CI, 0.29–2.75) (Hoffmeister et al., 2007). These findings were opposite to those from a previous large study in the USA, which showed an increase in colon cancer risk only in estrogen-positive women (i.e. women who were premenopausal or who were users of postmenopausal HRT; OR, 2.38; 95% CI, 1.50–3.77 for BMI > 30 kg/m^2 compared with BMI < 23 kg/m^2, based on 77 cases in the highest BMI category) compared with no association in estrogen-negative women (i.e. women

who were postmenopausal and were non-users of HRT; OR, 1.02; 95% CI, 0.71–1.46 for BMI > 30 kg/m^2 compared with BMI < 23 kg/m^2, based on 134 cases in the highest BMI category) (Slattery et al., 2003). Another study, conducted in Shanghai, China, in a relatively lean population, showed a direct association of BMI with colon cancer risk in premenopausal women (OR, 2.9; 95% CI, 1.7–8.6 for BMI > 23.6 kg/m^2 compared with BMI < 19.0 kg/m^2, based on 62 cases in the highest BMI category) and an inverse association in postmenopausal women (OR, 0.6; 95% CI, 0.3–0.9 for BMI > 23.6 kg/m^2 compared with BMI < 19.0 kg/m^2, based on 50 cases in the highest BMI category) (Hou et al., 2006). A fourth study, in Canada, found an absence of association both in "estrogen-positive" women and in "estrogen-negative" women (Campbell et al., 2007).

With regard to molecular tumour subtypes, Campbell et al. (2010) showed a BMI-associated increase in risk for tumours that have a microsatellite-stable phenotype (recent BMI, OR per 5 kg/m^2 increase, 1.38; 95% CI, 1.24–1.54), whereas no association was observed for tumours characterized by microsatellite instability (OR, 1.05; 95% CI, 0.84–1.31) (see Section 4.2.3c).

(c) Mendelian randomization studies

Two recent studies have applied Mendelian randomization to assess the association between BMI and CRC risk (Table 2.2.1d). In the first study, Thrift et al. (2015) used a genetic risk score (GRS) derived from 77 single nucleotide polymorphisms (SNPs) associated with higher BMI, identified by the Genetic Investigation of Anthropometric Traits (GIANT) consortium, which involved more than 300 000 individuals of European descent. In their analysis, higher BMI was associated with an increased risk of CRC (GRS-related OR per 5 kg/m^2 increase in BMI, 1.50; 95% CI, 1.13–2.01). The point estimate obtained using the Mendelian randomization approach was greater in magnitude than the point estimate obtained from conventional covariate-adjusted analysis (minimally adjusted OR per 5 kg/m^2 increase in BMI, 1.18; 95% CI, 1.15–1.22); however, the 95% confidence intervals overlapped and they were not statistically significantly different from one another ($P_{difference}$ = 0.10). In addition, there was a positive association between BMI and CRC risk in women (GRS-related OR per 5 kg/m^2 increase in BMI, 1.82; 95% CI, 1.26–2.61), and this estimate was much greater than that obtained from conventional observational analyses (OR, 1.14; 95% CI, 1.10–1.18; $P_{difference}$ = 0.01); although there was no strong evidence from Mendelian randomization analyses for an association in men (GRS-related OR per 5 kg/m^2 increase in BMI, 1.18 (95% CI, 0.73–1.92), the results were in the same direction as in the observational results in the same sample ($P_{difference}$ = 0.70). [This discrepancy between the sexes may be due to sex-specific residual confounding or measurement error in observational analyses. Alternatively, the distribution of body fat, rather than total body fatness (reflected by BMI), may be a more important predictor of CRC risk for men than for women.]

In the second study, Gao et al. used 15 SNPs reliably associated with childhood BMI (Felix et al., 2016) and 77 SNPs reliably associated with adult BMI (Locke et al., 2015) as Mendelian randomization instruments and assessed their association with CRC risk (Gao et al., 2016). Mendelian randomization analyses showed an 8% increase in risk of CRC with each increase of 1 kg/m^2 in adult BMI [assuming that a standard deviation was equivalent to 4.5 kg/m^2]. There was no evidence of an association with childhood BMI.

Table 2.2.1a Cohort studies of measures of body fatness and cancer of the colorectum

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Terry et al. (2001) Women in Swedish mammography programme (ages 40–76 yr) Sweden 1987–1998	61 463 Women Incidence	Colon	BMI < 22 22–24.2 24.2–26.7 > 26.7 [P_{trend}]	291 total	 1.0 1.05 (0.72–1.51) 1.09 (0.77–1.56) 1.21 (0.86–1.70) [0.25]	Age, education level, alcohol consumption, diet	Stronger risk within the women in age group 40–54 yr (P_{trend} = 0.06)
	61 463 Women Incidence	Rectum	BMI < 22 22–24.2 24.2–26.7 > 26.7 [P_{trend}]	159 total	 1.0 0.92 (0.56–1.54) 1.14 (0.71–1.83) 1.32 (0.83–2.08) [0.13]	Age, education level, alcohol consumption, diet	
Terry et al. (2002) Women in Canadian mammography programme (ages 40–59 yr) Canada 1980–1993	89 835 Women Incidence	Colon and rectum	BMI < 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	527 total	 1.0 1.03 (0.84–1.26) 1.08 (0.82–1.41) [0.57]	Age, smoking, education level, physical activity, OC use, HRT use, parity	Association stronger in premenopausal ages than postmenopausal ages ($P_{interaction}$ = 0.01)
Calle et al. (2003) Population-based cohort USA 1982–1998	404 576 Men Mortality	Colon and rectum	BMI 18.5–24.9 25–29.9 30–34.9 35–39.9 [P_{trend}]	 1292 1811 337 54	 1.00 1.20 (1.12–1.30) 1.47 (1.30–1.66) 1.84 (1.39–2.41) [< 0.001]	Age, education level, smoking, physical activity, alcohol consumption, marital status, race, aspirin use, fat intake, vegetable intake	
	495 477 Women Mortality		BMI 18.5–24.9 25–29.9 30–34.9 35–39.9 ≥ 40 [P_{trend}]	 1706 906 312 67 21	 1.00 1.10 (1.01–1.19) 1.33 (1.17–1.51) 1.36 (1.06–1.74) 1.46 (0.94–2.24) [< 0.001]	Additionally adjusted for HRT use	

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Lin et al. (2004) Women's Health Study USA 1993–2002	39 876 Women Incidence	Colon and rectum	BMI < 23 23–24.9 25–26.9 27–29.9 ≥ 30 [P_{trend}]	 44 45 31 40 42	 1.0 1.45 (0.96–2.20) 1.28 (0.81–2.04) 1.72 (1.12–2.66) 1.67 (1.08–2.59) [0.018]	Age, study group, family history, history polyps, physical activity, smoking, aspirin use, consumption of red meat, alcohol consumption, HRT use	Stronger association with proximal colon. Similar findings by HRT status in never-users of HRT. Proximal and distal subsites similar
MacInnis et al. (2004) Population-based cohort Australia 1990–2003	16 556 Men Incidence	Colon	BMI < 24.8 24.8–26.9 27–29.2 ≥ 29.2 [P_{trend}]	 26 37 39 51	 1.0 1.3 (0.8–2.2) 1.4 (0.8–2.3) 1.7 (1.1–2.8) [0.02]	Age, education level, country of birth	
	16 556 Men Incidence		WC < 87 87–93 93–99.3 ≥ 99.3 [P_{trend}]	 22 19 48 64	 1.0 10.8 (0.4–1.4) 1.7 (1.0–2.8) 2.1 (1.3–3.5) [< 0.001]	Age, education level, country of birth	
Moore et al. (2004) Framingham Study cohort USA 1948–1999	3764 Men and women aged 30–54 yr at baseline Incidence	Colon	BMI 18.5–24.9 25–29.9 ≥ 30	 67 69 21	 1.0 1.3 (0.91–1.8) 1.5 (0.92–2.5)	Age, sex, education level, height, alcohol consumption, smoking, physical activity	
			WC Small Medium Large Extra large	 17 61 46 33	 1.0 1.1 (0.66–2.0) 1.6 (0.91–2.9) 2.0 (1.1–3.7)	Age, sex, education level, height, alcohol consumption, smoking, physical activity	Additional adjustment for BMI has no effect on estimates

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Moore et al. (2004) (cont.)	3802 Men and women aged 55–79 yr at baseline Incidence	Colon	BMI 18.5–24.9 25–29.9 ≥ 30	 39 79 31	 1.0 1.8 (1.2–2.6) 2.4 (1.5–3.9)	Age, sex, education level, height, alcohol consumption, smoking, physical activity	Associations more evident in men than in women, and stronger in the proximal site
			WC Small Medium Large Extra large	 11 53 47 38	 1.0 1.4 (0.74–2.7) 2.1 (1.1–4.0) 2.6 (1.3–5.2)	Age, sex, education level, height, alcohol consumption, smoking, physical activity	Adjustment for BMI has no effect on estimates
Samanic et al. (2004) United States Veterans cohort USA 1969–1996	4 500 700 Men Incidence	Colon	Obesity Non-obese Obese Non-obese Obese	 White men: 16 704 1420 Black men: 3830 262	 1.00 1.47 (1.39–1.55) 1.00 1.45 (1.28–1.64)	Age, calendar year	Obesity defined as discharge diagnosis of obesity: ICD-8: 277; ICD-9: 278.0 No significant differences in risk observed between White and Black veterans
	4 500 700 Men Incidence	Rectum	Obesity Non-obese Obese Non-obese Obese	 White men: 9849 719 Black men: 1773 93	 1.00 1.23 (1.14–1.33) 1.00 1.11 (0.90–1.37)	Age, calendar year	No significant differences in risk observed between White and Black veterans
Wei et al. (2004) Nurses' Health Study USA 1976–2000	46 632 Men Incidence	Colon	BMI < 23 23–24.9 25–29.9 ≥ 30 [P_{trend}]	 57 119 225 51	 1.0 1.33 (0.97–1.83) 1.54 (1.15–2.07) 1.85 (1.26–2.72) [0.001]	Age, family history, physical activity, smoking, diet, screening history. alcohol consumption, height	

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Wei et al. (2004) (cont.)	87 733 Women Incidence		BMI < 23 23–24.9 25–29.9 ≥ 30 [P_{trend}]	 210 141 207 113 	 1.0 1.10 (0.88–1.36) 1.11 (0.91–1.35) 1.28 (1.10–1.62) [0.05]		
	46 632 Men Incidence	Rectum	BMI < 23 23–24.9 25–29.9 ≥ 30 [P_{trend}]	 24 42 55 11 	 1.0 1.16 (0.70–1.94) 0.93 (0.57–1.53) 1.03 (0.49–2.14) [0.70]	Age, family history, physical activity, smoking, diet, screening history, alcohol consumption, height	
	87 733 Women Incidence		BMI < 23 23–24.9 25–29.9 ≥ 30 [P_{trend}]	 56 46 68 34 	 1.0 1.37 (0.92–2.02) 1.40 (0.98–2.01) 1.56 (1.01–2.42) [0.04]		
Engeland et al. (2005) Population-based cohort Norway 1963–2001	963 709 Men Incidence	Colon and rectum	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 90 11 432 9953 1512 	 0.84 (0.68–1.03) 1.0 1.15 (1.12–1.18) 1.40 (1.32–1.48) [< 0.001]	Age at BMI measurement, birth cohort	Relationships similar for colon vs rectum
	1 038 010 Women Incidence		BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 298 11 136 8780 3916 	 1.04 (0.93–1.17) 1.0 1.02 (0.99–1.05) 1.06 (1.02–1.10) [0.01]	Age at BMI measurement, birth cohort	Relationships similar for colon vs rectum. In women, associations stronger for colon
Kuriyama et al. (2005) Population-based prospective cohort Japan 1984–1992	12 485 Men Incidence	Colon and rectum	BMI < 18.5–24.9 25–27.5 27.5–29.9 ≥ 30 [P_{trend}]	 114 25 11 5 	 1.00 1.04 (0.67–1.60) 1.58 (0.85–2.94) 1.78 (0.73–4.38) [0.3710]	Age, smoking, alcohol consumption, diet, health insurance	

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Kuriyama et al. (2005) (cont.)	15 052 Women Incidence		BMI < 18.5–24.9 25–27.5 27.5–29.9 ≥ 30 [P_{trend}]	 73 22 11 9	 1.00 1.11 (0.69–1.80) 1.28 (0.68–2.43) 2.06 (1.03–4.13) [0.06]		
Oh et al. (2005) Civil servants and private school workers cohort Republic of Korea 1992–2001	781 283 Men Incidence	Colon (excluding rectosigmoid)	BMI < 18.5 18.5–22.9 23.0–24.9 25.0–26.7 27.0–29.9 ≥ 30 [P_{trend}]	 14 359 316 190 63 11	 1.00 (0.62–1.63) 1.00 1.24 (1.07–1.43) 1.33 (1.13–1.57) 1.07 (0.83–1.38) 1.92 (1.15–3.22) [0.001]	Age, smoking, alcohol consumption, physical activity, family history, residence area	
	781 283 Men Incidence	Rectosigmoid	BMI < 18.5 18.5–22.9 23.0–24.9 25.0–26.7 27.0–29.9 ≥ 30 [P_{trend}]	 20 606 480 326 117 14	 0.64 (0.36–1.13) 1.00 1.06 (0.92–1.22) 1.29 (1.10–1.52) 1.15 (0.91–1.46) 1.08 (0.56–2.10) [0.003]	Age, smoking, alcohol consumption, physical activity, family history, residence area	
Rapp et al. (2005) VHM&PP (population-based cohort) Austria 1985–2002	67 447 Men Incidence	Colon	BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 86 128 39 7	 1.00 1.14 (0.86–1.50) 1.56 (1.06–2.30) 2.48 (1.15–5.39) [0.005]	Age, smoking status, occupational group	
	78 484 Women Incidence		BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 122 106 35 8	 1.00 1.13 (0.86–1.47) 1.11 (0.76–1.62) 0.88 (0.43–1.81) [0.73]	Age, smoking status, occupational group	

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Rapp et al. (2005) (cont.)	67 447 Men Incidence	Rectum	BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 45 69 24 – 	 1.00 1.20 (0.82–1.75) 1.66 (1.01–2.73) – [0.05]	Age, smoking status, occupational group	All obese categories were merged (from BMI 30 kg/m^2 onwards) to ensure at least 5 cases
	78 484 Women Incidence		BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 68 48 12 5 	 1.00 0.90 (0.62–1.31) 0.66 (0.36–1.23) 0.96 (0.38–2.39) [0.32]	Age, smoking status, occupational group	
Bowers et al. (2006) ATBC cohort Finland 1985–2002	29 133 Men Incidence	Colon	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 2 77 98 50	 1.47 (0.36–5.98) 1.00 1.07 (0.79–1.44) 1.78 (1.25–2.55)	Age, number of cigarettes smoked per day, total cholesterol, height, type 2 diabetes	Cohort of smokers
	29 133 Men Incidence	Rectum	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 1 61 87 34	 0.96 (0.13–6.96) 1.0 1.18 (0.85–1.64) 1.51 (0.99–2.29)		
	29 133 Men Incidence	Colon and rectum	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 3 138 185 84	 1.25 (0.40–3.93) 1.0 1.12 (0.90–1.39) 1.66 (1.27–2.18)		
Larsson et al. (2006) Population-based cohort Sweden 1997–2005	45 906 Men Incidence	Colon	BMI < 23 23–24.9 25–26.9 27–29.9 ≥ 30 [P_{trend}]	 47 72 65 61 39 	 1.00 1.11 (0.77–1.61) 1.07 (0.73–1.56) 1.15 (0.78–1.70) 1.60 (1.03–2.48) [0.08]	Age, education level, family history, diabetes, smoking, aspirin use, physical activity	Proximal and distal subsites similar. WC also positively associated

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Larsson et al. (2006) (cont.)	45 906 Men Incidence	Rectum	BMI < 23 23–24.9 25–26.9 27–29.9 ≥ 30 [P_{trend}]	 25 39 49 46 21	 1.00 1.08 (0.65–1.80) 1.35 (0.83–2.19) 1.53 (0.93–2.51) 1.44 (0.79–2.61) [0.06]	Age, education level, family history, diabetes, smoking, aspirin use, physical activity	
	45 906 Men Incidence	Colon and rectum	WC < 88 88–92 93–97 98–103 ≥ 104 [P_{trend}]	 47 67 95 96 102	 1.00 1.06 (0.73–1.55) 1.32 (0.92–1.88) 1.37 (0.96–1.96) 1.29 (0.90–1.85) [0.03]	Age, education level, family history, diabetes, smoking, aspirin use, physical activity	
Lukanova et al. (2006) Population-based cohort Sweden 1985–2003	33 424 Men Incidence	Colon and rectum	BMI < 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 45 69 22	 1.0 1.17 (0.80–1.71) 1.61 (0.95–2.65) [0.08]	Age, calendar year, smoking	Association with obesity significant only when excluding cases diagnosed within 1 yr of recruitment
	35 362 Women Incidence		BMI < 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 43 39 26	 1.0 1.27 (0.82–1.97) 2.01 (1.22–3.27) [0.005]	Age, calendar year, smoking	
MacInnis et al. (2006a) Melbourne Collaborative Cohort Study Australia 1990–2003	24 072 Women Incidence	Colon	BMI, tertiles T1 (< 25) T2 (25–29) T3 (≥ 30) [P_{trend}]	212 total	 1.0 0.8 (0.6–1.1) 1.0 (0.7–1.4) [0.59]	Age, education level, country of birth, HRT use	No differences between proximal and distal, or by disease stage (early vs late)
			WC, tertiles T1 (< 75) T2 (75–79) T3 (≥ 80) [P_{trend}]	212 total	 1.0 1.4 (1.0–1.9) 1.4 (1.0–1.9) [0.02]	Age, education level, country of birth, HRT use	No differences between proximal and distal, or by disease stage (early vs late)

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
MacInnis et al. (2006b) Population-based cohort Australia 1990–2003	16 867 Men Incidence	Rectum	BMI, tertiles			Age, country of birth, SES, height	Similar results in women (n = 24 247), no sex interaction
			< 25	24	1.0		
			25–29.9	86	1.7 (1.1–2.7)		
			≥ 30	24	1.3 (0.8–2.4)		
			[P_{trend}]		[0.48]		
			WC			Age, country of birth	Similar results in women (n = 24 247), no sex interaction
			< 94	57	1.0		
			94–101.9	43	1.3 (0.9–1.9)		
			≥ 102	34	1.4 (0.9–2.2)		
			[P_{trend}]		[0.11]		
Pischon et al. (2006) EPIC cohort Europe 1992–2003	129 731 Men Incidence	Colon	BMI			Age, centre, smoking, education level, alcohol consumption, physical activity, diet	
			< 23.6	64	1.0		
			23.6–25.3	85	1.18 (0.85–1.63)		
			25.4–27	74	1.00 (0.71–1.41)		
			27.1–29.3	88	1.19 (0.85–1.66)		
			≥ 29.4	110	1.55 (1.12–2.15)		
			[P_{trend}]		[0.006]		
			WC			Age, centre, smoking, education level, alcohol consumption, physical activity, diet, height	
			< 86	63	1.00		
			86–91.8	57	0.73 (0.50–1.04)		
			91.9–96.5	78	0.97 (0.69–1.36)		
			96.6–102.9	95	1.10 (0.79–1.53)		
			≥ 103	125	1.39 (1.01–1.93)		
			[P_{trend}]		[0.001]		

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Pischon et al. (2006) (cont.)	238 546 Women Incidence	Colon	BMI < 23.6 23.6–25.3 25.4–27 27.1–29.3 ≥ 29.4 [P_{trend}]	 87 96 120 137 135 123 	 1.0 0.92 (0.68–1.23) 1.02 (0.77–1.35) 1.09 (0.83–1.45) 1.06 (0.79–1.42) [0.40]	Age, centre, smoking, education level, alcohol consumption, physical activity, diet	
			WC < 70.2 70.2–75.8 75.9–80.9 81–88.9 ≥ 89 [P_{trend}]	 62 91 125 135 149 	 1.0 1.10 (0.80–1.52) 1.23 (0.90–1.68) 1.25 (0.91–1.70) 1.48 (1.08–2.03) [0.008]	Age, centre, smoking, education level, alcohol consumption, physical activity, diet, height	
	129 731 Men Incidence	Rectum	BMI < 23.6 23.6–25.3 25.4–27 27.1–29.3 ≥ 29.4 [P_{trend}]	 52 52 58 69 64 	 1.0 0.88 (0.60–1.30) 0.96 (0.66–1.40) 1.11 (0.77–1.62) 1.05 (0.72–1.55) [0.47]	Age, centre, smoking, education level, alcohol consumption, physical activity, diet	WC, null association
	238 546 Women Incidence		BMI < 23.6 23.6–25.3 25.4–27 27.1–29.3 ≥ 29.4 [P_{trend}]	 47 44 72 63 65 	 1.0 0.78 (0.51–1.18) 1.14 (0.78–1.66) 0.95 (0.64–1.41) 1.06 (0.71–1.58) [0.51]	Age, centre, smoking, education level, alcohol consumption, physical activity, diet	WC, null association
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1971–1999	362 552 Men Incidence	Colon	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 763 842 190 	 1.00 1.24 (1.12–1.37) 1.74 (1.48–2.04) [< 0.001]	Age, year, smoking status	

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Samanic et al. (2006) (cont.)	362 552 Men Incidence	Rectum	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 626 610 126	 1.00 1.08 (0.96–1.21) 1.36 (1.13–1.66) [< 0.01]	Age, year, smoking status	
Adams et al. (2007) NIH-AARP cohort USA 1995–2000	307 708 Men Incidence	Colon	BMI 18.5–22.9 23–24.9 25–27.4 27.5–29.9 30–32.5 32.5–34.9 35–39.9 ≥ 40 [P_{trend}]	 136 260 479 367 219 110 76 29	 1.0 1.11 (0.90–1.37) 1.22 (1.01–1.48) 1.44 (1.18–1.76) 1.53 (1.23–1.90) 1.57 (1.22–2.03) 1.71 (1.29–2.27) 2.39 (1.59–3.58) [< 0.0005]	Age, alcohol consumption, smoking, supplemental calcium intake, consumption of red meat	
	209 436 Women Incidence		BMI 18.5–22.9 23–24.9 25–27.4 27.5–29.9 30–32.5 32.5–34.9 35–39.9 ≥ 40 [P_{trend}]	 151 141 172 106 77 42 52 28	 1.0 1.20 (0.95–1.51) 1.29 (1.03–1.60) 1.31 (1.01–1.68) 1.28 (0.97–1.69) 1.13 (0.80–1.60) 1.46 (1.06–2.02) 1.49 (0.98–2.25) [0.02]	Additionally adjusted for HRT use	Similar findings by HRT status
	307 708 Men Incidence	Rectum	BMI 18.5–22.9 23–24.9 25–27.4 27.5–29.9 30–32.5 32.5–34.9 ≥ 35 [P_{trend}]	 74 101 218 135 74 42 33	 1.0 0.78 (0.58–1.06) 1.01 (0.77–1.31) 0.96 (0.72–1.28) 0.94 (0.68–1.30) 1.10 (0.75–1.61) 1.0 (0.68–1.58) [0.31]	Age, alcohol consumption, smoking, supplemental calcium intake, consumption of red meat	

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Adams et al. (2007) (cont.)	209 436 Women Incidence		BMI 18.5–22.9 23–24.9 25–27.4 27.5–29.9 30–32.5 32.5–34.9 ≥ 35 [P_{trend}]	 60 49 60 37 26 14 32	 1.0 1.05 (0.72–1.53) 1.13 (0.79–1.63) 1.16 (0.76–1.76) 1.09 (0.68–1.75) 0.95 (0.52–1.71) 1.44 (0.92–2.25) [0.20]	Additionally adjusted for HRT use	Similar findings by HRT status
Driver et al. (2007) Physicians' Health Study USA 1982–2004	22 071 Men Incidence	Colon and rectum	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 190 171 20	 1.0 1.26 (1.05–1.52) 1.62 (1.09–2.42) [P_{trend}]	Age, smoking, alcohol consumption, diabetes, exercise	
Fujino et al. (2007) JACC cohort Japan 1988–1997	46 465 Men Incidence	Colon	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 12 155 36 1	 0.86 (0.48–1.57) 1.0 1.14 (0.79–1.65) 0.54 (0.07–3.90)	Age, study area	Weight at age 20 yr also positively associated with risk
	64 327 Women Incidence		BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 14 128 42 8	 0.98 (0.56–1.71) 1.0 1.09 (0.77–1.56) 1.94 (0.94–3.98)	Age, study area	Weight at age 20 yr also positively associated with risk
	46 465 Men Incidence	Rectum	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 6 128 21 2	 0.57 (0.25–1.30) 1.0 0.78 (0.49–1.24) 1.27 (0.31–5.17)	Age, study area	Weight at age 20 yr also positively associated with risk
	64 321 Women Incidence		BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 2 58 19 2	 0.36 (0.08–1.48) 1.0 1.04 (0.62–1.76) 1.00 (0.24–4.12)	Age, study area	

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Lundqvist et al. (2007) Twin cohorts Sweden and Finland 1961–2004	24 821 older twins (mean baseline age, 56 yr) 10 804 men and 14 017 women Incidence	Colon and rectum	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 7 274 196 36	 1.0 (0.5–2.1) 1.0 1.1 (0.9–1.3) 1.3 (0.9–1.8) [0.12]	Smoking, sex, country, physical activity, education level, diabetes	No association with rectal cancer
	43 328 younger twins (mean baseline age, 30 yr) 20 992 men and 22 336 women Incidence		BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 4 146 47 7	 0.6 (0.2–1.7) 1.0 1.0 (0.7–1.4) 1.1 (0.5–2.5) [0.53]	Smoking, physical activity, education level, diabetes	No association with rectal cancer
Reeves et al. (2007) Population-based cohort United Kingdom 1996–2001	1.2 million Women Incidence	Colon and rectum	BMI < 22.5 22.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 per 10 kg/m²	 789 1034 913 555 717	 1.02 (0.95–1.10) 1.00 1.04 (0.97–1.11) 1.01 (0.93–1.10) 1.01 (0.94–1.09) 1.00 (0.92–1.08)	Age, region, SES, reproductive history, smoking, alcohol consumption, physical activity, time since menopause, HRT use	
Wang et al. (2007) Cancer Prevention Study II (CPS II) Nutrition Cohort USA 1992–2003	73 842 Women	Colon and rectum	BMI < 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 399 274 141	 1.0 1.08 (0.93–1.27) 1.19 (0.97–1.45) [0.04]	Age, education level, endoscopy history, baseline HRT use, NSAID use, multivitamin use, smoking, physical activity, diabetes	Cohort of postmenopausal women Similar findings by HRT status (never, former, current use)
Song et al. (2008) Korean medical insurance cohort Republic of Korea 1994–2003	107 481 Women Incidence	Colon (above rectosigmoid junction)	BMI < 18.5 18.5–20.9 21–22.9 23.0–24.9 25.0–26.9 27.0–29.9 ≥ 30 [risk per 1 kg/m²]	 11 46 86 141 129 64 32	 0.94 (0.37–2.39) 1.03 (0.63–1.70) 1.00 1.69 (1.17–2.44) 1.73 (1.18–2.53) 1.21 (0.77–1.90) 2.43 (1.40–4.23) [1.05 (1.02–1.09)]	Age, height, smoking, alcohol consumption, exercise, pay level at study entry	Cohort of postmenopausal women (age 40–64 yr) Results presented are those after excluding patients diagnosed within the first 5 yr of follow-up

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Song et al. (2008) (cont.)	107 481 Women Incidence	Rectum (below rectosigmoid junction)	BMI < 18.5 18.5–20.9 21–22.9 23.0–24.9 25.0–26.9 27.0–29.9 ≥ 30 [risk per 1 kg/m^2]	 10 69 110 140 102 85 20	 1.00 (0.43–2.33) 1.06 (0.67–1.67) 1.00 1.26 (0.88–1.81) 0.94 (0.63–1.40) 1.62 (1.10–2.38) 1.13 (0.57–2.24) [1.03 (0.99–1.06)]	Age, height, smoking, alcohol consumption, exercise, pay level at study entry	
Thygesen et al. (2008) Health Professionals Follow-Up Study USA 1986–2004	46 349 Men Incidence	Colon	BMI < 20 20.1–22.5 22.6–25 25.1–30 30.1–35 > 35	 9 50 205 341 75 13	 1.69 (0.83–3.44) 1.0 1.40 (1.03–1.92) 1.64 (1.21–2.22) 2.29 (1.58–3.31) 2.29 (1.23–4.26)	Age, physical activity, alcohol consumption, diet, smoking, aspirin use, family history, prior screening. All confounders were lagged 2 yr	Weight gain since age 21 yr positively associated with risk. The association became stronger when 2–4 yr of lag time for weight change was allowed
Wang et al. (2008) Cancer Prevention Study II (CPS II) Nutrition Cohort USA 1997–2005	44 068 Men Incidence	Colon	BMI < 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}] WC < 95 95–105 105–120 ≥ 120 [P_{trend}]	 143 179 64 16 165 195 157 29 	 1.0 0.93 (0.75–1.17) 1.34 (0.99–1.82) 1.93 (1.14–3.28) [0.01] 1.0 0.95 (0.77–1.17) 1.21 (0.96–1.52) 1.68 (1.12–2.53) [< 0.006]	Height, education level, physical activity, smoking, alcohol consumption, NSAID use, multivitamin use, screening history	

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Wang et al. (2008) (cont.)	51 083 Women Incidence	Colon	BMI < 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 156 97 44 17	 1.0 0.92 (0.71–1.19) 1.25 (0.88–1.76) 1.40 (0.84–2.36) [0.18]	Height, education level, physical activity, smoking, alcohol consumption, NSAID use, multivitamin use, screening history, HRT use	
			WC < 85 85–95 95–110 ≥ 110 [P_{trend}]	 158 109 104 36	 1.0 1.01 (0.79–1.29) 1.27 (0.98–1.64) 1.75 (1.20–2.54) [0.003]	Height, education level, physical activity, smoking, alcohol consumption, NSAID use, multivitamin use, screening history, HRT use	
	44 068 Men Incidence	Rectum	BMI < 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 50 63 23 6	 1.0 0.80 (0.55–1.16) 1.01 (0.61–1.68) 1.38 (0.58–3.28) [0.70]	Height, education level, physical activity, smoking, alcohol consumption, NSAID use, multivitamin use, screening history; for women, also adjusted for HRT use	WC, also null association
	51 083 Women Incidence		BMI < 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 37 31 19 6	 1.0 1.34 (0.82–2.17) 2.62 (1.48–4.66) 2.67 (1.09–6.54) [0.001]		Similar association with WC
Andreotti et al. (2010) Agricultural workers USA 1993–2005	39 628 Men Incidence	Colon	BMI < 18.5 18.5–24.9 25.0–29.9 30–34.9 ≥ 35 per 1 kg/m^2	 1 44 112 58 15	 – 1.0 1.26 (0.86–1.86) 1.88 (1.23–2.91) 2.03 (1.05–3.93) 1.05 (1.02–1.09)	Race, education level, family history of colon cancer	

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Andreotti et al. (2010) (cont.)	28 319 Women Incidence		BMI < 18.5 18.5–24.9 25.0–29.9 30–34.9 ≥ 35 per 1 kg/m^2 [P_{trend}]	 1 40 49 19 4 	 – 1.0 1.48 (0.97–2.26) 1.36 (0.79–2.36) – 1.00 (0.96–1.04) [0.92]		
	39 628 Men Incidence	Rectum	BMI < 18.5 18.5–24.9 25.0–29.9 30–34.9 ≥ 35 per 1 kg/m^2 [P_{trend}]	 0 23 53 16 10 	 – 1.0 0.96 (0.51–1.82) 0.60 (0.24–1.50) 3.21 (1.34–7.71) 1.06 (1.00–1.12) [0.06]	Additionally adjusted for meat consumption	Results in women not presented due to too few incident cases
Bassett et al. (2010) Population-based cohort Australia 1990–2007	16 188 Men Incidence	Colon	BMI < 23 23–24.9 25.0–29.9 ≥ 30 [P_{trend}]	 13 38 160 66 	 0.60 (0.32–1.13) 1.0 1.31 (0.91–1.87) 1.51 (1.00–2.28) [< 0.01]	Place of birth, education level, diet, smoking, alcohol consumption	BMI at age 18 yr, null association. Positive association with weight gain since age 18 yr. Association stronger for proximal colon
	23 438 Women Incidence		BMI < 23 23–24.9 25.0–29.9 ≥ 30 [P_{trend}]	 64 59 102 67 	 0.95 (0.67–1.36) 1.0 0.84 (0.61–1.17) 1.00 (0.70–1.44) [0.90]		BMI at age 18 yr, null association. Weight gain since age 18 yr, also null association

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Laake et al. (2010) Population-based cohort Norway 1974–2005	38 822 Men Incidence	Colon	BMI < 18.5–22.9 23–24.9 25–27.4 27.5–29.9 ≥ 30 [P_{trend}]	 695 112 140 75 54	 1.0 1.16 (0.86–1.56) 1.19 (0.89–1.60) 1.20 (0.86–1.68) 1.80 (1.25–2.59) [0.004]	Age, physical activity, height, energy intake, smoking, education level, county	Association stronger for distal colon than proximal
	37 357 Women Incidence		BMI < 18.5–22.9 23–24.9 25–27.4 27.5–29.9 ≥ 30 [P_{trend}]	 115 95 81 57 71	 1.0 1.05 (0.80–1.38) 1.03 (0.77–1.38) 1.27 (0.92–1.76) 1.48 (1.09–2.02) [0.01]	Age, physical activity, height, energy intake, smoking, education level, county	Association stronger for distal colon
Oxentenko et al. (2010) Iowa Women's Health Study USA 1986–2005	36 941 Women Incidence after age 55 yr	Colon and rectum	BMI < 18.5 18.5–24.9 25–29.9 30–34.9 35–39.9 ≥ 40 [P_{trend}]	 19 495 548 272 93 37	 1.62 (0.98–2.66) 1.0 1.12 (0.99–1.28) 1.31 (1.12–1.54) 1.32 (1.03–1.68) 1.56 (1.10–2.22) [< 0.001]	Age, HRT use, OC use, smoking, physical activity, diabetes, alcohol consumption, diet, calcium intake, folate intake, vitamin E intake	Proximal and distal subsites similar. Association stronger for distal site
			WC, quartiles Q1 Q2 Q3 Q4 [P_{trend}]	 292 351 431 390	 1.0 1.18 (1.00–1.39) 1.34 (1.14–1.576) 1.32 (1.11–1.56) [< 0.001]	Age, HRT use, OC use, smoking, physical activity, diabetes, alcohol consumption, diet, calcium intake, folate intake, vitamin E intake	Proximal and distal subsites similar

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Parr et al. (2010) Pooled analysis of 39 cohort studies Asia, Australia, and New Zealand 1961–1999, median follow-up 4 yr	424 519 Men and women Incidence	Colon	BMI < 12–18.4 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	429 total	 0.63 (0.26–1.56) 1.0 1.13 (0.94–1.36) 1.50 (1.13–1.99) [0.02]	Age, sex, tobacco use	Stronger positive association in obese men
	424 519 Men and women Mortality	Rectum	BMI < 12–18.4 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	233 total	 0.86 (0.37–2.02) 1.0 1.44 (1.11–1.86) 1.68 (1.06–2.67) [0.03]	Age, sex, tobacco use	
Hughes et al. (2011) Population-based cohort The Netherlands 1986–2002	58 297 Men Incidence	Colon and rectum	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 232 238 240 247 254	 1.0 0.95 (0.74–1.24) 0.99 (0.77–1.28) 1.05 (0.81–1.36) 1.25 (0.96–1.62) [0.08]	Age, diet, occupation, physical activity, education level, family history, alcohol consumption, smoking	Rectal cancer not associated with BMI. Proximal and distal sites similar. Stronger associations with distal sites, P_{trend} significant. BMI at age 20 yr weakly associated
	62 573 Women Incidence		BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 228 211 223 222 222	 1.0 0.88 (0.69–1.13) 0.94 (0.73–1.20) 0.91 (0.71–1.16) 0.97 (0.76–1.24) [0.90]	Age, diet, occupation, physical activity, education level, family history, alcohol consumption, smoking	BMI at age 20 yr, null association Rectal cancer also not associated with BMI

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Odegaard et al. (2011) Singapore Chinese Health Study cohort Shanghai, China 1993–2007	51 251 Men and women Incidence	Colon	BMI < 18.5 18.5–21.4 21.5–24.4 24.5–27.4 ≥ 27.5 [P_{trend}]	 51 162 181 123 79	 1.23 (0.90–1.68) 1.17 (0.95–1.45) 1.0 1.12 (0.89–1.43) 1.48 (1.13–1.92) [0.44]	Age, sex, year enrolment, dialect, education level, diabetes, family history, smoking, alcohol consumption, diet, physical activity, sleep duration	Significant U-shaped quadratic association (P_{trend} = 0.014). Stronger association in older subjects (> 65 yr) and non-smokers
	51 251 Men and women Incidence	Rectum	BMI < 18.5 18.5–21.4 21.5–24.4 24.5–27.4 ≥ 27.5 [P_{trend}]	 25 111 137 76 35	 0.77 (0.50–1.19) 1.04 (0.81–1.34) 1.0 0.95 (0.71–1.25) 0.93 (0.64–1.36) [0.92]	Age, sex, year of enrolment, dialect, education level, diabetes, family history, smoking, alcohol consumption, diet, physical activity, sleep duration	
Matsuo et al. (2012) 8 population-based cohorts (pooled) Japan 1984–2006	157 927 Men Incidence	Colon	BMI < 19 19–20.9 21–22.9 23–24.9 25–26.9 27–29.9 ≥ 30 [P_{trend}]	 98 317 473 512 319 168 32	 0.91 (0.70–1.17) 1.0 (0.85–1.16) 0.87 (0.75–1.00) 1.0 1.17 (1.01–1.36) 1.31 (1.09–1.58) 1.47 (0.99–2.18) [< 0.001]	Age, area, smoking, alcohol consumption, diet, physical activity	Association stronger for proximal colon
	183 457 Women Incidence		BMI < 19 19–20.9 21–22.9 23–24.9 25–26.9 27–29.9 ≥ 30 [P_{trend}]	 76 215 330 512 217 136 48	 0.71 (0.52–0.97) 0.87 (0.71–1.07) 1.00 (0.84–1.19) 1.0 1.21 (1.02–1.44) 1.11 (0.88–1.39) 1.18 (0.83–1.68) [0.003]	Age, area, smoking, alcohol consumption, diet, physical activity	Association stronger for proximal colon

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Matsuo et al. (2012) (cont.)	157 927 Men Incidence	Rectum	BMI < 19 19–20.9 21–22.9 23–24.9 25–26.9 27–29.9 ≥ 30 [P_{trend}]	 59 179 325 284 158 80 26	 0.91 (0.65–1.27) 0.98 (0.80–1.21) 1.12 (0.94–1.33) 1.0 1.12 (0.91–1.37) 1.20 (0.91–1.58) 1.57 (0.97–2.53) [0.20]	Age, area, smoking, alcohol consumption, diet, physical activity	
	183 457 Women Incidence		BMI < 19 19–20.9 21–22.9 23–24.9 25–26.9 27–29.9 ≥ 30 [P_{trend}]	 53 97 147 284 80 54 20	 1.44 (0.99–2.08) 1.12 (0.84–1.50) 1.05 (0.81–1.35) 1.0 0.88 (0.64–1.20) 0.99 (0.70–1.39) 1.39 (0.81–2.39) [0.785]	Age, area, smoking, alcohol consumption, diet, physical activity	
Park et al. (2012) EPIC-Norfolk study cohort England 1993–2006	11 166 Men Incidence	Colon and rectum	BMI < 23.9 23.9–25.5 25.5–26.9 27–28.8 ≥ 28.9 [P_{trend}]	 67 41 30 32 27	 1.00 0.75 (0.50–1.12) 0.74 (0.48–1.14) 0.90 (0.58–1.38) 0.97 (0.61–1.54) [0.85]	Age, sex, smoking, alcohol consumption, education level, exercise, family history, diet	WC, also null association
	13 078 Women Incidence		BMI < 23.9 23.9–25.5 25.5–26.9 27–28.8 ≥ 28.9 [P_{trend}]	 34 31 44 21 30	 1.00 1.20 (0.72–1.98) 1.87 (1.17–2.99) 1.10 (0.62–1.93) 1.97 (1.18–3.30) [0.02]	Age, sex, smoking, alcohol consumption, education level, exercise, family history, diet	WC, null association

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Park et al. (2012) (cont.)	13 078 Women Incidence		WC < 73 73–78 78–83.3 83.4–90.4 ≥ 90.5 [P_{trend}]	 20 22 30 41 47	 1.00 0.86 (0.46–1.62) 1.16 (0.65–2.06) 1.52 (0.88–2.62) 1.65 (0.97–2.86) [0.001]	Age, sex, smoking, alcohol consumption, education level, exercise, family history, diet	
Renehan et al. (2012) NIH-AARP cohort USA 1995–2006	168 294 Men Incidence	Colon	BMI < 18.5 18.5–21.9 22.0–22.9 23.0–24.9 25.0–27.4 27.5–29.9 30.0–32.4 32.5–34.9 ≥ 35 [P_{trend}]	 6 98 93 349 600 438 249 124 113	 0.89 (0.39–2.02) 1.0 0.91 (0.68–1.22) 1.01 (0.80–1.27) 1.07 (0.86–1.34) 1.26 (1.01–1.58) 1.29 (1.01–1.64) 1.33 (1.01–1.75) 1.53 (1.16–2.03) [< 0.0001]	Age, race, education level, physical activity, smoking, alcohol consumption	BMI at ages 18, 35, and 50 yr shows similar associations as baseline BMI (mean baseline age, 62.8 yr)
	105 385 Women Incidence		BMI < 18.5 18.5–21.9 22.0–22.9 23.0–24.9 25.0–27.4 27.5–29.9 30.0–32.4 32.5–34.9 ≥ 35 [P_{trend}]	 14 148 68 176 207 127 82 54 86	 1.33 (0.76–2.30) 1.0 1.00 (0.75–1.34) 1.08 (0.87–1.35) 1.11 (0.89–1.38) 1.15 (0.90–1.47) 1.00 (0.76–1.32) 1.07 (0.78–1.48) 1.23 (0.93–1.64) [0.20]	Age, race, education level, physical activity, smoking, alcohol consumption, HRT use	BMI at ages 35 yr and 50 yr shows similar associations as baseline BMI, but BMI at age 18 yr null association

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Renehan et al. (2012) (cont.)	168 294 Men Incidence	Rectum	BMI < 18.5 18.5–21.9 22.0–22.9 23.0–24.9 25.0–27.4 27.5–29.9 30.0–32.4 32.5–34.9 ≥ 35 [P_{trend}]	 4 37 45 150 215 149 78 44 40	 1.63 (0.58–4.59) 1.0 1.22 (0.78–1.91) 1.20 (0.82–1.74) 1.06 (0.74–1.53) 1.15 (0.79–1.67) 0.99 (0.65–1.49) 1.22 (0.77–1.92) 1.43 (0.90–2.28) [0.51]	Age, race, education level, physical activity, smoking, alcohol consumption	BMI at ages 18, 35, and 50 yr shows similar associations as baseline BMI (mean baseline age, 62.8 yr)
	105 385 Women Incidence		BMI < 18.5 18.5–21.9 22.0–22.9 23.0–24.9 25.0–27.4 27.5–29.9 30.0–32.4 32.5–34.9 ≥ 35 [P_{trend}]	 6 43 22 50 64 32 20 20 25	 1.94 (0.82–4.58) 1.0 1.15 (0.68–1.93) 1.07 (0.71–1.63) 1.21 (0.82–1.81) 1.01 (0.63–1.61) 0.85 (0.49–1.47) 1.45 (0.84–2.51) 1.28 (0.76–2.16) [0.45]	Age, race, education level, physical activity, smoking, alcohol consumption, HRT use	BMI at ages 18, 35, and 50 yr also null association

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Aleksandrova et al. (2013) EPIC cohort (6 centres) Europe 1992–2010	74 091 Men Incidence	Colon	Weight change from age 20 yr			Age, weight at age 20 yr, smoking, education level, alcohol consumption, physical activity, consumption of red meat, fish and shellfish intake, intake of fruits and vegetables, fibre intake	
			Loss	37	0.84 (0.43–1.64)		
			Stable	67	1.0		
			2–5 kg gain	65	1.20 (0.67–2.14)		
			5–10 kg gain	122	0.97 (0.58–1.63)		
			10–15 kg gain	127	0.88 (0.53–1.48)		
			15–20 kg gain	114	1.09 (0.65–1.84)		
			≥ 20 kg gain	165	1.31 (0.78–2.19)		
			[P_{trend}]		[0.13]		
	127 605 Women Incidence		Weight change from age 20 yr				Similar findings by HRT status
			Loss	70	0.97 (0.56–1.68)		
			Stable	66	1.0		
			2–5 kg gain	87	1.34 (0.81–2.23)		
			5–10 kg gain	158	1.07 (0.68–1.69)		
			10–15 kg gain	139	1.05 (0.65–1.69)		
			15–20 kg gain	112	1.36 (0.83–2.23)		
			≥ 20 kg gain	141	1.49 (0.92–2.42)		
			[P_{trend}]		[0.05]		
	74 091 Men Incidence	Rectum	Weight change from age 20 yr				
			Loss	31	1.15 (0.53–2.49)		
			Stable	45	1.0		
			2–5 kg gain	48	0.64 (0.30–1.35)		
			5–10 kg gain	107	1.37 (0.74–2.52)		
			10–15 kg gain	103	1.28 (0.69–2.35)		
			15–20 kg gain	72	1.22 (0.65–2.30)		
			≥ 20 kg gain	91	1.36 (0.73–2.52)		
			[P_{trend}]		[0.16]		
	127 605 Women Incidence		Weight change from age 20 yr				
			Loss	32	1.77 (0.84–3.76)		
			Stable	39	1.0		
			2–5 kg gain	50	2.15 (1.12–4.11)		
			5–10 kg gain	84	1.34 (0.78–2.31)		
			10–15 kg gain	88	1.65 (0.93–2.93)		
			15–20 kg gain	53	1.82 (0.94–3.51)		
			≥ 20 kg gain	71	1.45 (0.79–2.66)		
			[P_{trend}]		[0.96]		

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Kitahara et al. (2013) PLCO trial subjects (screening arm) USA 1993–2001	36 912 Men Incidence	Colon and rectum	BMI < 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 128 270 148	 1.0 1.19 (0.96–1.48) 1.48 (1.16–1.89) [0.002]	Age, study centre, screening history, race/ethnicity, tobacco use, HRT use	Proximal, distal, and rectal associations with BMI all similar, but only proximal significant
	37 562 Women Incidence		BMI < 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 156 154 106	 1.0 1.07 (0.86–1.34) 1.03 (0.80–1.33) [0.74]	Age, study centre, screening history, race/ethnicity, tobacco use, HRT use	All subsites null for BMI associations
Bhaskaran et al. (2014) Health system clinical database United Kingdom 1987–2012	5 243 978 Men and women Incidence	Colon	per 5 kg/m^2	13 465	1.10 (1.07–1.13)	Age, sex, year, diabetes, alcohol consumption, smoking, SES	Similar association in never-smokers. Significant sex interaction above 22 kg/m^2 (stronger association in men)
	5 243 978 Men and women Incidence	Rectum	per 5 kg/m^2	6123	1.04 (1.00–1.08)		Similar association in never-smokers

Table 2.2.1a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Kabat et al. (2015) Women's Health Initiative cohort USA 1992–2013	143 901 Women Incidence	Colon and rectum	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	1908 total	 1.0 1.18 (1.01–1.38) 1.15 (0.98–1.38) 1.27 (1.09–1.48) 1.44 (1.23–1.68) [< 0.0001]	Age, alcohol consumption, smoking, physical activity, age at menarche, age at first birth, parity, HRT use, family history, ethnicity, education level, aspirin use, diabetes, treatment allocation	Associations stronger in ever-users of HRT Similar findings by HRT status
			WC, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	1908 total	 1.0 1.49 (1.26–1.75) 1.36 (1.15–1.61) 1.67 (1.41–1.96) 1.90 (1.61–2.25) [< 0.0001]		

ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; BMI, body mass index (in kg/m^2); CI, confidence interval; CRC, colorectal cancer; EPIC, European Prospective Investigation into Cancer and Nutrition; HRT, hormone replacement therapy; JACC, Japan Collaborative Cohort Study for Evaluation of Cancer Risk; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; NSAID, non-steroidal anti-inflammatory drug; OC, oral contraceptive; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SES, socioeconomic status; VHM&PP, Vorarlberg Health Monitoring and Prevention Program; WC, waist circumference (in cm); yr, year or years

Table 2.2.1b Case–control studies of measures of body fatness and cancer of the colorectum

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Boutron-Ruault et al. (2001) France (Burgundy) Period NR	CRC: Men: 109 Women: 62 Population	BMI, quintiles (sex-specific) Men: Women: < 22.9 < 20.3 23–24.4 20.4–22.6 25–25.9 22.7–23.9 26–28.7 24–26.1 > 28.7 > 26.1 [P_{trend}]	 29 45 23 40 34	 1.0 1.7 (0.9–3.0) 0.8 (0.4–1.6) 1.4 (0.8–2.6) 1.1 (0.6–2.1) [0.92]	Age	
Slattery et al. (2003) USA (Northern California, Utah, Minnesota) 1991–1994	Colon cancer: Men: 1095 Women: 1286 Population	BMI < 23 23–24 25–27 28–30 > 30 BMI < 23 23–24 25–27 28–30 > 30 BMI in estrogen-positive women < 23 23–24 25–27 28–30 > 30 BMI in estrogen-negative women < 23 23–24 25–27 28–30 > 30	Men: 56 119 320 305 295 Women: 144 146 224 152 211 56 60 59 49 77 88 86 165 103 134	 1.00 0.06 (0.64–1.44) 1.13 (0.79–1.63) 1.54 (1.06–2.23) 1.88 (1.29–2.74) 1.00 1.22 (0.90–1.65) 1.27 (0.96–1.67) 1.30 (0.96–1.76) 1.45 (1.09–1.92) 1.00 1.28 (0.81–2.02) 1.09 (0.69–1.73) 1.56 (0.95–2.56) 2.38 (1.50–3.77) 1.00 1.21 (0.80–1.82) 1.28 (0.90–1.82) 1.10 (0.75–1.62) 1.02 (0.71–1.46)	Age	Additional adjustment for dietary factors, NSAID use, physical activity level, and family history of CRC did not significantly alter associations

Table 2.2.1b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Pan et al. (2004) Canada (eight Canadian provinces), NECSS study 1994–1997	Colon cancer: Men: 959 Women: 768 Population	BMI Men: < 25 25– < 30 ≥ 30 [P_{trend}] Women: < 25 25– < 30 ≥ 30 [P_{trend}]	 NR NR 	 1.00 1.54 (1.27–1.86) 2.16 (1.68–2.78) [< 0.0001] 1.00 1.22 (0.98–1.52) 1.77 (1.35–2.32) [< 0.0001]	5-yr age group, province, education level, smoking, alcohol consumption, total energy intake, diet, recreational physical activity Women only: menopausal status, number of live births, age at menarche, age at end of first pregnancy	
	Rectal cancer: Men: 858 Women: 589 Population	Men: < 25 25– < 30 ≥ 30 [P_{trend}] Women: < 25 25– < 30 ≥ 30 [P_{trend}]	NR NR 	1.00 1.41 (1.15–1.71) 1.75 (1.35–2.28) [0.0001] 1.00 1.28 (1.02–1.61) 1.50 (1.11–2.02) [0.0045]		
Chung et al. (2006) Republic of Korea 2002–2004	CRC: 105 Hospital	BMI < 22.9 23.0–24.9 ≥ 25.0	 37 32 36	 1.0 1.4 (0.6–3.3) 2.3 (0.9–5.8)	Age, sex, glucose, triglycerides, cholesterol	
Hou et al. (2006) China (Shanghai) 1990–1993	Colon cancer: Men: 461 Women: 465 Population	BMI, quintiles < 19.2 19.2–20.3 20.4–21.3 21.4–22.8 > 22.8 [P_{trend}]	Men: 80 85 68 109 119	 1.0 1.0 (0.7–1.4) 1.0 (0.7–1.4) 1.2 (0.9–1.8) 1.7 (1.1–2.4) [0.005]	Age, education level, family income, marital status, total energy intake, diet Women only: number of pregnancies, years of menstruation	In women, a significant interaction was observed by menopausal status ($P_{interaction}$ = 0.03)

Table 2.2.1b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Hou et al. (2006) (cont.)		BMI, quintiles	Women:			
		< 19	86	1.0		
		19.1–20.5	91	1.2 (0.8–1.7)		
		20.6–21.9	80	0.9 (0.6–1.3)		
		22.0–23.6	92	1.1 (0.8–1.7)		
		> 23.6	116	1.4 (1.0–2.1)		
		[P_{trend}]		[0.08]		
		BMI in premenopausal women				
		< 19	15	1.0		
		19.1–20.5	19	1.2 (0.6–2.8)		
		20.6–21.9	20	1.2 (0.3–3.1)		
		22.0–23.6	24	1.3 (0.6–3.2)		
		> 23.6	62	2.9 (1.7–8.6)		
		[P_{trend}]		[0.01]		
		BMI in postmenopausal women				
		< 19	66	1.0		
		19.1–20.5	72	1.1 (0.6–1.5)		
		20.6–21.9	58	0.8 (0.5–1.2)		
		22.0–23.6	71	0.8 (0.6–1.4)		
		> 23.6	50	0.6 (0.3–0.9)		
		[P_{trend}]		[0.03]		
Campbell et al. (2007) Canada (Ontario and Newfoundland) 1997–2003	CRC: Men: 1292 Women: 1404 Population	BMI	Men:		Age, education level, consumption of red meat, physical activity, province of residence, CRC screening endoscopy, history of high cholesterol/ triglycerides Women only: menopausal status, use of postmenopausal HRT	Associations were moderately stronger for colon than rectum. Significant associations with weight gain since age 20 yr were observed in men only (≥ 20 kg vs reference 1–5 kg)
		18.5–24.99	298	1.0		
		25–29.99	627	1.29 (1.07–1.56)		
		≥ 30	322	1.80 (1.43–2.27)		
		BMI	Women:			
		18.5–24.99	616	1.0		
		25–29.99	443	0.99 (0.83–1.20)		
		≥ 30	260	0.94 (0.75–1.18)		
		BMI in estrogen-positive women				
		18.5–24.99	260	1.0		
		25–29.99	148	0.89 (0.66–1.21)		
		≥ 30	80	0.67 (0.45–0.98)		

Table 2.2.1b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Campbell et al. (2007) (cont.)		BMI in estrogen-negative women				
		18.5–24.99	356	1.0		
		25–29.99	295	1.08 (0.85–1.37)		
		≥ 30	180	1.05 (0.79–1.40)		
Hoffmeister et al. (2007) Germany 2003–2004	CRC: Women: 208 Population	BMI			Age, county of residence, history of rheumatic disease, hyperlipidaemia, former health check-up, former colorectal endoscopy, smoking, alcohol consumption, regular NSAID use, use of statins, OC use	Cohort of postmenopausal women
		< 23	51	1.00		
		23– < 25	39	0.80 (0.42–1.53)		
		25– < 27	25	0.78 (0.39–1.58)		
		27– < 30	46	1.71 (0.89–3.31)		
		≥ 30	40	1.82 (0.92–3.62)		
		[P_{trend}]		[0.02]		
		BMI in never-users of HRT				
		< 23	24	1.00		
		23– < 25	31	1.31 (0.55–3.12)		
		25– < 27	18	1.60 (0.58–4.44)		
		27– < 30	33	2.76 (1.07–7.12)		
		≥ 30	31	3.30 (1.25–8.72)		
		[P_{trend}]		[0.01]		
		BMI in ever-users of HRT				
		< 23	27	1.00		
		23– < 25	8	0.49 (0.16–1.48)		
		25– < 27	7	0.36 (0.11–1.13)		
		27– < 30	13	1.18 (0.40–3.48)		
		≥ 30	9	0.89 (0.29–2.75)		
		[P_{trend}]		[0.96]		
Sriamporn et al. (2007) North-eastern Thailand 2002–2006	CRC: 253 Hospital	BMI			Age, sex, place of residence	
		< 25	34	1		
		≥ 25		0.5 (0.3–0.8)		
		[P_{trend}]		[< 0.5]		

Table 2.2.1b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Campbell et al. (2010) Canada (Ontario and Newfoundland) 1997–2003	CRC: Men: 877 Women: 917 Sibling controls	BMI			Age, endoscopy screening, smoking Women only: postmenopausal HRT use	Only microsatellite stable tumours showed increased risk at higher BMI
			Women:			
		< 18.5	24	1.77 (0.91–3.45)		
		18.5–24.99	404	1.00		
		25–29.99	252	1.00 (0.80–1.25)		
		≥ 30	212	1.34 (1.03–1.75)		
		per 5 kg/m²		1.20 (1.10–1.32)		
		[P_{trend}]		[< 0.001]		
			Men:			
		< 18.5	2	0.51 (0.09–2.89)		
		18.5–24.99	223	1.00		
		25–29.99	408	1.33 (1.06–1.68)		
		≥ 30	222	1.79 (1.33–2.40)		
		per 5 kg/m²		1.30 (1.15–1.47)		
		[P_{trend}]		[< 0.001]		
		Adult weight change				
			Women:			
		Loss	94	0.70 (0.049–1.00)		
		0–5 kg gain	158	1.00		
		6–10 kg gain	155	0.88 (0.64–1.20)		
		11–20 kg gain	249	0.93 (0.70–1.23)		
		≥ 21 kg gain	229	1.08 (0.80–1.47)		
		per 5 kg		1.06 (1.01–1.12)		
		[P_{trend}]		[< 0.01]		
			Men:			
		Loss	104	1.40 (0.95–2.06)		
		0–5 kg gain	93	1.00		
		6–10 kg gain	143	1.47 (1.05–2.07)		
		11–20 kg gain	257	1.72 (1.25–2.36)		
		≥ 21 kg gain	233	2.23 (1.58–3.14)		
		per 5 kg		1.08 (1.03–1.14)		
		[P_{trend}]		[0.003]		

Table 2.2.1b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Choe et al. (2013) Republic of Korea (Seoul) 2004–2008	CRC: 153 (stage I) Hospital	BMI, quartiles Q1 Q2 Q3 Q4	NR	 1.0 0.81 (0.48–1.38) 1.32 (0.80–2.19) 1.58 (0.95–2.63)	Current smoking status, alcohol consumption	No significant associations were observed when comparing CRC risk vs colorectal adenoma (554 cases in total) across quartiles of BMI
Boyle et al. (2014) Australia 2005–2007	CRC: 918 Population	BMI at age 20 yr Normal Overweight Obese [P_{trend}]	NR	 1.00 1.25 (0.92–1.71) 0.89 (0.44–1.77) [0.401]	Age group, sex, SES, energy intake, lifetime vigorous recreational physical activity, alcohol consumption, tobacco use, diabetes	No differences in associations were observed with BMI at age 40 yr

BMI, body mass index (in kg/m^2); CI, confidence interval; CRC, colorectal cancer; HRT, hormone replacement therapy; NECSS, National Enhanced Cancer Surveillance System; NR, not reported; NSAID, non-steroidal anti-inflammatory drug; OC, oral contraceptive; SES, socioeconomic status; yr, year or years

Table 2.2.1c Meta-analyses of measures of body fatness and cancer of the colorectum

Reference	Total number of studies Total number of cases	Organ site	Exposure categories	Relative risk (95% CI)	Adjustment for confounding
Moghaddam et al. (2007)	31 studies (23 cohort studies, 8 case–control studies) 70 906 cases (49% women)	Colon and rectum	BMI ≥ 30 vs < 25	1.35 (1.24–1.46)	Age (all studies) and other factors (not in all studies): sex, diabetes, smoking, alcohol consumption, hypertension, hypercholesterolaemia, medication, race, family history, physical activity, diet, education level, SES, pregnancy (for women), menstruation (for women), study centre
	8 cohort studies N/A	Colon and rectum	WC Highest vs lowest category	1.50 (1.35–1.67)	
Renehan et al. (2008)	22 prospective studies in men 22 440 incident cases	Colon	BMI per 5 kg/m² increase	1.24 (1.20–1.28)	Age (all studies) and other factors (not in all studies): family history, inflammatory bowel disease, Western diet, increased weight, alcohol consumption, previous CRC, medical conditions (e.g. type 2 diabetes, acromegaly), intake of fruits and vegetables, fat intake, vitamin D and calcium intake, physical activity, aspirin use, HRT use
	19 prospective studies in women 20 975 incident cases	Colon	BMI per 5 kg/m² increase	1.09 (1.05–1.12)	
	18 prospective studies in men 14 894 incident cases	Rectum	BMI per 5 kg/m² increase	1.09 (1.06–1.12)	Age (all studies) and other factors (not in all studies): family history, inflammatory bowel disease, Western diet, increased weight, alcohol consumption, previous CRC, medical conditions (e.g. type 2 diabetes, acromegaly), intake of fruits and vegetables, fat intake, vitamin D and calcium intake, physical activity, aspirin use, HRT use
	14 prospective studies in women 9052 incident cases	Rectum	BMI per 5 kg/m² increase	1.02 (1.00–1.05)	
Ning et al. (2010)	51 studies (39 prospective and 12 retrospective) 93 812 cases	Colon and rectum	BMI per 5 kg/m² increase	1.18 (1.14–1.21)	Cancer site, sex, menopausal status (for women), directly measured BMI or self-reported BMI, and adjustment for physical activity
Ma et al. (2013)	41 prospective studies 85 935 cases	Colon and rectum	BMI ≥ 30 vs < 25	1.33 (1.25–1.42)	Age (36 studies), smoking (32 studies), physical activity (23 studies), alcohol consumption (23 studies). Fewer adjusted for energy intake (9 studies), NSAID/aspirin use (8 studies), folate intake (7 studies), calcium intake (6 studies), diabetes (6 studies)
	13 prospective studies 6546 cases	Colon and rectum	WC Highest vs lowest category	1.46 (1.33–1.60)	

BMI, body mass index (in kg/m²); CI, confidence interval; CRC, colorectal cancer; HRT, hormone replacement therapy; N/A, not applicable; NSAID, non-steroidal anti-inflammatory drug; SES, socioeconomic status; WC, waist circumference

Table 2.2.1d Mendelian randomization studies of measures of body fatness and cancer of the colorectum

Reference Study	Characteristics of study population	Sample size	Exposure (unit)	Odds ratio (95% CI)	Adjustment for confounding	Comments
Thrift et al. (2015) Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO)	11 studies of individuals of European descent (6 cohort and 5 case–control)	20 512 (10 226 cases and 10 286 controls)	Weighted genetic risk score representing an increase of 5 kg/m^2 in BMI	All: 1.50 (1.13–2.01) Men: 1.18 (0.73–1.92) Women: 1.82 (1.26–2.61)	Study, and the top three principal components of ancestry	
Gao et al. (2016) Genetic Associations and Mechanisms in Oncology (GAME-ON) Consortium	6 studies of individuals of European ancestry	9931 (5100 cases and 4831 controls)	Increase of 1 SD in genetically predicted childhood BMI or adult BMI	Childhood BMI: 1.20 (0.90–1.59) Adult BMI: 1.39 (1.06–1.82)	N/A	Waist-to-hip ratio, null association: 1.29 (0.75–2.22)

BMI, body mass index (in kg/m^2); CI, confidence interval; N/A, not applicable; SD, standard deviation

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2.2.2 Cancer of the oesophagus

There are two main histological subtypes of cancer of the oesophagus: adenocarcinoma and squamous cell carcinoma. Oesophageal squamous cell carcinoma arises from epithelial cells that line the oesophagus and typically occurs in the upper and middle parts of the oesophagus. Oesophageal adenocarcinoma originates from glandular cells; it occurs in the lower portion of the oesophagus and can spread into the gastric cardia.

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that there was *sufficient evidence* for a cancer-preventive effect of avoidance of weight gain for oesophageal adenocarcinoma. Although recent pathological classification recognizes the histological similarity between oesophageal adenocarcinoma and gastric cardia cancer, most epidemiological studies classify gastric cardia cancer with stomach cancer, and therefore these studies are considered in Section 2.2.3. Also, because evidence to date strongly suggests differences in etiological factors between oesophageal adenocarcinoma and squamous cell carcinoma, the results are presented separately for each histological subtype, and no results are presented for oesophageal cancer overall.

(a) Cohort studies

See Table 2.2.2a.

(i) Adenocarcinoma of the oesophagus

Several cohort studies (with at least 75 incident cases) have been published since the previous IARC evaluation (IARC, 2002). In all of those studies, BMI and/or weight were positively associated with risk (Engeland et al., 2004; Lindblad et al., 2005; Samanic et al., 2006; Merry et al., 2007; Reeves et al., 2007; Abnet et al., 2008; Corley et al., 2008; O'Doherty et al., 2012; Lindkvist et al., 2014; Steffen et al., 2015). Associations were similar across follow-up periods in one study (Engeland et al., 2004) and in another study that excluded the first 5 years of follow-up (Abnet et al., 2008). There did not appear to be any meaningful differences in associations when stratifying by smoking status (O'Doherty et al., 2012; Lindkvist et al., 2014) or when limiting results to non-smokers or never-smokers only (Reeves et al., 2007; Abnet et al., 2008).

In a meta-analysis including five prospective studies (Renehan et al., 2008), a relative risk of 1.5 for a 5 kg/m^2 increase in BMI at baseline was reported, with similar values in men and in women.

Few studies have examined the association between BMI measured at younger ages and subsequent risk of oesophageal adenocarcinoma. In the Netherlands Cohort Study, there was evidence of a positive association between high BMI at age 20 years and risk, although the relative risk estimate was not statistically significant (Merry et al., 2007).

The association between BMI change and incidence of oesophageal adenocarcinoma was examined in two prospective studies (Samanic et al., 2006; Merry et al., 2007). The first study, which considered BMI change during a period of 6 years, did not find evidence for a positive association [the analysis was based on only 28 incident cases] (Samanic et al., 2006). The second study, which included 113 cases, found that a 1 kg/m^2 increase in BMI from age 20 years to baseline was significantly associated with a 14% higher risk (95% CI, 1.06–1.23) (Merry et al., 2007).

There have been few prospective studies of abdominal fatness in relation to risk of oesophageal adenocarcinoma. A study nested within the Multiphasic Health Check-up cohort of Kaiser Permanente Northern California members observed a positive association between sagittal abdominal diameter [distance from the anterior to the posterior of the abdomen] and incidence

of oesophageal adenocarcinoma (Corley et al., 2008). Similarly, strong positive associations were reported of both waist circumference and waist-to-hip ratio with incidence of oesophageal adenocarcinoma in the National Institutes of Health–AARP Diet and Health Study (NIH-AARP) cohort ($P_{trend} \leq 0.01$ for both) (O'Doherty et al., 2012) and with oesophageal adenocarcinoma incidence/mortality in the European Prospective Investigation into Cancer and Nutrition (EPIC) study ($P_{trend} \leq 0.0001$) (Steffen et al., 2015).

(ii) Squamous cell carcinoma of the oesophagus

Since 2001, the association between BMI and/or weight assessed at baseline and the incidence and/or mortality of oesophageal squamous cell carcinoma has been examined in at least nine individual prospective studies (Engeland et al., 2004; Lindblad et al., 2005; Tran et al., 2005; Samanic et al., 2006; Merry et al., 2007; Reeves et al., 2007; Corley et al., 2008; Steffen et al., 2009; Lindkvist et al., 2014) and in one meta-analysis (Renehan et al., 2008). In all of the studies, BMI and/or weight were inversely associated with risk. Notably, higher risks were found in the lowest BMI categories (i.e. BMI < 20 kg/m^2) compared with categories within the normal range of BMI, whereas lower risks were observed in the overweight and obese categories. Although most studies adjusted for tobacco use, not all studies included alcohol consumption, another strong risk factor for oesophageal squamous cell carcinoma in their model. Furthermore, in two studies that stratified by smoking status, there was an inverse association in current smokers but no association in non-smokers [supporting a possible confounding effect of tobacco smoking] (Steffen et al., 2009; Lindkvist et al., 2014). In contrast, in the Million Women Study, an inverse association with both incidence and mortality of oesophageal squamous cell carcinoma was noted even in the never-smokers group (Reeves et al., 2007). An inverse association was also observed in the only study in Asia, which included 1958 incident cases in China (Tran et al., 2005). There was no evidence of differences in associations based on follow-up time (Engeland et al., 2004).

A meta-analysis of five prospective studies by Renehan et al. (2008) reported a relative risk per 5 kg/m^2 increase in BMI of 0.71 (95% CI, 0.60–0.85) in men and 0.57 (95% CI, 0.47–0.69) in women.

The association between BMI measured at age 20 years and risk of oesophageal squamous cell carcinoma was examined in the Netherlands Cohort Study (Merry et al., 2007). The relative risk for BMI ≥ 25 kg/m^2 compared with BMI 20–21.4 kg/m^2 was 2.49 (95% CI, 1.15–5.40), but there was no evidence of dose–response [$P_{trend} = 0.58$]. In that study, weight loss from age 20 years to baseline was associated with a statistically significant increased risk, with a relative risk of 2.57, but there was no evidence that weight gain was associated with risk.

Only two prospective studies examined measures of abdominal fatness in relation to risk of oesophageal squamous cell carcinoma. In the Kaiser Permanente Multiphasic Health Check-up nested case–control study, there was no association between sagittal abdominal diameter and risk (Corley et al., 2008), whereas in the EPIC study, there was some evidence of a weak inverse trend of waist circumference with incidence/mortality ($P_{trend} = 0.08$) (Steffen et al., 2009).

(b) Case–control studies

See Table 2.2.2b.

(i) Adenocarcinoma of the oesophagus

Of the case–control studies reporting on oesophageal adenocarcinoma, most studies showed increases of 2.5-fold and higher in risk of oesophageal adenocarcinoma when comparing the highest and lowest BMI categories, although in a few studies these associations were not statistically significant. When assessed, adjustments

for self-reported frequency or severity, or stratification by presence or absence of gastric reflux symptoms did not substantially alter the relative risk estimates (Chow et al., 1998; Lagergren et al., 1999; de Jonge et al., 2006; Anderson et al., 2007; Löfdahl et al., 2008; Whiteman et al., 2008; Olsen et al., 2011).

A pooled analysis of data from 10 case–control studies and 2 cohort studies (Hoyo et al., 2012), including a total of 3719 adenocarcinoma cases and 10 481 controls, showed significant trends of increasing adenocarcinoma risk with increasing BMI, up to odds ratios of 4.76 (95% CI, 2.96–7.66) for oesophageal adenocarcinoma and 3.07 (95% CI, 1.89–4.99) for oesophagogastric junction adenocarcinoma when comparing BMI ≥ 40 kg/m^2 with BMI < 25 kg/m^2. Subset analyses showed similar increases in risk of adenocarcinoma when stratifying by symptoms of gastro-oesophageal reflux disease. No differences in associations were observed by sex.

(ii) Squamous cell carcinoma of the oesophagus

For oesophageal squamous cell carcinoma, several case–control studies reported an inverse association between risk and recent BMI (Vaughan et al., 1995; Chow et al., 1998; Lahmann et al., 2012), and this inverse association was observed within both smokers and never-smokers (Lahmann et al., 2012). Of the two studies that investigated the association of risk of oesophageal squamous cell carcinoma with recalled BMI at age 20 years, one found a non-significant decrease in risk in relation to higher BMI (Lahmann et al., 2012), whereas the other study, based on a total of 167 cases in Sweden, showed an increase in risk with higher BMI (Lagergren et al., 1999).

(c) Mendelian randomization studies

See Table 2.2.2c.

One Mendelian randomization study estimated the causal association between BMI and risk of oesophageal adenocarcinoma (Thrift et al., 2014). Using a genetic risk score based on 29 SNPs previously shown to be associated with BMI (Speliotes et al., 2010), this Mendelian randomization study showed that each 1 kg/m^2 increase in BMI was associated with a 23% increase in risk (95% CI, 6–43%; P = 0.01), compared with a 6% increase in risk (95% CI, 5–8%; P < 0.001) observed in the same sample by conventional epidemiological analyses.

Table 2.2.2a Cohort studies of measures of body fatness and cancer of the oesophagus

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Adenocarcinoma							
Engeland et al. (2004) Population-based Norwegian cohort Norway 1963–2002	Men: 963 709 Women: 1 038 010 Incidence	Oesophageal adenocarcinoma ICD-7: 150	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	448 total	Men: – 1.00 1.80 (1.48–2.19) 2.58 (1.81–3.68) [< 0.001]	Age at measurement, height, birth cohort	
			BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	127 total	Women: 4.07 (1.44–11) 1.00 1.64 (1.08–2.49) 2.06 (1.25–3.39) [0.002]		
Lindblad et al. (2005) Case–control study nested in General Practitioner Research Database United Kingdom 1994–2001	10 287 Men and women Incidence	Oesophageal adenocarcinoma	BMI < 20 20–24 25–29 ≥ 30 [P_{trend}]	8 49 94 36	1.44 (0.67–3.10) 1.00 1.68 (1.18–2.40) 1.93 (1.24–3.01) [0.005]	Age, sex, calendar year, smoking, alcohol consumption, reflux	
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1958–1999	362 552 Men Incidence	Oesophageal adenocarcinoma	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	34 38 10	1.00 1.58 (0.98–2.53) 2.72 (1.33–5.55) [< 0.01]	Attained age (10-yr interval), calendar year, smoking	

Table 2.2.2a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Samanic et al. (2006) (cont.)			BMI, 6-yr change				
			−4% to +4.9%	19	1.00		
			5–9.9%	3	0.44 (0.13–1.49)		
			10–14.9%	5	2.24 (0.81–6.21)		
			> 15%	1	1.21 (0.16–9.45)		
			[P_{trend}]		[> 0.5]		
Merry et al. (2007) Netherlands Cohort Study The Netherlands 1986–1999	4774 (case–cohort sample from 120 852 main cohort) Men and women Incidence	Oesophageal adenocarcinoma ICD-10: C15 Histology: 8140–8141, 8190–8231, 8260–8263, 8310, 8430, 8480–8490, 8560, 8570–8572	BMI at baseline			Age, sex For BMI change only: adjustment for BMI at age 20 yr	First year of follow-up excluded from the analyses
			< 20	3	1.29 (0.40–4.16)		
			20–24.9	51	1.00		
			25–29.9	60	1.40 (0.95–2.04)		
			≥ 30	19	3.96 (2.27–6.88)		
			[P_{trend}]		[0.001]		
			per 1 kg/m²		1.14 (1.08–1.21)		
			BMI at age 20 yr				
			< 20	21	1.07 (0.59–1.94)		
			20–21.4	24	1.00		
			21.5–22.9	37	1.61 (0.95–2.72)		
			23.0–24.9	18	1.02 (0.55–1.90)		
			≥ 25	13	1.97 (0.99–3.94)		
			[P_{trend}]		[0.17]		
			per 1 kg/m²		1.04 (0.95–1.14)		
			BMI change, age 20 yr to baseline				
			< 0	8	0.75 (0.34–1.64)		
			0–3.9	51	1.00		
			4–7.9	37	1.34 (0.86–2.08)		
			≥ 8	17	3.41 (1.88–6.18)		
			[P_{trend}]		[0.001]		
			per 1 kg/m²		1.14 (1.06–1.23)		
Reeves et al. (2007) Million Women Study United Kingdom 1996–2005	1 222 630 Women Incidence and mortality	Oesophageal adenocarcinoma ICD-10: C15	BMI	Incidence:		Age, geographical region, SES, reproductive history, smoking status, alcohol consumption, physical activity	Results remained significant after excluding never-smokers and excluding the first 2 yr of follow-up
			< 22.5	22	1.06 (0.70–1.62)		
			22.5–24.9	27	1.00 (0.68–1.46)		
			25–27.4	30	1.28 (0.90–1.83)		
			27.5–29.9	23	1.57 (1.04–2.36)		
			≥ 30	48	2.54 (1.89–3.41)		
			per 10 kg/m²		2.38 (1.59–3.56)		

Table 2.2.2a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Reeves et al. (2007) (cont.)			BMI	Mortality:			
			< 22.5	20	1.35 (0.87–2.11)		
			22.5–24.9	19	1.00 (0.64–1.57)		
			25–27.4	20	1.21 (0.78–1.87)		
			27.5–29.9	15	1.44 (0.87–2.39)		
			≥ 30	37	2.75 (1.97–3.85)		
			per 10 kg/m²		2.24 (1.40–3.58)		
Abnet et al. (2008) NIH-AARP cohort USA 1995–2003	480 475 Men and women Incidence	Oesophageal adenocarcinoma ICD-10: C15.0–15.9 Histology: "adenocarcinoma"	BMI			Age, sex, cigarette smoking, alcohol consumption, education level, physical activity	Results were stable after excluding the first 5 yr of follow-up
			< 18.5	2	1.61 (0.39–6.55)		
			18.5–24.9	71	1.00		
			25–29.9	194	1.65 (1.26–2.18)		
			30–34.9	77	1.91 (1.38–2.66)		
			≥ 35	27	2.27 (1.44–3.59)		
Corley et al. (2008) Nested case–control of Kaiser Permanente Multiphasic Health Check-up cohort USA 1964–1973	3150 Men and women Incidence	Oesophageal adenocarcinoma ICD-10: C15.0–15.9 Histology: 8140–8573	BMI			Age, sex, year of health check-up BMI results also adjusted for ethnicity	
			< 18.5	1	1.36 (0.12–15.52)		
			18.5–24.9	28	1.00		
			25–29.9	51	2.20 (1.31–3.67)		
			≥ 30	14	3.17 (1.43–7.04)		
			per 1 kg/m² increase		1.10 (1.04–1.17)		
			Sagittal abdominal diameter (cm)				
			< 20	8	1.00		
			20–22.4	13	0.92 (0.31–2.74)		
			22.5–25	12	2.35 (0.78–7.12)		
			≥ 25	22	3.47 (1.29–9.33)		
			per 1 cm increase		1.10 (1.03–1.17)		
Renehan et al. (2008) Meta-analysis 1966–2007	4 673 213 Men and women Incidence	Oesophageal adenocarcinoma	BMI	Men:		Geographical region, age (all studies), and other factors (not in all studies) such as Western diet, alcohol consumption, medical conditions (e.g. type 2 diabetes, acromegaly), or physical activity	
			per 5 kg/m² increase	1315 total	1.52 (1.33–1.74)		
			BMI	Women:			
			per 5 kg/m² increase	735 total	1.51 (1.31–1.74)		

Table 2.2.2a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
O'Doherty et al. (2012) NIH-AARP cohort USA 1995–2006	218 854 Men and women Incidence	Oesophageal adenocarcinoma ICD-10: C15.0–15.9 Histology: "adenocarcinoma"	BMI			Age, sex, total energy intake, antacid use, aspirin use, NSAID use, marital status, diabetes, cigarette smoking, education level, ethnicity, alcohol consumption, physical activity, intake of red and white meat, intake of fruits and vegetables; for weight, also adjusted for height	Waist-to-hip ratio also significantly associated with risk (Q3 and Q4)
			< 18.5	0	–		
			18.5–24.9	59	1.00		
			25–29.9	119	1.30 (0.94–1.78)		
			30–34.9	64	2.28 (1.57–3.30)		
			≥ 35	11	2.11 (1.09–4.09)		
			[P_{trend}]		[< 0.01]		
			Weight, quartiles (sex-specific)				
			Q1	41	1.00		
			Q2	58	1.49 (0.99–2.23)		
			Q3	53	1.37 (0.89–2.10)		
			Q4	101	2.66 (1.76–4.02)		
			[P_{trend}]		[< 0.01]		
			WC, quartiles (sex-specific)				
			Q1	37	1.00		
			Q2	49	1.36 (0.89–2.09)		
			Q3	79	1.51 (1.02–2.25)		
			Q4	88	2.01 (1.35–3.00)		
			[P_{trend}]		[< 0.01]		
Lindkvist et al. (2014) Me-Can cohort (prospective cohorts) Austria, Norway, and Sweden 1972–2006	587 700 Men and women Incidence	Oesophageal adenocarcinoma ICD-7: 150	BMI, quintiles			Sex, age, study cohort, smoking status	
			Q1	5	1.00		
			Q2	18	3.37 (1.25–9.10)		
			Q3	18	3.17 (1.17–8.57)		
			Q4	31	5.19 (2.00–13.42)		
			Q5	42	7.34 (2.88–18.68)		
			[P_{trend}]		[< 0.0001]		
			per 5 kg/m^2		1.78 (1.45–2.17)		

Table 2.2.2a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Steffen et al. (2015) EPIC cohort 10 European countries 1992–2008	391 456 Men and women Incidence/ mortality	Oesophageal adenocarcinoma ICD-10: C15	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}] Weight, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}] WC, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 15 22 24 30 33 17 25 23 26 33 7 22 20 26 39 	 1.00 1.30 (0.67–2.52) 1.36 (0.71–2.62) 1.76 (0.93–3.31) 2.15 (1.14–4.05) [0.004] 1.00 1.54 (0.82–2.88) 1.41 (0.74–2.70) 1.57 (0.82–3.01) 2.19 (1.14–4.21) [0.03] 1.00 2.78 (1.18–6.54) 2.47 (1.03–5.92) 3.19 (1.36–7.49) 5.08 (2.21–11.7) [< 0.0001]	Age at recruitment, centre, sex, education level, smoking, alcohol consumption, physical activity, diet, height	Sex-specific quintiles for weight, BMI, and WC. Cut-off points not provided, only the median values for each Positive associations with waist-to-hip ratio (Q4 and Q5)
Squamous cell carcinoma							
Engeland et al. (2004) Population-based Norwegian cohort Norway 1963–2002	Men: 963 709 Incidence	Oesophageal squamous cell carcinoma ICD-7: 150	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	1023 total 	 2.80 (1.73–4.54) 1.00 0.72 (0.63–0.82) 0.68 (0.50–0.93) [< 0.001]	Age at measurement, height, birth cohort	
	Women: 1 038 010 Incidence	Oesophageal squamous cell carcinoma ICD-7: 150	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	472 total 	 2.11 (1.23–3.62) 1.00 0.52 (0.42–0.65) 0.43 (0.32–0.59) [< 0.001]	Age at measurement, height, birth cohort	

Table 2.2.2a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Lindblad et al. (2005) Case–control study nested in General Practitioner Research Database United Kingdom 1994–2001	10 140 Men and women Incidence	Oesophageal squamous cell carcinoma	BMI < 20 20–24 25–29 ≥ 30 [P_{trend}]	 9 34 39 4	 1.93 (0.90–4.11) 1.00 1.13 (0.71–1.80) 0.28 (0.10–0.79) [0.01]	Age, sex, calendar year, smoking, alcohol consumption, reflux	
Tran et al. (2005) Linxian General Population Trial China 1986–2001	29 584 Men and women Incidence	Oesophageal squamous cell carcinoma	BMI < 20 20–21 22 ≥ 23 [P_{trend}]	1958 total	 1.00 0.96 (0.85–1.08) 0.80 (0.71–0.91) 0.81 (0.72–0.92) [< 0.001]	Age, sex	
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1958–1999	362 552 Men Incidence	Oesophageal squamous cell carcinoma	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 134 57 13	 1.00 0.53 (0.39–0.72) 0.77 (0.43–1.36) [< 0.01]	Attained age, calendar year, smoking	

Table 2.2.2a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Merry et al. (2007) Netherlands Cohort Study The Netherlands 1986–1999	4774 (case–cohort sample from 120 852 main cohort) Men and women Incidence	Oesophageal squamous cell carcinoma ICD-10: C15 Histology: 8050–8076	BMI at baseline			Age, sex, current smoking, cigarettes per day, number of years of smoking For BMI change only: adjustment for BMI at age 20 yr	
			< 20	9	2.21 (0.99–4.92)		
			20–24.9	51	1.00		
			25–29.9	26	0.63 (0.39–1.02)		
			≥ 30	6	0.93 (0.38–2.26)		
			[P_{trend}]		[0.04]		
			per 1 kg/m^2		0.90 (0.82–0.98)		
			BMI at age 20 yr				
			< 20	22	1.35 (0.70–2.62)		
			20–21.4	16	1.00		
			21.5–22.9	11	0.72 (0.33–1.57)		
			23.0–24.9	13	1.03 (0.48–2.21)		
			≥ 25	12	2.49 (1.15–5.40)		
			[P_{trend}]		[0.58]		
			per 1 kg/m^2		1.07 (0.96–1.20)		
			BMI change, age 20 yr to baseline				
			< 0	18	2.57 (1.40–4.72)		
			0–3.9	32	1.00		
			4–7.9	16	0.73 (0.39–1.36)		
			≥ 8	8	1.39 (0.62–3.15)		
			[P_{trend}]		[0.10]		
			per 1 kg/m^2		0.90 (0.81–1.00)		
Reeves et al. (2007) Million Women Study United Kingdom 1996–2005	1 222 630 Women Incidence and mortality	Oesophageal squamous cell carcinoma ICD-10: C15	BMI	Incidence:		Age, geographical region, SES, reproductive history, smoking status, alcohol consumption, physical activity	Negative associations remained stable in non-smokers and excluding the first 2 yr of follow-up
			< 22.5	106	2.04 (1.67–2.48)		
			22.5–24.9	63	1.00 (0.78–1.28)		
			25–27.4	52	0.96 (0.73–1.26)		
			27.5–29.9	21	0.61 (0.40–0.94)		
			≥ 30	21	0.47 (0.31–0.73)		
			per 10 kg/m^2		0.26 (0.18–0.38)		

Table 2.2.2a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Reeves et al. (2007) (cont.)			BMI < 22.5 22.5–24.9 25–27.4 27.5–29.9 ≥ 30 per 10 kg/m²	Mortality: 75 44 39 11 13	 2.10 (1.66–2.65) 1.00 (0.74–1.35) 1.02 (0.75–1.40) 0.45 (0.25–0.82) 0.42 (0.24–0.73) 0.22 (0.14–0.35)		
Corley et al. (2008) Nested case–control of Kaiser Permanente Multiphasic Health Check-up cohort USA 1964–1973	3150 Men and women Incidence	Oesophageal squamous cell carcinoma ICD-10: C15.0–15.9 Histology 8050–8082	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 per 1 kg/m² increase Sagittal abdominal diameter (cm) < 20 20–22.4 22.5–25 ≥ 25 per 1 cm increase	 3 78 46 9 19 24 14 15	 0.91 (0.19–4.29) 1.00 0.66 (0.44–1.00) 0.30 (0.13–0.72) 0.89 (0.84–0.94) 1.00 0.91 (0.43–1.94) 0.89 (0.35–2.24) 0.78 (0.32–1.92) 1.00 (0.94–1.06)	Matched for age, sex, year of health check-up BMI results also adjusted for ethnicity	
Renehan et al. (2008) Meta-analysis 1966–2007	4 673 213 Men and women Incidence	Oesophageal squamous cell carcinoma	BMI per 5 kg/m² increase BMI per 5 kg/m² increase	Men: 6201 total Women: 1114 total	0.71 (0.60–0.85) 0.57 (0.47–0.69)	Geographical region, age (all studies), and other factors (not in all studies) such as Western diet, alcohol consumption, medical conditions (e.g. type 2 diabetes, acromegaly), or physical activity	

Table 2.2.2a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Steffen et al. (2009) EPIC cohort 10 European countries 1992–2007	346 554 Men and women Incidence/ mortality	Oesophageal squamous cell carcinoma ICD-10: C15	BMI, quintiles (sex-specific) Men: Women: < 23.4 < 21.7 23.4–25.2 21.7–23.6 25.2–26.9 23.6–25.6 26.9–29.1 25.6–28.7 ≥ 29.2 ≥ 28.8 [P_{trend}]	 42 22 15 14 17	 1.00 0.47 (0.27–0.79) 0.31 (0.17–0.57) 0.27 (0.14–0.51) 0.26 (0.14–0.51) [< 0.0001]	Age, study centre, education level, smoking, alcohol consumption, physical activity, consumption of fruits/vegetables/meat	BMI and WC were significantly inversely related to oesophageal squamous cell carcinoma only in smokers
			Weight, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 41 28 14 10 17	 1.00 0.61 (0.37–1.01) 0.30 (0.16–0.57) 0.19 (0.09–0.40) 0.33 (0.18–0.60) [< 0.0001]		
			WC, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 23 19 23 16 22	 1.00 0.76 (0.41–1.43) 0.78 (0.43–1.43) 0.51 (0.26–1.00) 0.62 (0.32–1.20) [0.08]		
Lindkvist et al. (2014) Me-Can cohort (prospective cohorts) Austria, Norway, and Sweden 1972–2006	587 700 Men and women Incidence	Oesophageal squamous cell carcinoma ICD-7: 150	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}] per 5 kg/m^2	 55 29 46 30 24	 1.00 0.50 (0.32–0.79) 0.76 (0.51–1.12) 0.46 (0.30–0.72) 0.38 (0.23–0.62) [< 0.0001] 0.62 (0.50–0.79)	Sex, age, study cohort, smoking status	

BMI, body mass index (in kg/m^2); CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; ICD, International Classification of Diseases; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; NSAID, non-steroidal anti-inflammatory drug; SES, socioeconomic status; WC, waist circumference; yr, year or years

Table 2.2.2b Case–control studies of measures of body fatness and cancer of the oesophagus

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Vaughan et al. (1995) USA (13 counties of Western Washington State) 1993–1990	EAC: Men and women: 133 Population	BMI, percentiles 1–10% 10–49% 50–89% 90–100%	 12 43 50 26	 1.6 (0.7–3.6) 1.0 1.2 (0.7–2.1) 2.5 (1.2–5.0)	Age, sex, education level, race, cigarette use, alcohol consumption	BMI percentiles based on sex-specific distribution in controls (1 yr before diagnosis in cases, 1 yr before interview in controls)
	ESCC: Men and women: 106 Population	BMI, percentiles 1–10% 10–49% 50–89% 90–100%	 34 41 24 6	 3.2 (1.4–7.1) 1.0 0.7 (0.3–1.4) 0.2 (0.1–1.0)		
Chow et al. (1998) USA 1993–1995	EAC: Men and women: 292 Population	BMI up to 1 yr before diagnosis (sex-specific) Men: / Women: < 23.12 / < 21.95 23.12–25.08 / 21.95–24.12 25.09–27.31 / 24.13–27.43 ≥ 27.32 / ≥ 27.44 [P_{trend}]	 45 63 85 99	 1.0 1.3 (0.8–2.2) 2.0 (1.3–3.3) 2.9 (1.8–4.7) [< 0.0001]	Geographical location, age, sex, race, cigarette smoking, respondent status	No effect modification was observed by history of gastro-oesophageal reflux disease
	ESCC: Men and women: 220 Population	BMI up to 1 yr before diagnosis (sex-specific) Men: / Women: < 23.12 / < 21.95 23.12–25.08 / 21.95–24.12 25.09–27.31 / 24.13–27.43 ≥ 27.32 / ≥ 27.44 [P_{trend}]	 79 50 53 38	 1.0 0.5 (0.3–0.9) 0.8 (0.5–1.3) 0.6 (0.3–1.0) [< 0.11]		
Lagergren et al. (1999) Sweden 1995–1997	EAC: Men and women: 189 Population	BMI 20 yr before interview < 22 22–24.9 25–30 > 30 [P_{trend}]	 10 68 89 22	 1.0 3.2 (1.6–6.7) 6.9 (3.3–14.4) 16.2 (6.3–41.4) [< 0.001]	Age, sex, tobacco smoking, alcohol consumption, SES, reflux symptoms, intake of fruits and vegetables, energy intake, physical activity	No differences were observed in the associations for both cancer types when stratifying by presence of reflux symptoms

Table 2.2.2b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories		Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Lagergren et al. (1999) (cont.)		BMI at age 20 yr, quartiles (sex-specific)					
		Men:	Women:				
		< 20.7	< 19.3	28	1.0		
		20.7–22.1	19.3–20.4	29	0.9 (0.5–1.6)		
		22.2–23.7	20.5–22.1	51	1.6 (0.9–2.8)		
		> 23.7	> 22.1	81	2.7 (1.6–4.6)		
		[P_{trend}]			[< 0.001]		
	ESCC: Men and women: 820 Population	BMI 20 yr before interview					
		< 22		48	1.0		
		22–24.9		67	1.0 (0.6–1.7)		
		25–30		42	1.3 (0.8–2.3)		
		> 30		10	2.0 (0.8–4.9)		
		[P_{trend}]			[0.12]		
		BMI at age 20 yr, quartiles (sex-specific)					
		Men:	Women:				
		< 20.7	< 19.3	36	1.0		
		20.7–22.1	19.3–20.4	38	1.2 (0.7–2.1)		
		22.2–23.7	20.5–22.1	40	1.4 (0.8–2.4)		
		> 23.7	> 22.1	53	1.8 (1.1–3.1)		
		[P_{trend}]			[0.03]		
Wu et al. (2001) USA 1992–1997	EAC: Men and women: 222 Population (proxy control)	BMI at age 40 yr, quartiles (sex-specific)				Smoking, sex, race, birthplace, education level	
		Men:	Women:	202 total			
		≤ 22	≤ 21		1.00		
		> 22–25	> 21–23		1.13 (0.7–1.7)		
		> 25– ≤ 27	> 23– ≤ 25		1.76 (1.1–2.9)		
		> 27	> 25		2.78 (1.7–4.4)		
		[P_{trend}]			[< 0.0001]		
		BMI at age 20 yr, quartiles (sex-specific)					
		Men:	Women:	207 total			
		≤ 20	≤ 18		1.00		
		> 20–22	> 18–20		1.23 (0.8–1.9)		
		> 22– ≤ 24	> 20– ≤ 22		1.34 (0.9–2.1)		
		> 24	> 22		1.77 (1.1–2.7)		
		[P_{trend}]			[0.011]		

Table 2.2.2b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
de Jonge et al. (2006) The Netherlands 2003–2005	EAC: Men and women: 91 Hospital	BMI 10 yr before questionnaire			Age, sex, education level, smoking status, alcohol consumption, reflux symptoms	Controls were patients with Barrett oesophagus
		< 25	29	1.0		
		> 25	58	1.8 (1.1–3.3)		
		BMI at age 20 yr				
		< 25	63	1.0		
		> 25	20	2.6 (1.2–5.5)		
Anderson et al. (2007) Ireland 2002–2004	EAC: 227 (192 men and 35 women) Population	Current BMI, tertiles			Sex, age at interview date, smoking status, alcohol consumption, years of full-time education, job type, gastro-oesophageal reflux	
		< 25.8	115	1.00		
		25.8–29.0	54	0.35 (0.21–0.58)		
		> 29.0	50	0.33 (0.20–0.56)		
		BMI 5 yr before, tertiles				
		< 25.0	51	1.00		
		25.0–28.1	55	1.74 (0.66–1.97)		
		> 28.1	120	2.69 (1.62–4.46)		
		BMI at age 21 yr				
		< 22.1	55	1.00		
		22.1–24.1	64	1.10 (0.65–1.25)		
		> 24.1	96	1.81 (1.08–3.02)		
Löfdahl et al. (2008) Sweden 1995–1997	EAC + EJAC: Men: 388 Women: 63 Population	BMI 20 yr before interview			Age, education level, alcohol consumption, cigarette smoking, intake of fruits and vegetables, *Helicobacter pylori* infection Maximum and minimum adult BMI, also adjusted for gastro-oesophageal reflux	The associations for maximum adult BMI and for minimum adult BMI were weaker, but also showed a stronger association in women than in men
			Men:			
		< 22	45	1.0		
		22–24.9	143	1.5 (1.0–2.3)		
		25–29.9	164	2.7 (1.8–4.1)		
		≥ 30	36	5.4 (2.6–10.8)		
			Women:			
		< 22	12	1.0		
		22–24.9	25	2.4 (0.9–6.0)		
		25–29.9	16	4.3 (1.4–13.1)		
		≥ 30	10	10.3 (2.6–42.3)		

Table 2.2.2b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Whiteman et al. (2008) Australia 2001–2005	EAC: Men and women: 367 Population	BMI in the last year			Age, sex, state, household income, cumulative smoking history, mean alcohol consumption, frequency of aspirin use in the 5 yr before diagnosis	Results did not significantly change when additionally adjusted for gastro-oesophageal reflux; significantly higher risk in men than in women; no significant associations or trend between change in BMI and risk of EAC or EJAC
		< 18.5	1	0.3 (0.0–2.6)		
		18.5–24.9	71	1.0		
		25.0–29.9	150	1.4 (1.0–1.9)		
		30.0–34.9	89	2.7 (1.8–3.9)		
		35.0–39.9	25	3.1 (1.8–5.5)		
		≥ 40	16	7.0 (3.3–15.0)		
		[P_{trend}]		[< 0.001]		
		Maximum BMI				
		< 18.5	1	0.9 (0.1–8.7)		
		18.5–24.9	39	1.0		
		25.0–29.9	136	1.4 (0.9–2.0)		
		30.0–34.9	114	2.5 (1.6–3.7)		
		35.0–39.9	43	4.1 (2.4–6.8)		
		≥ 40	24	5.2 (2.7–9.9)		
		[P_{trend}]		[< 0.001]		
		BMI at age 20 yr				
		< 18.5	14	0.8 (0.4–1.4)		
		18.5–24.9	227	1.0		
		25.0–29.9	81	1.7 (1.2–2.3)		
		30.0–34.9	13	2.6 (1.3–5.2)		
		35.0–39.9	5	3.6 (1.0–13.0)		
		[P_{trend}]		[< 0.001]		
	EJAC: Men and women: 426 Population	BMI in the last year				
		< 18.5	1	0.2 (0.0–1.7)		
		18.5–24.9	107	1.0		
		25.0–29.9	168	1.1 (0.8–1.4)		
		30.0–34.9	98	1.9 (1.3–2.6)		
		35.0–39.9	27	2.0 (1.2–3.4)		
		≥ 40	9	2.6 (1.1–6.2)		
		[P_{trend}]		[< 0.001]		

Table 2.2.2b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Whiteman et al. (2008) (cont.)		Maximum BMI				
		< 18.5	0	–		
		18.5–24.9	55	1.0		
		25.0–29.9	178	1.3 (0.9–1.8)		
		30.0–34.9	122	1.9 (1.3–2.7)		
		35.0–39.9	47	2.9 (1.8–4.6)		
		≥ 40	13	2.1 (1.1–4.2)		
		[P_{trend}]		[< 0.001]		
		BMI at age 20 yr				
		< 18.5	9	0.4 (0.2–0.8)		
		18.5–24.9	282	1.0		
		25.0–29.9	97	1.6 (1.2–2.1)		
		30.0–34.9	13	2.1 (1.0–4.1)		
		≥ 35.0	2	1.1 (0.2–5.9)		
		[P_{trend}]		[< 0.001]		
Olsen et al. (2011) Australia 2002–2005	EAC: Men and women: 364 Population	BMI 1 yr before			Age, sex, education level, NSAID use, smoking status, heartburn/acid reflux in the past 10 yr	
		18–24.9	71	1.0		
		25–29.9	149	1.4 (1.0–2.0)		
		30–34.9	89	2.5 (1.7–3.6)		
		≥ 35	40	3.7 (2.2–6.2)		
		Overweight or obese		1.8 (1.3–2.5)		
	EJAC: Men and women: 425 Population	BMI 1 yr before				
		18–24.9	107	1.0		
		25–29.9	168	1.1 (0.8–1.5)		
		30–34.9	98	2.0 (1.4–2.9)		
		≥ 35	36	2.5 (1.5–4.1)		
		Overweight or obese		1.8 (1.3–2.5)		

Table 2.2.2b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Hoyo et al. (2012) International Barrett's and Esophageal Adenocarcinoma Consortium (BEACON) Pooled analysis of 10 case–control and 2 cohort studies from Australia, Europe, and USA	EAC: Men and women: 1997 Population	BMI			Age, sex, smoking, education level, and other study-specific adjustment variables (e.g. study centre)	In stratified analyses, results were independent of the presence of symptoms of gastro-oesophageal reflux No differences in associations by sex
		< 25	577	1.00		
		25.0–29.9	862	1.54 (1.26–1.88)		
		30.0–34.9	331	2.39 (1.86–3.06)		
		35.0–39.9	86	2.79 (1.89–4.12)		
		≥ 40	41	4.76 (2.96–7.66)		
		continuous	1897	1.09 (1.06–1.12)		
	EJAC: Men and women: 1900 Population	BMI				
		< 25	663	1.00		
		25.0–29.9	742	1.28 (1.13–1.45)		
		30.0–34.9	304	2.08 (1.75–2.47)		
		35.0–39.9	85	2.36 (1.75–3.17)		
		≥ 40	28	3.07 (1.89–4.99)		
		continuous	1822	1.07 (1.05–1.09)		
Lahmann et al. (2012) Australia 2002–2005	ESCC: Men and women: 287 Population	BMI in the last year, quintiles (sex-specific)			Age, sex, education level, alcohol consumption, smoking status, NSAID/aspirin use, physical activity BMI at age 20 yr (only for BMI in the last year)	
		Men: / Women:				
		< 22.1 / < 23.7	108	1.00		
		22.1– ≤ 24.6 / 23.7– < 25.6	65	0.61 (0.42–0.90)		
		24.6– ≤ 27.0 / 25.6– ≤ 27.2	35	0.32 (0.20–0.50)		
		27.0– ≤ 31.9 / 27.2– ≤ 29.7	41	0.40 (0.26–0.61)		
		> 31.9 / > 29.7	38	0.36 (0.23–0.57)		
		[P_{trend}]		[< 0.001]		
		Maximum BMI, quintiles (sex-specific)				
		Men: / Women:				
		≤ 23.5 / < 25.1	90	1.00		
		23.5– ≤ 26.0 / 25.1– ≤ 27.0	73	0.78 (0.53–1.15)		
		26.0– ≤ 28.7 / 27.0– ≤ 28.9	42	0.49 (0.32–0.76)		
		28.7– ≤ 33.9 / 28.9– ≤ 31.7	43	0.45 (0.29–0.69)		
		> 33.9 / > 31.7	39	0.44 (0.28–0.69)		
		[P_{trend}]		[< 0.001]		
		BMI at age 20 yr				
		< 25	233	1.00		
		≥ 25	42	0.85 (0.57–1.25)		
		[P_{trend}]		[< 0.40]		

BMI, body mass index (in kg/m²); CI, confidence interval; EAC, oesophageal adenocarcinoma; EJAC, oesophagogastric junction adenocarcinoma; ESCC, oesophageal squamous cell carcinoma; GCAC, gastric cardia adenocarcinoma; NSAID, non-steroidal anti-inflammatory drug; SES, socioeconomic status; yr, year or years

Table 2.2.2c Mendelian randomization studies of measures of body fatness and cancer of the oesophagus

Reference Study	Characteristics of study population	Sample size	Exposure (unit)	Odds ratio (95% CI)	Adjustment for confounding	Comments
Thrift et al. (2014) Barrett's and Esophageal Adenocarcinoma Genetic Susceptibility Study (BEAGESS)	Subset of ethnically homogenous individuals from 14 studies in Australia, North America, and western Europe	5229 (999 EAC cases and 2169 controls)	1 kg/m^2 increase based on a genetic risk score of 29 SNPs	1.23 (1.06–1.43)	NR	Similar associations in men and women. Associations with the genetic instrument were stronger than those of conventional epidemiological analyses in the same sample

CI, confidence interval; EAC, oesophageal adenocarcinoma; NR, not reported; SNP, single nucleotide polymorphism

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2.2.3 Cancer of the stomach

In 2012, gastric cancer, or cancer of the stomach, was the fifth most commonly diagnosed cancer worldwide, with heterogeneous geographical distribution (Jemal et al., 2014). Gastric cancer can generally be classified into two subsites: cancer of the gastric cardia, which arises from the area of the stomach adjoining the gastro-oesophageal junction, and non-cardia gastric cancer, which develops in the distal stomach and represents about 73% of all gastric cancer cases globally (Colquhoun et al., 2015). Several risk factors for gastric cardia and non-cardia cancer have been identified. For example, infection with *Helicobacter pylori* has been strongly associated with non-cardia gastric cancer, whereas diets rich in smoked foods, salted foods (especially fish), or pickled foods, as well as cigarette smoking, appear to increase the risk of both types of gastric cancer (Kamangar et al., 2006; IARC, 2012).

In 2001, the *IARC Handbook* on weight control and physical activity (IARC, 2002) reviewed the studies of cancer of the gastric cardia together with studies of oesophageal adenocarcinoma, but did not provide a separate evaluation for stomach cancer (cardia or non-cardia). Since then, numerous individual and pooled cohort studies and meta-analyses, as well as several case–control studies of anthropometric measures and risk of stomach cancer have been published. Results from studies that examined this association for gastric cancer not otherwise specified (NOS) and separately for gastric cardia and non-cardia cancers are summarized here and in Tables 2.2.3a, 2.2.3b, and 2.2.3c. Studies that had fewer than 75 incident cases or that overlapped with a more recent study, as well as those that considered gastric cardia and oesophageal cancers together, were excluded.

(a) Cohort studies

(i) Gastric cancer NOS

Since 2000, at least 20 individual cohort studies (Table 2.2.3a) and six meta-analyses or pooled analyses (Table 2.2.3c) of prospective studies have examined associations of baseline BMI with gastric cancer incidence and/or mortality. Most of the individual prospective studies showed no associations with gastric cancer incidence or mortality (Table 2.2.3a). A few studies found inconsistent evidence of either positive or negative associations (Calle et al., 2003; Samanic et al., 2006; Jee et al., 2008; Persson et al., 2008; Camargo et al., 2014).

Although three pooled analyses and one meta-analysis also showed no association between high BMI and incidence of gastric cancer (Lindkvist et al., 2013) or incidence and/or mortality (Renehan et al., 2008; Whitlock et al., 2009; Parr et al., 2010), others were suggestive of a positive association (Yang et al., 2009; Chen et al., 2013; Lin et al., 2014). In the most recent meta-analysis of 12 prospective studies of gastric cancer incidence and mortality combined and more than 41 791 gastric cancer cases, strong associations with overweight and obesity were reported in men only, but there was no evidence of heterogeneity of results according to sex (Chen et al., 2013). The same study did not show heterogeneity in results between Asian and non-Asian populations.

No associations of weight or BMI in early adulthood, usually defined as age 18–21 years, with gastric cancer incidence or mortality were found in three studies (Fujino et al., 2007; Merry et al., 2007; Tanaka et al., 2007), or of BMI change during adulthood in relation to incidence of gastric cancer (Merry et al., 2007; Rapp et al., 2008). No prospective studies of waist circumference and total gastric cancer were identified.

(ii) Cancer of the gastric cardia

Most individual prospective studies of the association between baseline BMI (or weight) and cardia gastric cancer incidence (or incidence and mortality) showed a positive association (see Table 2.2.3a), except for four studies (Tran et al., 2005; Samanic et al., 2006; Corley et al., 2008; Steffen et al., 2015). In the large meta-analysis by Chen et al., overweight was associated with a 21% higher risk (based on six studies) and obesity was associated with an 82% higher risk (based on seven studies) compared with normal BMI (18.5–24.9 kg/m^2) (Chen et al., 2013). These findings were similar to those reported in an earlier meta-analysis of three prospective studies (Yang et al., 2009).

Associations of BMI in early adulthood and adult BMI change with incidence of cardia gastric cancer were examined in only one study of mortality (Merry et al., 2007). In that study, BMI at age 20 years was not associated with risk, whereas increasing BMI from age 20 years to baseline showed a positive association (P_{trend} = 0.02).

Although one study showed no association between sagittal abdominal diameter and risk of gastric cardia cancer (Corley et al., 2008), in the NIH-AARP cohort a 2.2-fold higher risk for the fourth versus the first quartile of waist circumference was reported, with a significant trend (O'Doherty et al., 2012). A similar positive trend of waist circumference and gastric cardia cancer risk (incidence and mortality) was also found in the EPIC study (Steffen et al., 2015).

(iii) Non-cardia gastric cancer

Findings from cohort studies and meta-analyses of excess body weight at baseline in relation to incidence of non-cardia gastric cancer are inconsistent. Neither BMI nor weight was associated with risk in most individual prospective studies (see Table 2.2.3a). Similarly, several meta-analyses did not show an association between BMI and risk either (Yang et al., 2009; Chen et al., 2013; Lin et al., 2014). However, in the Linxian General Population Trial, a significant inverse association was reported with a relative risk of 0.68 for BMI ≥ 23 kg/m^2 versus BMI < 20 kg/m^2 (Tran et al., 2005), and a significant inverse association was also reported in a Swedish cohort study (P_{trend} < 0.01) (Samanic et al., 2006). Conversely, one individual study suggested a positive association of BMI and/or weight and risk of non-cardia gastric cancer (O'Doherty et al., 2012).

No associations were reported in the only study of BMI in early adulthood and adult BMI change in relation to incidence of non-cardia gastric cancer (Merry et al., 2007), or in the three studies that examined waist circumference and risk of non-cardia gastric cancer (MacInnis et al., 2006; O'Doherty et al., 2012; Steffen et al., 2015).

(b) Case–control studies

See Table 2.2.3b.

There were a total of 11 independent reports from case–control studies on the association of BMI with risk of gastric cancer, in China, Europe, Japan, the Republic of Korea, the USA, and Venezuela. With the exception of one hospital-based study (Kim et al., 2015), in which BMI was measured at the time of initial endoscopic diagnosis, BMI was assessed through self-reports of height and body weight, referring to either a recent period (mostly 1 year) before disease diagnosis or a period in the more distant past (e.g. at age 18 years or 20 years), or both. In addition to standard adjustments for age and sex, studies were reported with variable adjustments for further confounding factors such as smoking, alcohol consumption, family history of gastric cancer, dietary variables, or *H. pylori* infection.

With regard to gastric cardia cancer, three out of four studies showed a positive association of BMI with risk. Three studies specifically addressing non-cardia cancer showed no association of recent BMI with risk, whereas two studies reported a positive association of risk

with BMI at age 20 years. With regard to overall gastric cancer – without specification by subsite – three studies showed an increase in risk with increasing BMI, one showed a decrease in risk, and two showed no significant association.

Table 2.2.3a Cohort studies of measures of body fatness and cancer of the stomach

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Stomach not otherwise specified							
Calle et al. (2003) Cancer Prevention Study II (CPS II) USA 1982–1998	404 576 Men Mortality	Stomach ICD-9: 151.0–151.9	BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 388 455 84 18	 1.00 1.01 (0.88–1.16) 1.20 (0.94–1.52) 1.94 (1.21–3.13) [0.03]	Age, education level, smoking, physical activity, alcohol consumption, marital status, race, aspirin use, consumption of fat and vegetables; for women, also adjusted for HRT use	
	495 477 Women Mortality		BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 304 134 57 13	 1.00 0.89 (0.72–1.09) 1.30 (0.97–1.74) 1.08 (0.61–1.89) [0.46]		
Samanic et al. (2004) United States Veterans cohort USA 1969–1996	4 500 700 Men Incidence	Stomach ICD-9: 151	Obesity Non-obese Obese Non-obese Obese	 White men: 4989 309 Black men: 2089 99	 1.00 1.07 (0.95–1.20) 1.00 0.98 (0.79–1.20)	Age, calendar year	Obesity defined as discharge diagnosis of obesity: ICD-8: 277; ICD-9: 278.0

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Batty et al. (2005) Whitehall study of London-based male government employees United Kingdom 1967–2002	18 403 Men Mortality	Stomach	BMI 18.5–24.9 25.0–29.9 ≥ 30 [P_{trend}]	 100 81 9	 1.00 1.05 (0.76–1.44) 1.23 (0.59–2.58) [0.60]	Age, employment grade, physical activity, smoking, marital status, prevalent disease, weight loss in past year, BP medication, height, skinfold thickness, systolic BP, plasma cholesterol, glucose intolerance, diabetes	
Kuriyama et al. (2005) Population-based cohort Japan 1984–1992	12 485 Men Incidence	Stomach ICD-9: 151.0–151.9	BMI 18.5–24.9 25.0–27.4 27..5–29.9 ≥ 30 [P_{trend}]	 243 50 14 7	 1.00 1.01 (0.74–1.37) 0.96 (0.56–1.65) 1.13 (0.53–2.41) [0.91]	Age, smoking, alcohol consumption, diet, type of health insurance; for women, also adjusted for menopausal status, parity, age at menarche, age at first pregnancy	
	15 054 Women Incidence		BMI 18.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 [P_{trend}]	 79 26 17 4	 1.00 1.19 (0.76–1.86) 1.80 (1.06–3.05) 0.79 (0.29–2.17) [0.25]		

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Lindblad et al. (2005) Case–control study nested in General Practitioner Research Database United Kingdom 1994–2001	11 023 Men and women Incidence	Stomach	BMI < 20 20–24 25–29 ≥ 30 [P_{trend}]	 29 217 254 98	 1.05 (0.69–1.58) 1.00 1.09 (0.90–1.32) 1.21 (0.94–1.56) [0.21]	Age, sex, calendar year, smoking, alcohol consumption, reflux	
Rapp et al. (2005) VHM&PP (population-based cohort) Austria 1985–2001	67 447 Men Incidence	Stomach ICD-9: 151	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 58 75 13	 1.00 1.04 (0.73–1.47) 0.72 (0.40–1.33) [0.44]	Age, smoking status, occupation	
			BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 56 36 20 6	 1.00 0.78 (0.51–1.20) 1.28 (0.76–2.15) 1.34 (0.57–3.13) [0.48]	Age, smoking status, occupation	
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1958–1999	362 552 Men Incidence	Stomach ICD-7: 151	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 666 531 84	 1.00 0.87 (0.77–0.97) 0.83 (0.66–1.05) [< 0.05]	Attained age, calendar year, smoking	

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Fujino et al. (2007) JACC cohort Japan 1988–1997	46 465 Men Mortality	Stomach	BMI			Age, study area	
			< 18.5	54	1.00 (0.75–1.32)		
			18.5–24	569	1.00		
			25–29	89	0.78 (0.62–0.97)		
			≥ 30	7	1.04 (0.49–2.20)		
			Weight (kg)				
			< 55	280	1.00		
			55–62	260	0.88 (0.74–1.04)		
			≥ 63	198	0.83 (0.69–1.01)		
			Weight (kg) at age 20 yr				
			< 55	339	1.00		
			55–60	210	1.04 (0.84–1.30)		
			≥ 61	157	1.17 (0.93–1.48)		
	46 465 Women Mortality	Stomach	BMI			Age, study area	
			< 18.5	37	1.44 (1.01–2.05)		
			18.5–24	227	1.00		
			25–29	66	0.98 (0.74–1.30)		
			≥ 30	11	1.52 (0.82–2.80)		
			Weight (kg)				
			< 47	156	1.00		
			47–54	84	0.79 (0.60–1.03)		
			≥ 55	118	1.01 (0.78–1.29)		
			Weight (kg) at age 20 yr				
			< 47	167	1.00		
			47–52	72	0.97 (0.70–1.34)		
			≥ 53	95	1.25 (0.92–1.70)		
Máchová et al. (2007) National Cancer Registry Czech Republic 1987–2002	17 218 Men Incidence	Stomach ICD-10: C16	BMI	222 total		Age, smoking, hypertension, height	Nested case–control study, reporting odds ratios
			18.5–24.9		1.00		
			25–29.9		1.05 (0.74–1.47)		
			≥ 30		0.92 (0.57–1.50)		
	20 932 Women Incidence		BMI	156 total		Age, smoking, hypertension, height	
			18.5–24.9		1.00		
			25–29.9		0.81 (0.51–1.27)		
			≥ 30		0.97 (0.60–1.57)		

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Merry et al. (2007) Netherlands Cohort Study The Netherlands 1986–1999	4774 Men and women Incidence	Stomach, unspecified location ICD-O-3: C16.6–16.9 Histology: 8140–8141, 8190–8231, 8260–8263, 8310, 8430, 8480–8490, 8560, 8570–8572	BMI at baseline			Age, sex, smoking, education level, history of gastric ulcer or bleeding	
			< 20	6	0.92 (0.38–2.25)		
			20–24.9	93	1.00		
			25–29.9	67	0.85 (0.61–1.19)		
			≥ 30	7	0.77 (0.35–1.68)		
			[P_{trend}]		[0.33]		
			BMI at age 20 yr				
			< 20	26	0.60 (0.37–0.99)		
			20–21.4	49	1.00		
			21.5–22.9	40	0.92 (0.59–1.44)		
			23.0–24.9	26	0.70 (0.42–1.18)		
			≥ 25	12	0.82 (0.42–1.60)		
			[P_{trend}]		[0.72]		
			BMI change, age 20 yr to baseline				
			< 0	16	0.85 (0.47–1.55)		
			0–3.9	82	1.00		
			4–7.9	45	0.85 (0.56–1.27)		
			≥ 8	10	0.86 (0.41–1.80)		
			[P_{trend}]		[0.70]		
Reeves et al. (2007) Million Women Study United Kingdom 1996–2005	1 222 630 Women Incidence and mortality	Stomach ICD-10: C16	BMI	Incidence:		Age, geographical region, SES, reproductive history, smoking status, alcohol consumption, physical activity, menopausal status, time since menopause, HRT use	
			< 22.5	117	1.26 (1.05–1.51)		
			22.5–24.9	121	1.00 (0.84–1.20)		
			25–27.4	111	1.04 (0.86–1.25)		
			27.5–29.9	76	1.10 (0.88–1.38)		
			≥ 30	96	1.04 (0.84–1.27)		
			BMI	Mortality:			
			< 22.5	92	1.47 (1.19–1.81)		
			22.5–24.9	82	1.00 (0.80–1.24)		
			25–27.4	85	1.16 (0.93–1.43)		
			27.5–29.9	64	1.34 (1.05–1.71)		
			≥ 30	80	1.24 (0.99–1.55)		

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Tanaka et al. (2007) Population cohort from Takayama Japan 1992–2000	13 211 Men Mortality	Stomach ICD-9: 151 ICD-10: C16	BMI at baseline < 20.3 20.3–22.2 > 22.2 [P_{trend}] BMI at age 20 yr < 20.3 20.3–22.2 > 22.2 [P_{trend}]	 29 20 16 12 33 41 	 1.00 0.68 (0.34–1.33) 0.53 (0.24–1.20) [0.12] 1.00 2.53 (1.18–5.43) 1.72 (0.79–3.73) [0.76]	Age, smoking, alcohol consumption, education level, physical activity, marital status	Too few incident cases in women (results not shown)
Jee et al. (2008) Cohort from the National Health Insurance Corporation Republic of Korea 1992–2006	770 556 Men Incidence	Stomach	BMI < 20.0 20.0–22.9 23.0–24.9 25.0–29.9 ≥ 30.0 [P_{trend}]	 1808 5602 3839 3188 131 	 1.04 (0.97–1.13) 1.07 (1.01–1.13) 1.00 1.09 (1.02–1.16) 1.31 (1.05–1.64) [0.50]	Age, smoking	
	423 273 Women Incidence	Stomach	BMI < 20.0 20.0–22.9 23.0–24.9 25.0–29.9 ≥ 30.0 [P_{trend}]	 524 1314 1035 1132 111 	 0.86 (0.75–1.00) 0.90 (0.80–1.00) 1.00 0.94 (0.84–1.05) 0.84 (0.64–1.11) [0.25]	Age, smoking	
Rapp et al. (2008) VHM&PP (population-based cohort) Austria 1985–2002	28 711 Men Incidence	Stomach ICD-10: C16	BMI change per year < –0.1 –0.1– < 0.1 0.1– < 0.3 ≥ 0.3 [P_{trend}]	 11 25 20 10 	 0.75 (0.36–1.54) 1.00 1.18 (0.65–2.13) 1.22 (0.58–2.59) [0.49]	Age, smoking status, blood glucose, occupational group, baseline BMI	

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Rapp et al. (2008) (cont.)	36 938 Women Incidence		BMI change per year < −0.1 −0.1– < 0.1 0.1– < 0.3 ≥ 0.3 [P_{trend}]	 19 12 19 9	 1.73 (0.82–3.63) 1.00 1.73 (0.84–3.57) 1.11 (0.46–2.65) [0.73]	Age, smoking status, blood glucose, occupational group, baseline BMI	
Sjödahl et al. (2008) Nord-Trondelag Health Study Norway 1984–2002	73 133 Men and women Incidence	Stomach, adenocarcinoma ICD-7: 151.0, 151.8, 151.9	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 3 104 110 32	 0.7 (0.1–5.2) 1.0 1.0 (0.7–1.4) 1.1 (0.7–1.8) [0.74]	Age, sex, physical activity, occupation, salt intake, smoking, alcohol consumption	
Whitlock et al. (2009) Pooled analysis of 57 cohort studies Europe and North America Follow-up varied by cohort	894 576 Men and women Mortality	Stomach ICD-9: 151	BMI, per 5 kg/m² For BMI 15–25 For BMI 25–50 For BMI 15–50	 934 651	 0.86 (0.70–1.05) 1.11 (0.94–1.32) 0.98 (0.90–1.07)	Study, sex, age, smoking	
Parr et al. (2010) Pooled analysis of 39 cohort studies Asia, Australia, and New Zealand 1961–1999, median follow-up 4 yr	326 387 Men and women Mortality	Stomach ICD-9: 151 ICD-10: C16	BMI 12–< 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	NR	 1.19 (0.87–1.62) 1.00 1.05 (0.88–1.25) 1.04 (0.67–1.63) [0.66]	Age, sex, smoking	
Chen et al. (2012) Population-based cohort of men China 1990–2006	142 214 Men Mortality	Stomach	BMI 15–23.5 23.5–35	 757 198	 0.74 (0.59–0.94) 0.96 (0.61–1.49)	Age, area, smoking, alcohol consumption, education level	

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Lindkvist et al. (2013) Metabolic Syndrome and Cancer Project (Me-Can) pooled analysis of prospective cohorts Austria, Norway, and Sweden 1972–2006, follow-up varied by cohort	289 866 Men Incidence	Stomach ICD-7: 151	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 157 134 154 197 186	 1.00 0.79 (0.62–0.99) 0.84 (0.67–1.05) 1.02 (0.83–1.26) 1.00 (0.80–1.24) [0.26]	Smoking, age, study cohort, year of birth	Ranges of BMI quintiles not specified
	288 834 Women Incidence	Stomach ICD-7: 151	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 59 65 63 104 91	 1.00 0.92 (0.65–1.31) 0.73 (0.51–1.05) 1.01 (0.72–1.40) 0.85 (0.61–1.20) [0.68]	Smoking, age, study cohort, year of birth	Ranges of BMI quintiles not specified
Bhaskaran et al. (2014) Population-based cohort: Clinical Practice Research Datalink United Kingdom 1987–2012	5 243 978 Incidence	Stomach ICD-10: C16	BMI per 5 kg/m^2 increase [P_{trend}]	3337 total	 1.03 (0.98–1.09) [0.16]	Age, sex, diabetes, smoking, alcohol consumption, SES, calendar year	Stronger association in non-smokers
Camargo et al. (2014) NIH-AARP cohort USA 1995–2006	483 700 Men and women Incidence	Stomach ICD-10: C16.0–16.9	BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 Weight, tertiles T1 T2 T3	1000 total	 1.00 1.05 (0.90–1.22) 1.40 (1.16–1.68) 1.57 (1.21–2.04) 1.00 1.00 (0.86–1.17) 1.18 (1.01–1.38)	Age, sex, education level, cigarette smoking	

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Gastric cardia							
Samanic et al. (2004) United States Veterans cohort USA 1969–1996	4 500 700 Men Incidence	Gastric cardia ICD-9: 151.0	Obesity Non-obese Obese	White men: 841 72	 1.00 1.38 (1.09–1.77)	Age, calendar year	Obesity defined as discharge diagnosis of obesity: ICD-8: 277; ICD-9: 278.0 Only 5 cases were available among Black men
Lindblad et al. (2005) Case–control study nested in General Practitioner Research Database United Kingdom 1994–2001	10 195 Men and women Incidence	Gastric cardia	BMI < 20 20–24 25–29 ≥ 30 [P_{trend}]	 2 36 55 20	 0.50 (0.12–2.10) 1.00 1.37 (0.89–2.10) 1.46 (0.84–2.54) [0.04]	Age, sex, calendar year, smoking, alcohol consumption, reflux	
Tran et al. (2005) Linxian General Population Trial China 1986–2001	29 584 Men and women Incidence	Gastric cardia	BMI < 20 20–21 22 ≥ 23 [P_{trend}]	1089 total	 1.00 0.98 (0.84–1.16) 0.96 (0.81–1.13) 0.95 (0.80–1.13) [0.51]	Age, sex	
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1958–1999	362 552 Men Incidence	Gastric cardia ICD-7: 151.0	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 108 105 16	 1.00 1.16 (0.88–1.52) 1.09 (0.64–1.85) [0.40]	Attained age, calendar year, smoking	

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Merry et al. (2007) Netherlands Cohort Study The Netherlands 1986–1999	4774 Men and women Incidence	Gastric cardia ICD-O-3: C16.0 Histology: 8140–8141, 8190–8231, 8260–8263, 8310, 8430, 8480–8490, 8560, 8570–8572	BMI at baseline < 20 20–24.9 25–29.9 ≥ 30 [P_{trend}] BMI at age 20 yr < 20 20–21.4 21.5–22.9 23.0–24.9 ≥ 25 [P_{trend}] BMI change, age 20 yr to baseline < 0 0–3.9 4–7.9 ≥ 8 [P_{trend}]	 2 68 76 17 21 40 39 22 16 10 70 45 13 	 0.67 (0.16–2.80) 1.00 1.32 (0.94–1.85) 2.73 (1.56–4.79) [0.002] 0.66 (0.39–1.14) 1.00 1.02 (0.65–1.60) 0.75 (0.44–1.28) 1.47 (0.81–2.70) [0.17] 0.68 (0.34–1.35) 1.00 1.22 (0.82–1.82) 2.07 (1.08–3.97) [0.02]	Age, sex	
Abnet et al. (2008) NIH-AARP cohort USA 1995–2003	480 475 Men and women Incidence	Gastric cardia ICD-O-3: C16.0 Histology: “adenocarcinoma”	BMI < 18.5 18.5–24.9 25–29.9 30–34.9 ≥ 35	 1 76 128 71 31	 0.70 (0.10–5.06) 1.00 1.06 (0.79–1.41) 1.70 (1.22–2.36) 2.46 (1.60–3.80)	Age, sex, cigarette smoking, alcohol consumption, education level, physical activity	

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Corley et al. (2008) Nested case–control of Kaiser Permanente Multiphasic Health Check-up cohort USA 1964–1973	3150 Men and women Incidence	Gastric cardia ICD-10: C16.0 Histology: 8140–8573	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 per 1 kg/m² increase Sagittal abdominal diameter (cm) < 20 20–22.4 22.5–25 ≥ 25 per 1 cm increase	 0 43 40 16 16 12 12 14 	 – 1.00 0.91 (0.55–1.53) 2.04 (0.99–4.21) 1.04 (0.98–1.09) 1.00 0.69 (0.29–1.60) 1.17 (0.49–2.84) 1.28 (0.38–4.25) 1.03 (0.95–1.11)	Age, sex, year of health check-up BMI results also adjusted for ethnicity	
O'Doherty et al. (2012) NIH-AARP cohort USA 1995–2006	218 854 Men and women Incidence	Gastric cardia ICD-10: C16.0	BMI < 18.5 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}] Weight, quartiles (sex-specific) Q1 Q2 Q3 Q4 [P_{trend}]	 2 50 79 45 15 28 46 44 73 	 2.57 (0.62–10.65) 1.00 1.15 (0.80–1.65) 2.16 (1.41–3.29) 3.67 (2.00–6.71) [< 0.01] 1.00 1.66 (1.03–2.67) 1.53 (0.93–2.51) 2.52 (1.55–4.11) [< 0.01]	Age, sex, total energy intake, antacid use, aspirin use, NSAID use, marital status, diabetes, cigarette smoking, education level, ethnicity, alcohol consumption, physical activity, diet	

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
O'Doherty et al. (2012) (cont.)			WC, quartiles (sex-specific)				
			Q1	30	1.00		
			Q2	38	1.32 (0.82–2.14)		
			Q3	51	1.29 (0.82–2.04)		
			Q4	72	2.22 (1.43–3.47)		
			[P_{trend}]		[< 0.01]		
Camargo et al. (2014) NIH-AARP cohort USA 1995–2006	483 700 Men and women Incidence	Gastric cardia ICD-10: C16.0	BMI	478 total		Age, sex, education level, cigarette smoking	
			18.5–24.9		1.00		
			25–29.9		1.10 (0.87–1.38)		
			30–34.9		1.64 (1.26–2.14)		
			≥ 35		2.24 (1.58–3.17)		
			Weight, tertiles				
			T1		1.00		
			T2		1.20 (0.94–1.52)		
			T3		1.53 (1.21–1.92)		
Steffen et al. (2015) EPIC cohort 10 European countries 1992–2008	391 456 Men and women Incidence/mortality	Gastric cardia ICD-10: C16.0	BMI, quintiles			Age, centre, sex, education level, smoking, alcohol consumption, physical activity, diet, height	Sex-specific quintiles for weight, BMI, and WC. Cut-off points not provided, only the median values for each
			Q1	31	1.00		
			Q2	37	1.09 (0.68–1.77)		
			Q3	48	1.37 (0.87–2.17)		
			Q4	41	1.20 (0.74–1.94)		
			Q5	36	1.17 (0.71–1.92)		
			[P_{trend}]		[0.53]		
			Weight, quintiles				
			Q1	33	1.00		
			Q2	37	1.14 (0.71–1.84)		
			Q3	43	1.29 (0.81–2.08)		
			Q4	38	1.11 (0.68–1.83)		
			Q5	42	1.26 (0.75–2.10)		
			[P_{trend}]		[0.48]		

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Steffen et al. (2015) (cont.)			WC, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 22 31 40 42 45	 1.00 1.20 (0.69–2.09) 1.41 (0.83–2.40) 1.52 (0.89–2.58) 1.59 (0.93–2.73) [0.06]		
Gastric non-cardia							
Samanic et al. (2004) United States Veterans cohort USA 1969–1996	4 500 700 Men Incidence	Gastric non-cardia ICD-9: 151.x	Obesity Non-obese Obese Non-obese Obese	White men: 4148 237 Black men: 1958 94	 1.00 1.00 (0.88–1.14) 1.00 0.99 (0.80–1.22)	Age, calendar year	Obesity defined as discharge diagnosis of obesity: ICD-8: 277; ICD-9: 278.0
Lindblad et al. (2005) Case–control study nested in General Practitioner Research Database United Kingdom 1994–2001	10 327 Men and women Incidence	Gastric non-cardia	BMI < 20 20–24 25–29 ≥ 30 [P_{trend}]	 16 70 83 23	 1.75 (1.00–3.08) 1.00 1.11 (0.80–1.54) 0.87 (0.54–1.41) [0.18]	Age, sex, calendar year, smoking, alcohol consumption, reflux	
Tran et al. (2005) Linxian General Population Trial China 1986–2001	29 584 Men and women Incidence	Gastric non-cardia	BMI < 20 20–21 22 ≥ 23 [P_{trend}]	363 total	 1.00 1.00 (0.76–1.32) 0.91 (0.68–1.20) 0.68 (0.49–0.93) [0.017]	Age, sex	

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
MacInnis et al. (2006) Melbourne Collaborative Cohort Study Australia 1990–2004	41 295 Men and women Incidence/mortality	Gastric non-cardia ICD-9: 151.1–151.9 ICD-10: C16.1–16.9	BMI < 25 25–29 ≥ 30 [P_{trend}] Weight (kg) Men: Women: < 75 < 62 75–83 62–70 ≥ 84 ≥ 71 [P_{trend}] WC (cm) Men: Women: < 94 < 80 94–101 80–87 ≥ 102 ≥ 88 [P_{trend}]	68 total	1.0 0.5 (0.3–1.0) 1.0 (0.5–1.8) [0.76] 1.0 0.6 (0.3–1.1) 1.1 (0.6–1.9) [0.62] 1.0 0.8 (0.4–1.4) 1.1 (0.6–2.0) [0.57]	Sex, country of birth, education level, physical activity	
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1958–1999	362 552 Men Incidence	Gastric non-cardia ICD-7: 151.x	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	558 426 68	1.00 0.81 (0.72–0.92) 0.78 (0.61–1.01) [< 0.01]	Attained age, calendar year, smoking	
Merry et al. (2007) Netherlands Cohort Study The Netherlands 1986–1999	4774 Men and women Incidence	Gastric non-cardia ICD-10: C16.1–16.5 Histology: 8140–8141, 8190–8231, 8260–8263, 8310, 8430, 8480–8490, 8560, 8570–8572	BMI at baseline < 20 20–24.9 25–29.9 ≥ 30 [P_{trend}]	12 115 99 9	1.80 (0.96–3.39) 1.00 0.97 (0.73–1.30) 0.68 (0.34–1.35) [0.13]	Age, sex, current smoking, number of cigarettes smoked per day, smoking duration, education level	

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Merry et al. (2007) (cont.)			BMI at age 20 yr				
			< 20	53	1.40 (0.91–2.15)		
			20–21.4	40	1.00		
			21.5–22.9	49	1.24 (0.80–1.91)		
			23.0–24.9	36	1.12 (0.69–1.80)		
			≥ 25	20	1.60 (0.91–2.83)		
			[P_{trend}]		[0.93]		
			BMI change, age 20 yr to baseline				
			< 0	17	0.77 (0.44–1.36)		
			0–3.9	106	1.00		
			4–7.9	61	0.85 (0.60–1.21)		
			≥ 8	14	0.86 (0.46–1.59)		
			[P_{trend}]		[0.77]		
Abnet et al. (2008) NIH-AARP cohort USA 1995–2003	480 475 Men and women Incidence	Gastric non-cardia ICD-O-3: C16.1–16.9 Histology: "adenocarcinoma"	BMI			Age, sex, cigarette smoking, alcohol consumption, education level, physical activity	
			< 18.5	7	2.97 (1.38–6.39)		
			18.5–24.9	107	1.00		
			25–29.9	123	0.80 (0.61–1.04)		
			30–34.9	61	1.08 (0.78–1.50)		
			≥ 35	17	0.84 (0.50–1.42)		
Persson et al. (2008) Japan Public Health Center-based Prospective Study Japan 1990–2004	44 453 Women Incidence	Stomach, non-cardia ICD-10: C16.2-16.7	BMI			Age, family history of gastric cancer, study area	Similar results in postmenopausal women only
			< 20	53	1.00		
			20–24.9	225	0.82 (0.61–1.11)		
			≥ 25	90	0.74 (0.53–1.04)		
			[P_{trend}]		[0.10]		
		Stomach, non-cardia, differentiated cancer type ICD-10: C16.2-16.7	BMI				Similar results in postmenopausal women only
			< 20	12	1.00		
			20–24.9	56	0.93 (0.50–1.74)		
			≥ 25	29	1.12 (0.57–2.21)		
			[P_{trend}]		[0.59]		

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Persson et al. (2008) (cont.)		Stomach, non-cardia, undifferentiated cancer type ICD-10: C16.2-16.7	BMI < 20 20–24.9 ≥ 25 [P_{trend}]	 37 153 52	 1.00 0.79 (0.55–1.14) 0.60 (0.39–0.91) [0.01]		Similar results in postmenopausal women only
Sjödahl et al. (2008) Nord-Trondelag Health Study Norway 1984–2002	73 133 Men and women Incidence	Gastric non-cardia ICD-7: 151.0, 151.8, 151.9	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 2 84 92 29	 0.9 (0.1–6.7) 1.0 1.1 (0.7–1.6) 1.2 (0.7–2.1) [0.42]	Age, sex, physical activity, occupation, salt intake, smoking, alcohol consumption	
O'Doherty et al. (2012) NIH-AARP cohort USA 1995–2006	218 854 Men and women Incidence	Gastric non-cardia ICD-10: C16.1–16.7	BMI < 18.5 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}] Weight, quartiles (sex-specific) Q1 Q2 Q3 Q4 [P_{trend}] WC, quartiles (sex-specific) Q1 Q2 Q3 Q4 [P_{trend}]	 1 37 60 23 4 20 35 32 38 21 26 40 38 	 1.34 (0.18–9.79) 1.00 1.32 (0.86–2.00) 1.46 (0.84–2.51) 0.99 (0.34–2.84) [0.38] 1.00 1.93 (1.10–3.38) 1.73 (0.96–3.10) 1.93 (1.05–3.54) [0.07] 1.00 1.27 (0.71–2.26) 1.41 (0.82–2.41) 1.46 (0.83–2.55) [0.19]	Age, sex, total energy intake, antacid use, aspirin use, NSAID use, marital status, diabetes, cigarette smoking, education level, ethnicity, alcohol consumption, physical activity, diet	

Table 2.2.3a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Camargo et al. (2014) NIH-AARP cohort USA 1995–2006	483 700 Men and women Incidence	Gastric non-cardia ICD-10: C16.1–16.6	BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 Weight, tertiles T1 T2 T3	522 total	 1.00 1.09 (0.83–1.43) 1.38 (0.99–1.92) 1.05 (0.61–1.82) 1.00 1.00 (0.76–1.32) 1.02 (0.77–1.34)	Age, sex, education level, cigarette smoking	
Steffen et al. (2015) EPIC cohort 10 European countries 1992–2008	391 456 Men and women Incidence/mortality	Gastric non-cardia ICD-10: C16.1–16.9	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}] Weight, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}] WC, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 36 36 33 49 70 50 35 36 57 46 25 25 33 66 55 	 1.00 0.77 (0.48–1.22) 0.61 (0.38–0.99) 0.78 (0.50–1.22) 0.99 (0.64–1.54) [0.41] 1.00 0.68 (0.44–1.06) 0.67 (0.43–1.06) 1.02 (0.68–1.55) 0.84 (0.53–1.32) [0.94] 1.00 0.81 (0.46–1.42) 0.89 (0.52–1.52) 1.58 (0.97–2.57) 1.14 (0.68–1.91) [0.12]	Sex, education level, smoking, alcohol consumption, physical activity, diet, height	Sex-specific quintiles for weight, BMI, and WC. Cut-off points not provided, only the median values for each

BMI, body mass index (in kg/m^2); BP, blood pressure; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HRT, hormone replacement therapy; ICD, International Classification of Diseases; JACC, Japan Collaborative Cohort Study for Evaluation of Cancer Risk; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; NSAID, non-steroidal anti-inflammatory drug; SES, socioeconomic status; VHM&PP, Vorarlberg Health Monitoring and Prevention Program; WC, waist circumference; yr, year or years

Table 2.2.3b Case–control studies of measures of body fatness and cancer of the stomach

Reference Study location Period	Total number of cases Source of controls	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Stomach							
Hansson et al. (1994) Sweden 1989–1992	338 Population	Stomach	BMI at age 20 yr			Age, height	No differences were observed in the associations by age at interview (age groups: < 59 yr, 60–69 yr, and ≥ 70 yr) No associations were found between BMI and GC 20 yr before the interview
				Men:			
			≤ 21.20	37	1.00		
			21.21–22.60	40	1.06 (0.63–1.86)		
			22.62–24.20	45	1.09 (0.66–1.82)		
			≥ 24.21	84	2.16 (1.35–3.46)		
			continuous		1.12 (1.05–1.20)		
				Women:			
			≤ 19.20	12	1.00		
			19.21–20.80	18	1.39 (0.60–3.23)		
			20.81–23.30	40	3.06 (1.43–6.58)		
			≥ 23.21	28	2.14 (0.96–4.78)		
			continuous		1.11 (1.02–1.21)		
Muñoz et al. (2001) Venezuela 1991–1997	292 Population	Stomach	BMI			Age, sex	Similar results for self-reported weight at current age. Increased risk in overweight cases with self-reported weight in childhood, adolescence, and early adulthood
			< 18.5	51	11.0 (4.8–27.0)		
			18.5–25.0	200	1.0		
			> 25.0	41	0.3 (0.2–0.4)		
Inoue et al. (2002) Japan 1988–1998	Women: 365 Population	Stomach	Current BMI			Age, year, season of interview, family history of GC, smoking status, intake of raw vegetables and fish	Postmenopausal women only. *P* values for trend were non-significant among all subsites, both for current BMI and for BMI at age 20 yr
		Upper third		72 total			
			< 21.08		1.00		
			21.08–23.56		1.69 (0.91–3.12)		
			> 23.56		1.07 (0.54–2.10)		
		Middle third		155 total			
			< 21.08		1.00		
			21.08–23.56		0.75 (0.49–1.16)		
			> 23.56		0.80 (0.52–1.22)		
		Lower third		127 total			
			< 21.08		1.00		
			21.08–23.56		1.02 (0.63–1.66)		
			> 23.56		1.16 (0.72–1.89)		

Table 2.2.3b (continued)

Reference Study location Period	Total number of cases Source of controls	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Inoue et al. (2002) (cont.)			BMI at age 20 yr				
		Upper third		72 total			
			< 21.08		1.00		
			21.08–23.56		1.33 (0.69–2.55)		
			> 23.56		1.33 (0.69–2.58)		
		Middle third		155 total			
			< 21.08		1.00		
			21.08–23.56		1.83 (1.14–2.94)		
			> 23.56		1.81 (1.12–2.93)		
		Lower third		127 total			
			< 21.08		1.00		
			21.08–23.56		0.88 (0.52–1.50)		
			> 23.56		1.31 (0.81–2.12)		
Chung et al. (2010) Republic of Korea 1990–2008	Men: 374 Women: 270 Hospital	Stomach	Current BMI			Age	Study in young individuals (ages 18–45 yr)
			> 35 vs ≤ 35	Men: 374 total	1.94 (1.63–2.37)		
			> 35 vs ≤ 35	Women: 270 total	1.65 (1.34–2.04)		
Praud et al. (2014) Italy 1985–2007	Men: 612 Women: 387 Hospital	Stomach	BMI			Age, sex, study, year of interview, education level, tobacco smoking, family history, total energy intake	
			< 25 vs ≥ 25 [P_{trend}]	Men: 646 total	0.85 (0.79–0.90) [< 0.0001]		
			< 25 vs ≥ 25 [P_{trend}]	Women: 348 total	0.86 (0.79–0.93) [0.0009]		
Kim et al. (2015) Republic of Korea 2003–2013	Men: 663 Women: 335 Hospital	Stomach	BMI measured at endoscopy			Age, smoking status, drinking status, family history of GC, *Helicobacter pylori* infection, atrophic gastritis, intestinal metaplasia, serum pepsinogen I/II ratio	No significant associations were observed when stratifying by cardia and non-cardia GC
			< 23	Men: 286	1.00		
			23– < 25	193	1.25 (0.87–1.81)		
			≥ 25– < 30	175	1.33 (0.92–1.92)		
			≥ 30	9	1.27 (0.42–3.86)		
			[P_{trend}]		[0.43]		

Table 2.2.3b (continued)

Reference Study location Period	Total number of cases Source of controls	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Kim et al. (2015) (cont.)				Women:			
			< 23	182	1.00		
			23– < 25	73	0.92 (0.6–1.43)		
			≥ 25– < 30	69	1.11 (0.70–1.77)		
			≥ 30	11	0.86 (0.33–2.26)		
			[P_{trend}]		[0.904]		
Song et al. (2015) Republic of Korea 2010–2014	1492 Population	Stomach	BMI at age 18 yr			Age, smoking status, alcohol drinking status, regular exercise, family history of GC, past medical history	
				Men:			
			21.75		1.00		
			≥ 25.3		1.13 (1.01–1.55)		
				Women:			
			21.75		1.00		
			≥ 25.3		1.25 (1.01–1.55)		
Gastric cardia							
Vaughan et al. (1995) USA (13 counties of Washington State) 1993–1990	165 Population	Gastric cardia, adenocarcinoma	BMI, percentiles			Age, sex, education level, race, cigarette smoking, alcohol consumption	BMI percentiles (derived from in- person interviews) based on distribution of controls for each sex separately
			1–10%	13	0.8 (0.4–1.8)		
			10–49%	52	1.0		
			50–89%	74	1.3 (0.8–2.1)		
			90–100%	25	1.6 (0.8–3.0)		
Chow et al. (1998) USA 1993–1995	365 Population	Gastric cardia	BMI (sex-specific)			Geographical location, age, sex, race, cigarette smoking, respondent status	BMI up to 1 yr before diagnosis for cases and date of interview for controls
			Men: Women:				
			< 23.12 < 21.95	54	1.0		
			23.12–25.08 21.95–24.12	51	0.9 (0.6–1.5)		
			25.09–27.31 24.13–27.43	70	1.4 (0.9–2.1)		
			≥ 27.32 ≥ 27.44	86	1.6 (1.1–2.6)		
			[P_{trend}]		[0.008]		

Table 2.2.3b (continued)

Reference Study location Period	Total number of cases Source of controls	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Lagergren et al. (1999) Sweden 1995–1997	262 Population	Gastric cardia	BMI 20 yr before interview			Age, sex, tobacco smoking, alcohol consumption, SES, reflux symptoms, intake of fruits and vegetables, energy intake, physical activity	
			< 22	47	1.0		
			22–24.9	100	1.3 (0.8–1.9)		
			25–30	91	2.2 (1.4–3.4)		
			> 30	24	4.3 (2.1–8.7)		
			[P_{trend}]		[< 0.001]		
			BMI at age 20 yr, quartiles (sex-specific)				
			Men: Women:				
			< 20.7 < 19.3	52	1.0		
			20.7–22.1 19.3–20.4	46	0.8 (0.5–1.3)		
			22.2–23.7 20.5–22.1	65	1.2 (0.8–1.9)		
			> 23.7 > 22.1	99	1.9 (1.3–2.9)		
			[P_{trend}]		[< 0.001]		
Wu et al. (2001) USA 1992–1997	277 Population (proxy control)	Gastric cardia	BMI at age 40 yr, quartiles (sex-specific)			Smoking, age, sex, race, education level	
			Men: Women:	247 total			
			≤ 22 ≤ 21		1.00		
			> 22– ≤ 25 > 21– ≤ 23		1.49 (1.0–2.1)		
			> 25– ≤ 27 > 23– ≤ 25		1.45 (0.9–2.3)		
			> 27 > 25		2.08 (1.4–3.2)		
			[P_{trend}]		[0.016]		
			BMI at age 20 yr, quartiles (sex-specific)				
			Men: Women:	246 total			
			≤ 20 ≤ 18		1.00		
			> 20– ≤ 22 > 18– ≤ 20		1.13 (0.8–1.7)		
			> 22– ≤ 24 > 20– ≤ 22		1.36 (0.9–2.0)		
			> 24 > 22		1.71 (1.2–2.6)		
			[P_{trend}]		[0.006]		
Gastric non-cardia							
Chow et al. (1998) USA 1993–1995	365 Population	Gastric non-cardia	BMI up to 1 yr before diagnosis (sex-specific)			Geographical location, age, sex, race, cigarette smoking, respondent status	BMI up to 1 yr before diagnosis for cases and date of interview for controls
			Men: Women:				
			< 23.12 < 21.95	105	1.0		
			23.12–25.08 21.95–24.12	77	0.9 (0.6–1.4)		
			25.09–27.31 24.13–27.43	91	1.2 (0.8–1.8)		
			≥ 27.32 ≥ 27.44	92	1.2 (0.8–1.8)		
			[P_{trend}]		[2.14]		

Table 2.2.3b (continued)

Reference Study location Period	Total number of cases Source of controls	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Wu et al. (2001) USA 1992–1997	443 Population	Gastric non-cardia	BMI at age 40 yr, quartiles (sex-specific) Men: Women: ≤ 22 ≤ 21 > 22– ≤ 25 > 21– ≤ 23 > 25– ≤ 27 > 23– ≤ 25 > 27 > 25 [P_{trend}]	352 total	 1.00 0.86 (0.6–1.2) 1.00 (0.7–1.5) 1.10 (0.8–1.6) [0.57]	Smoking, age, sex, race, education level	Results did not change when stratifying by Whites/non-Whites or by sex
			BMI at age 20 yr, quartiles (sex-specific) Men: Women: ≤ 20 ≤ 18 > 20– ≤ 22 > 18– ≤ 20 > 22– ≤ 24 > 20– ≤ 22 > 24 > 22 [P_{trend}]	352 total	 1.00 1.21 (0.9–1.7) 1.39 (1.0–2.0) 1.43 (1.0–2.1) [0.03]		

BMI, body mass index (in kg/m^2); CI, confidence interval; GC, gastric cancer; SES, socioeconomic status; yr, year or years

Table 2.2.3c Meta-analyses of measures of body fatness and cancer of the stomach

Reference Period	Total number of studies Total number of cases	Organ site	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
Renehan et al. (2008) 1996–2007	Men: 8 prospective studies 817 incident cases	Stomach	BMI per 5 kg/m² increase	0.97 (0.88–1.06)	Age (all studies) and other factors (not in all studies)	
	Women: 5 prospective studies 325 incident cases	Stomach	BMI per 5 kg/m² increase	1.04 (0.90–1.20)		
Yang et al. (2009) 1950–2009	12 prospective studies 9492 incident cases	Stomach	BMI Overweight and obese vs normal Obese vs normal Overweight vs normal	 1.22 (1.06–1.41) 1.36 (1.21–1.54) 1.21 (1.08–1.36)	NR	No differences in risk by sex; normal, overweight, and obese are defined in most studies as BMI of 18.5–25, 25–29.9, and ≥ 30, respectively
	3 prospective studies	Cardia	BMI Overweight and obese vs normal Obese vs normal Overweight vs normal	 1.55 (1.31–1.84) 2.06 (1.63–2.61) 1.40 (1.16–1.68)	NR	
	4 prospective studies	Non-cardia	BMI Overweight and obese vs normal Obese vs normal Overweight vs normal	 1.18 (0.96–1.45) 1.26 (0.89–1.78) 1.16 (0.94–1.43)	NR	
Chen et al. (2013) 1994–2012	12 prospective studies 41 791 incident cases	Stomach	BMI 18.5– < 25 25–29.9 ≥ 30	 1.00 1.01 (0.96–1.07) 1.06 (0.99–1.12)		Stronger associations in men in both BMI groups
	7 prospective studies	Cardia	BMI 18.5– < 25 25–29.9 ≥ 30	 1.00 1.21 (1.03–1.42) 1.82 (1.32–2.49)		
	8 prospective studies	Non-cardia	BMI 18.5– < 25 25–29.9 ≥ 30	 1.00 0.93 (0.82–1.05) 1.00 (0.87–1.15)		

Table 2.2.3c (continued)

Reference Period	Total number of studies Total number of cases	Organ site	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
Lin et al. (2014) NR	13 prospective studies and 3 case–controls NR	Stomach	BMI		Age and others (not specified)	Stronger association of obesity with risk in men (5 studies) and in non-Asian population (11 studies)
			18.5– < 25	1.00		
			25–29.9	1.13 (1.03–1.24)		
			≥ 30	1.04 (0.96–1.12)		
		Cardia	BMI		Age and others (not specified)	
			18.5– < 25	1.00		
			25–29.9	1.61 (1.15–2.24)		
			≥ 30	1.22 (1.05–1.42)		
		Non-cardia	BMI		Age and others (not specified)	
			18.5– < 25	1.00		
			25–29.9	0.83 (0.68–1.01)		
			≥ 30	0.94 (0.81–1.10)		

BMI, body mass index (in kg/m^2); CI, confidence interval; CRC, colorectal cancer; HRT, hormone replacement therapy; IBD, inflammatory bowel disease; NR, not reported

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2.2.4 Cancer of the liver (hepatocellular carcinoma)

Hepatocellular carcinoma (HCC) is the most frequent primary malignancy of the liver (> 80% of primary liver cancers) and occurs predominantly in patients with underlying chronic liver disease or cirrhosis. Worldwide, liver cancer is among the most common causes of cancer death; the highest rates of liver cancer incidence and mortality occur in some areas in Asia and sub-Saharan Africa, as a result of chronic hepatitis infection (Jemal et al., 2014).

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and liver cancer was *inadequate*. Since then, numerous individual cohort studies with at least 100 cases (Table 2.2.4a), case–control studies (Table 2.2.4b), and pooled and meta-analyses of cohort studies and case–control studies (Table 2.2.4c) have been published examining the association of anthropometric factors with liver cancer incidence and/or mortality. Notably, because chronic liver disease is among the most common risk factors for cancer of the liver, results from cohort studies of anthropometric factors in relation to liver cancer incidence and/or mortality in patients with liver disease have also been included.

(a) Cohort studies

(i) Body weight and body mass index

Six cohort studies of BMI or weight in relation to risk of HCC specifically (Samanic et al., 2006; Joshi et al., 2008; Ohishi et al., 2008; Borena et al., 2012; Loomba et al., 2013; Schlesinger et al., 2013) have been published (Table 2.2.4a). Of these studies, four showed statistically significant positive associations and/or trends (Samanic et al., 2006; Ohishi et al., 2008; Borena et al., 2012; Schlesinger et al., 2013). In a large cohort of men in Sweden, a relative risk for BMI ≥ 30 kg/m^2 versus BMI < 25 kg/m^2 of 3.13 (95% CI, 2.04–4.79) was reported (Samanic et al., 2006).

At least eight other studies have examined the association between BMI and liver cancer (hepatocellular and intrahepatic bile duct combined, or NOS) incidence and/or mortality (Table 2.2.4a). One study of Japanese men and women showed no evidence of association with increased incidence (Kuriyama et al., 2005) [the number of liver cancer cases in the highest categories of BMI was small or zero in both sexes, and therefore power was limited to detect an association]. Conversely, in the large Korea National Health Insurance Corporation Study, risk of liver cancer increased significantly for BMI ≥ 30 kg/m^2 in men (relative risk [RR], 1.63; 95% CI, 1.27–2.10) and in women (RR, 1.39; 95% CI, 1.00–1.94), compared with the reference category of BMI of 23.0–24.9 kg/m^2. Significant P_{trend} values were found in both men and women (Jee et al., 2008). Strong positive associations were also observed in another prospective cohort study of BMI in relation to liver cancer incidence, a data linkage study in the United Kingdom where a 5 kg/m^2 increase in BMI was associated with a 19% increase in risk (95% CI, 1.12–1.27) (Bhaskaran et al., 2014).

In general, studies of BMI in relation to liver cancer mortality (Calle et al., 2003) or liver cancer incidence and mortality combined (Borena et al., 2012) showed strong positive associations. For example, in the Cancer Prevention Study II in the USA, there was a strong positive association between liver cancer mortality in men (RR, 4.52; 95% CI, 2.94–6.94 for BMI ≥ 35 kg/m^2 vs 18.5–24.9 kg/m^2; P_{trend} < 0.001), and to a lesser extent in women (RR, 1.68; 95% CI, 0.93–3.05 for BMI ≥ 35 kg/m^2 vs 18.5–24.9 kg/m^2; P_{trend} < 0.04) (Calle et al., 2003). In the Japan Collaborative Cohort Study, there was evidence of an association between higher BMI and liver cancer

mortality when men with liver disease were excluded (Li et al., 2013).

Associations of measures of body weight and liver cancer have been examined in at least six cohort studies of patients with cirrhosis, hepatitis infections, or other liver conditions. Of these studies, four showed statistically significant positive associations or trends between BMI and risk of HCC (N'Kontchou et al., 2006; Ioannou et al., 2007; Yu et al., 2008; Ohki et al., 2008). In the study with the largest number of HCC cases, the relative risk for BMI ≥ 30 kg/m^2 versus BMI < 18.5 kg/m^2 was 3.10 (95% CI, 1.41–6.81) in Japanese men and women who were patients at a liver clinic (Ohki et al., 2008). Two studies of cirrhosis patients also showed statistically significant 2.5–2.8-fold higher risks of HCC for obese versus normal-weight patients (N'Kontchou et al., 2006; Ioannou et al., 2007). The association was approximately of the same magnitude in a prospective study in Taiwan, China, of carriers of hepatitis B virus (HBV) (RR, 1.96; 95% CI, 0.72–5.38 for BMI ≥ 30 kg/m^2 vs 18.5–24.9 kg/m^2; P_{trend} = 0.048) [only 4 obese men developed HCC during follow-up] (Yu et al., 2008). A Japanese study of patients with hepatitis C virus (HCV) infection also found evidence of a borderline positive association when BMI was modelled as a continuous measure in women (RR per 1 kg/m^2 increase in BMI, 1.09; 95% CI, 0.99–1.19) but not in men (RR per 1 kg/m^2 increase in BMI, 1.01; 95% CI, 0.93–1.09) (Arano et al., 2011).

There have been numerous meta-analyses (Larsson & Wolk, 2007; Renehan et al., 2008; Chen et al., 2012; Rui et al., 2012; Tanaka et al., 2012; Wang et al., 2012; WCRF/AICR, 2015; Table 2.2.4c) and a large pooled analysis of 57 cohorts (Whitlock et al., 2009) on BMI and (primary) liver cancer incidence or mortality. Overall, these meta-analyses showed an increased risk of liver cancer in individuals with higher BMI independently of sex, geographical region, duration of follow-up, and potential confounders such as alcohol consumption, cigarette smoking, or diabetes history. The largest meta-analysis, by Chen et al. (2012), which included 26 prospective cohorts from Asia, Europe, and the USA, found a stronger risk of primary liver cancer in relation to higher BMI in patients with liver cirrhosis or HBV or HCV infection (n = 9 cohorts, summary RR, 1.73; 95% CI, 1.28–2.35) compared with the BMI-associated risk observed in the general population (n = 17 cohorts, summary RR, 1.36; 95% CI, 1.20–1.53) [the P value for difference was 0.15]. In the recent meta-analysis of the WCRF Continuous Update Project, a 5 kg/m^2 increase in BMI was associated with a 43% (95% CI, 1.19–1.70) increase in liver cancer incidence and a 13% (95% CI, 1.00–1.28) increase in liver cancer mortality based on 8 and 4 cohort studies, respectively, and the association was stronger in studies in Europe (summary RR, 1.59; 95% CI, 1.35–1.87) than in studies in Asia (summary RR, 1.18; 95% CI, 1.04–1.34) (WCRF/AICR, 2015).

(ii) Weight at different ages and weight change

Only a few cohort studies examined associations of BMI and/or weight at earlier ages or change in BMI or weight with risk of liver cancer. In the EPIC study, BMI at age 20 years was overall not associated with liver cancer mortality (Schlesinger et al., 2013). However, in that study there was a positive dose–response relationship between the average annual weight change from age 20 years to age at reporting and increased risk; the relative risk for each kilogram per year increase in weight of HCC was 3.51 (95% CI, 1.93–6.41), after adjustment for weight at age 20 years and other confounding factors. In a large Swedish occupational cohort, 6-year BMI change during adulthood in relation to liver cancer incidence was examined (Samanic et al., 2006). Although the results were somewhat suggestive of an increasing risk with increasing BMI gain, there were only 55 cases in total [and therefore statistical power was limited

to detect associations]. Similarly, in the Japan Collaborative Cohort Study, change in weight between age 20 years and baseline was not associated with liver cancer mortality in men or women, although some evidence for a trend could be observed in women (Li et al., 2013).

(iii) Waist circumference

A positive association between waist circumference and incidence of HCC was shown in the EPIC study, which was the only study to examine this association (Schlesinger et al., 2013). In that study, each increase of 5 cm in waist circumference was associated on average with a 25% (95% CI, 1.17–1.33) increase in risk in men and women combined.

(b) Case–control studies

A total of five case–control studies have been published since 2001 on the association of BMI with HCC in Canada, China, France, Italy, and the USA (Table 2.2.4b).

In the USA, a study of 622 cases and 660 population control subjects showed an increased risk of HCC for men and women with early adulthood (mid-20s to mid-40s) obesity (BMI > 30 kg/m^2) compared with normal-weight individuals (men: OR, 2.3; 95% CI, 1.2–4.4; women: OR, 3.6; 95% CI, 1.5–8.9) (Hassan et al., 2015), but no association was found for recalled BMI in the mid-50s. A hospital-based case–control study in Italy also showed an increased risk for subjects with elevated recalled BMI at about age 30 years, but not for BMI 1 year before cancer diagnosis (or equivalent time frame for the controls) (Polesel et al., 2009), and a study in France also showed a direct association of HCC risk with recalled past obesity in patients with non-viral liver cirrhosis (Archambeaud et al., 2015). In contrast, a population-based case–control study in Canada showed no association between risk of liver cancer and self-reported BMI 1 year before diagnosis (Pan et al., 2004).

Finally, using waist circumference as a measure of adiposity, a large population-based case–control study with 3649 cases all aged 68 years or older identified through the Surveillance, Epidemiology, and End Results (SEER) Program of the United States National Cancer Institute, and with 195 953 population control subjects, showed a significantly increased risk of HCC in men with waist circumference greater than 40 inches (101 cm) and in women with waist circumference greater than 35 inches (89 cm), compared with men or women with a smaller waist circumference (OR, 1.93; 95% CI, 1.71–2.18) (Welzel et al., 2011).

Several of the above-mentioned studies considered HBV or HCV infection as a confounder or effect modifier for the association between BMI and risk of liver cancer. In the study in Italy (Polesel et al., 2009), HCC risk was significantly increased in obese subjects without HBV and HCV infection (OR, 3.5; 95% CI, 1.3–9.2; compared with BMI < 30 kg/m^2) but not in subjects with HBV or HCV infection. The study by Hassan et al. (2015) in the USA showed a synergistic interaction between obesity and hepatitis virus infection, with highly increased risk in obese subjects with HBV or HCV infection.

Table 2.2.4a Cohort studies of measures of body fatness and cancer of the liver

Reference Cohort Location Follow-up period	Total no. of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Hepatocellular carcinoma							
N'Kontchou et al. (2006) Cohort of patients with cirrhosis France 1994–2004	771 Men and women Incidence	HCC	BMI < 25 25–30 ≥ 30	220 total	 1.0 2.0 (1.4–2.7) 2.8 (2.0–4.0)		Patients with alcohol- or hepatitis C-related cirrhosis
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1958–1999	362 552 Men Incidence	HCC	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 73 90 31	 1.00 1.45 (1.06–1.98) 3.13 (2.04–4.79) [< 0.001]	Attained age, calendar year, smoking	Based on fewer than 30 incident cases, no significant associations for cholangiocarcinoma or adenocarcinoma of the liver were found. No associations between BMI change and liver cancer overall observed (n = 469)
Ioannou et al. (2007) Cohort of cirrhosis patients in the Veterans Affairs facility USA 1994–2005	2126 Men and women Incidence	HCC ICD-9: 155.0	BMI 18.5–24.9 25–29 ≥ 30	 15 45 40	 1.00 2.8 (1.4–5.4) 2.5 (1.3–4.9)	Age, HCV infection, HBsAg, HBV core antibody, type 2 diabetes mellitus, platelet count	

Table 2.2.4a (continued)

Reference Cohort Location Follow-up period	Total no. of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Joshi et al. (2008) Korean male civil service workers cohort Republic of Korea 1999–2004	548 530 Men Mortality	HCC ICD-10: C22.0	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	989 total	 1.00 1.38 (0.90–2.11) 0.98 (0.85–1.12) 1.08 (0.67–1.72)	Age, serum glucose, alcohol consumption, tobacco use, HBsAg	
Ohishi et al. (2008) Nested case–control in the Adult Health Study (atomic bomb survivors) Japan 1970–2002	868 Men and women Incidence	HCC	BMI 10 yr before diagnosis < 19.6 19.6–21.2 21.3–22.9 23–25 > 25 per 1 kg/m^2 [P_{trend}]	 38 33 36 49 54	 1.31 (0.51–3.34) 1.24 (0.43–3.54) 1.00 2.51 (0.99–6.37) 4.57 (1.85–11.3) 1.12 (1.03–1.22) [0.01]	Hepatitis infection, alcohol consumption, smoking, coffee consumption, diabetes, radiation dose to liver	
Ohki et al. (2008) Hospital-based cohort of patients with chronic hepatitis C Tokyo, Japan 1994–2006	1431 Men and women Incidence	HCC	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	340 total	 1.00 1.52 (0.93–2.47) 1.86 (1.09–3.16) 3.10 (1.41–6.81)	Age, sex, heavy alcohol consumption, diabetes mellitus, serum albumin concentration, total bilirubin concentration, ALT levels, prothrombin time activity, platelet counts, AFP concentration	
Yu et al. (2008) Cohort of male government employees (HBV carriers) Taiwan, China 1989–2005	2903 Men Incidence	HCC	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 3 77 50 4	 1.55 (0.49–4.93) 1.00 1.48 (1.04–2.12) 1.96 (0.72–5.38) [0.048]	Age, number of clinic visits, smoking, alcohol consumption, diabetes	

Table 2.2.4a (continued)

Reference Cohort Location Follow-up period	Total no. of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Loomba et al. (2010) HBV-positive men part of the REVEAL-HBV cohort Taiwan, China 1991–2004	2260 Men Incidence	HCC	BMI per 1 kg/m² increase	136	1.00 (0.93–1.06)	Age, serum HBV DNA level, smoking, serum ALT level, HBeAg status, cirrhosis at baseline visit	Alcohol consumption–BMI interaction
Arano et al. (2011) Hospital-based cohort of patients with hepatitis C Japan 1994–2009	146 Men Incidence	HCC	BMI per 1 kg/m² increase	67	1.01 (0.93–1.09)	Age, alcohol consumption, serum biomarkers, platelet count, diabetes	
	179 Women Incidence	HCC	BMI per 1 kg/m² increase	55	1.09 (0.99–1.19)	Age, alcohol consumption, serum biomarkers, platelet count, diabetes	
Borena et al. (2012) Me-Can cohorts Austria, Norway, and Sweden 1972–2006, follow-up varied by cohort	578 700 Men and women Incidence and mortality	HCC	BMI, per unit SD	155 total	1.51 (1.29–1.77)	Age, cohort, year of birth, sex, smoking status	
Loomba et al. (2013) Population-based cohort of residents (7 townships) Taiwan, China 1991–2004	23 712 Men and women Incidence	HCC	BMI < 30 ≥ 30	 284 21	 1.00 1.47 (0.85–2.30)	Only univariate model available	A significant interaction was reported between alcohol drinkers (4 days per week for at least 1 yr) and BMI ≥ 30 kg/m², with a 7-fold increased risk of HCC

Table 2.2.4a (continued)

Reference Cohort Location Follow-up period	Total no. of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Schlesinger et al. (2013) EPIC cohort 10 European countries 1992–2010	Men and women Incidence	HCC ICD-10: C22.0	BMI, tertiles (sex-specific) Men: Women: < 24.93 < 23.04 24.93–27.8 23.04–26.64 ≥ 27.81 ≥ 26.65 [P_{trend}] per 5 kg/m^2 Weight, tertiles T1 T2 T3 [P_{trend}] per 5 kg Weight change from age 20 yr to age at reporting, tertiles T1 T2 T3 [P_{trend}] per kg/yr WC, tertiles T1 T2 T3 [P_{trend}] per 5 cm	33 49 95 46 50 81 30 32 46 27 50 100 	1.00 1.31 (0.84–2.05) 2.28 (1.50–3.45) [< 0.0001] 1.55 (1.31–1.83) 1.00 1.19 (0.78–1.80) 2.04 (1.36–3.06) [< 0.001] 1.18 (1.11–1.25) 1.00 1.30 (0.77–2.19) 2.48 (1.49–4.13) [< 0.001] 3.51 (1.93–6.41) 1.00 1.45 (0.90–2.34) 2.60 (1.66–4.07) [< 0.0001] 1.25 (1.17–1.33)	Age, sex, study centre, education level, smoking, alcohol consumption, height Analysis of weight change also adjusted for weight at age 20 yr	Associations were lost when BMI analyses were further adjusted for WC No significant associations were observed with weight at age 20 yr, when comparing extreme tertiles (P_{trend} = 0.95)
Liver NOS							
Calle et al. (2003) Cancer Prevention Study II (CPS II) USA 1982–1998	404 576 Men Mortality	Liver	BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	222 296 78 24 	1.00 1.13 (0.94–1.34) 1.90 (1.46–2.47) 4.52 (2.94–6.94) [< 0.001]	Age, education level, smoking, physical activity, alcohol consumption, marital status, race, aspirin use, consumption of fat and vegetables	

Table 2.2.4a (continued)

Reference Cohort Location Follow-up period	Total no. of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Calle et al. (2003) (cont.)	495 477 Women Mortality	Liver	BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 200 96 37 12	 1.00 1.02 (0.80–1.31) 1.40 (0.97–2.00) 1.68 (0.93–3.05) [0.04]	For women, also adjusted for HRT use	
Samanic et al. (2004) United States Veterans cohort USA 1969–1996	4 500 700 Men Incidence	Liver ICD-9: 155	Obesity Non-obese Obese Non-obese Obese	 White men: 3612 322 Black men: 1168 38	 1.00 1.44 (1.28–1.61) 1.00 0.68 (0.49–0.94)	Age, calendar year	Obesity defined as discharge diagnosis of obesity: ICD-8: 277; ICD-9: 278.0 Significantly different risk in White men and Black men ($P < 0.001$)
Kuriyama et al. (2005) Population-based cohort in Miyagi Prefecture Japan 1984–1992	12 485 Men Incidence 15 054 Women Incidence	Liver ICD-9: 155.0–155.2 Liver ICD-9: 155.0–155.2	BMI 18.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 [P_{trend}] BMI 18.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 [P_{trend}]	 55 9 5 – 220 7 4 –	 1.00 0.80 (0.40–1.63) 1.14 (0.46–2.87) – [0.92] 1.00 1.30 (0.54–3.16) 0.91 (0.30–2.80) – [0.94]	Age, smoking, alcohol consumption, consumption of red meat, fruits and vegetables, and bean paste, type of health insurance; for women, also adjusted for menopausal status, parity, age at menarche, age at first pregnancy	
Jee et al. (2008) Cohort from National Health Insurance Corporation Republic of Korea 1992–2006	770 556 Men Incidence	Liver	BMI < 20.0 20.0–22.9 23.0–24.9 25.0–29.9 ≥ 30.0 [P_{trend}]	 862 3260 2463 2062 112	 0.90 (0.81–1.00) 0.97 (0.90–1.04) 1.00 1.04 (0.96–1.13) 1.63 (1.27–2.10) [0.0002]	Age, smoking	

Table 2.2.4a (continued)

Reference Cohort Location Follow-up period	Total no. of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Jee et al. (2008) (cont.)	423 273 Women Incidence	Liver	BMI < 20.0 20.0–22.9 23.0–24.9 25.0–29.9 ≥ 30.0 [P_{trend}]	 195 505 411 587 63	 0.85 (0.67–1.06) 0.76 (0.64–0.91) 1.00 1.14 (1.97–1.35) 1.39 (1.00–1.94) [< 0.0001]	Age, smoking	
Whitlock et al. (2009) Pooled analysis of 57 cohort studies Europe, Japan, and USA Follow-up varied by cohort	894 576 Men and women Mortality	Liver ICD-9: 155	BMI For BMI 15–25 For BMI 25–50 For BMI 15–50	 201 221 422	 1.37 (0.87–2.15) 1.61 (1.26–2.05) 1.47 (1.26–1.71)	Study, sex, age, smoking	
Parr et al. (2010) Pooled analysis of 39 cohort studies Asia, Australia, and New Zealand 1961–1999, median follow-up 4 yr	326 387 Men and women Mortality	Liver ICD-9: 155 ICD-10: C22	BMI 12.0–18.4 18.5–24.9 25–29.99 ≥ 30 per 5 kg/m^2 [P_{trend}]	774	 1.13 (0.78–1.64) 1.00 (0.89–1.13) 1.06 (0.83–1.36) 1.10 (0.63–1.91) 1.11 (0.94–1.31) [0.58]	Age, sex, smoking status	
Borena et al. (2012) Me-Can cohorts Austria, Norway, and Sweden 1972–2006, follow-up varied by cohort	578 700 Incidence and mortality	Liver, primary cancer ICD-7: 155.0	BMI, quintiles (mean) Q1 (20.7) Q2 (23.0) Q3 (24.7) Q4 (26.8) Q5 (31.3) [P_{trend}]	 36 38 45 53 94	 1.00 0.91 (0.55–1.51) 0.97 (0.59–1.57) 1.02 (0.63–1.64) 1.92 (1.23–2.96) [0.001]	Age, smoking status, cohort, year of birth, sex	

Table 2.2.4a (continued)

Reference Cohort Location Follow-up period	Total no. of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Li et al. (2013) JACC cohort Japan 1988–2009	31 018 Men Mortality	Liver ICD-10: C22.0–22.9	BMI at baseline			Age, smoking status, alcohol consumption, physical activity, intake of coffee and fish, education level, area of residence, diabetes, gall bladder disease, blood transfusions, history of liver disease	In stratified analyses, significant associations were observed in men without liver disease (P_{trend} = 0.03)
			< 18.5	32	1.42 (0.93–2.15)		
			18.5–20.9	82	1.09 (0.81–1.48)		
			21–22.9	88	1.00		
			23–24.9	73	1.04 (0.76–1.42)		
			≥ 25	63	1.15 (0.83–1.60)		
			[P_{trend}]		[0.37]		
			BMI at age 20 yr				
			< 18.5	14	0.74 (0.42–1.29)		
			18.5–20.9	91	0.89 (0.68–1.18)		
			21–22.9	115	1.00		
			23–24.9	75	0.92 (0.69–1.24)		
			≥ 25	43	0.91 (0.64–1.31)		
			[P_{trend}]		[0.54]		
			Weight change (kg), age 20 yr to baseline				
			≤–10.0	27	0.68 (0.43–1.08)		
			–9.9 to –5.0	76	1.08 (0.80–1.46)		
			–4.9 to 4.9	124	1.00		
			5.0 to 9.9	55	1.06 (0.77–1.47)		
			≥ 10.0	56	0.98 (0.70–1.37)		
			[P_{trend}]		[0.88]		

Table 2.2.4a (continued)

Reference Cohort Location Follow-up period	Total no. of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Li et al. (2013) (cont.)	41 455 Women Mortality	Liver ICD-10: C22.0–22.9	BMI at baseline			Age, smoking status, alcohol consumption, physical activity, intake of coffee and fish, education level, area of residence, diabetes, gall bladder disease, blood transfusions, history of liver disease	
			< 18.5	8	0.74 (0.35–1.60)		
			18.5–20.9	36	1.08 (0.69–1.68)		
			21–22.9	42	1.00		
			23–24.9	41	1.16 (0.75–1.79)		
			≥ 25	62	1.42 (0.95–2.13)		
			[P_{trend}]		[0.10]		
			BMI at age 20 yr				
			< 18.5	11	0.98 (0.58–1.64)		
			18.5–20.9	17	0.85 (0.58–1.25)		
			21–22.9	28	1.00		
			23–24.9	13	0.91 (0.60–1.38)		
			≥ 25	14	0.73 (0.45–1.18)		
			[P_{trend}]		[0.18]		
			Weight change (kg), age 20 yr to baseline				
			≤–10.0	10	0.68 (0.34–1.40)		
			–9.9 to –5.0	24	0.83 (0.51–1.35)		
			–4.9 to 4.9	62	1.00		
			5.0 to 9.9	46	1.31 (0.89–1.94)		
			≥ 10.0	47	1.41 (0.94–2.11)		
			[P_{trend}]		[0.08]		
Bhaskaran et al. (2014) Clinical Practice Research Datalink United Kingdom 1987–2012	5 243 978 Men and women Incidence	Liver ICD-10: C22	BMI per 5 kg/m^2 [P_{trend}]	1859 total	1.19 (1.12–1.27) [< 0.0001]	Age, sex, diabetes, smoking, alcohol consumption, socioeconomic status, calendar year	Similar association in never-smokers only

AFP, α-fetoprotein; ALT, alanine aminotransferase; BMI, body mass index (in kg/m^2); CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICD, International Classification of Diseases; JACC, Japan Collaborative Cohort Study for Evaluation of Cancer Risk; Me-Can, Metabolic Syndrome and Cancer Project; NOS, not otherwise specified; SD, standard deviation; WC, waist circumference; yr, year or years

Table 2.2.4b Case–control studies of measures of body fatness and hepatocellular carcinoma

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Pan et al. (2004) Canada 1994–1997	Men: 225 Women: 84 Population	BMI 1 yr before diagnosis Men: < 25 25– < 30 ≥ 30 [P_{trend}] Women: < 25 25– < 30 ≥ 30 [P_{trend}]	225 total 85 total 	 1.00 0.99 (0.72–1.38) 1.30 (0.85–1.97) [0.31] 1.00 0.61 (0.35–1.07) 0.94 (0.48–1.84) [0.40]	Age, geographical region, education level, smoking, physical activity, total calorie intake, total vegetable consumption, dietary fibre intake, multivitamin intake; for women, also adjusted for menopausal status, parity, age at menarche, age at end of first pregnancy	Self-reported BMI
Polesel et al. (2009) Italy 1999–2003	185 Hospital	BMI 1 yr before interview < 25 25– < 30 ≥ 30 5 kg/m² increase BMI at age 30 yr < 25 ≥ 25 5 kg/m² increase BMI increase from age 30 yr < 1 1– < 4 ≥ 4	 71 76 38 109 69 73 53 52	 1.00 1.0 (0.5–1.9) 1.9 (0.9–3.9) 1.1 (0.8–1.5) 1.00 1.0 (0.6–1.7) 0.8 (0.6–1.2) 1.00 1.2 (0.6–2.4) 1.6 (0.8–3.2)	Centre, sex, age, education, drinking status, lifetime maximal alcohol consumption, smoking status, cigarettes smoked per day, HBsAg and/or anti-HCV positivity	BMI calculated from self-reported weights and heights
Welzel et al. (2011) USA 1993–2005	3649 Population	WC (≥ 40 inches [101 cm] in men, ≥ 35 inches [89 cm] in women)	308 total	1.93 (1.71–2.18)	Age, sex, race, geographical location, Medicare/Medicaid dual enrolment	
Archambeaud et al. (2015) France 2007–2010	200 Hospital	Maximum BMI < 30 ≥ 30	125 total 	 1.00 1.56 (1.02–2.37)	Sex, age, diabetes, smoking (past or present)	

Table 2.2.4b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Hassan et al. (2015) USA 2004–2013	Men: 473 Women: 149 Population	Normal weight (reference)			Sex, age, ethnicity, education level, HCV, HBV, alcohol consumption, cigarette smoking, history of diabetes, physical activity, family history of cancer	BMI calculated from self-reported weights and heights at different ages; overweight and obesity defined as BMI 24–29.9 and BMI ≥ 30, respectively
		Overweight at different ages				
			Men:			
		Mid-20s	124	1.5 (0.9–2.3)		
		Mid-30s	172	1.3 (0.9–2.1)		
		Mid-40s	174	0.9 (0.6–1.4)		
		Mid-50s	170	0.5 (0.3–0.9)		
			Women:			
		Mid-20s	11	2.4 (0.9–3.0)		
		Mid-30s	19	1.2 (0.5–2.6)		
		Mid-40s	29	0.8 (0.4–1.6)		
		Mid-50s	35	0.9 (0.5–1.7)		
		Obesity at different ages				
			Men:			
		Mid-20s	33	1.8 (0.8–4.1)		
		Mid-30s	58	3.1 (1.6–6)		
		Mid-40s	101	2.2 (1.2–4)		
		Mid-50s	104	0.8 (0.4–1.4)		
			Women:			
		Mid-20s	13	5.2 (1.6–7.2)		
		Mid-30s	15	3.3 (1.3–8.6)		
		Mid-40s	26	2.1 (1.1–4.5)		
		Mid-50s	30	1.2 (0.5–2.5)		
		Obesity in early adulthood (mid-20s to mid-40s)	Men: 192	2.3 (1.2–4.4)		
			Women: 54	3.6 (1.5–8.9)		

BMI, body mass index (in kg/m^2); CI, confidence interval; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; WC, waist circumference

Table 2.2.4c Meta-analyses of measures of body fatness and cancer of the liver

Reference	Total number of studies Total number of cases	Organ site	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
Larsson & Wolk (2007)	11 cohort studies (7 on overweight with 5037 cases, and 10 on obesity with 6042 cases)	Liver	BMI Overweight vs normal Obese vs normal	 1.17 (1.02–1.34) 1.89 (1.51–2.36)	Age and other covariates depending on study (calendar year, sex, race, diabetes, education, marital status, smoking, physical activity, diet, family history of cancer, alcohol consumption, occupational group, aspirin use, estrogen replacement therapy in women)	The relative risk for obesity compared with normal BMI was stronger in men than in women
Renehan et al. (2008)	4 cohort studies in men and 1 in women 2070	Liver	BMI per 5 kg/m^2 increase	Men: 1.24 (0.95–1.62) Women: 1.07 (0.55–2.08)	NR	Results are from random-effects models. Substantial heterogeneity was observed (I^2 = 83.1% in men)
Chen et al. (2012)	26 prospective cohort studies 25 337	Liver (primary cancer)	BMI < 25 25–29.9 ≥ 30 BMI < 25 25–29.9 ≥ 30 BMI < 25 25–29.9 ≥ 30	All: 1.00 1.48 (1.31–1.67) 1.83 (1.59–2.11) Men: 1.00 1.42 (1.22–1.65) 1.91 (1.51–2.41) Women: 1.00 1.18 (1.08–1.30) 1.55 (1.30–1.85)	Age (all studies), and most of the studies included alcohol consumption, HBV and/or HCV infection, diabetes mellitus	Significant heterogeneity in the overall analyses, and in analyses in men; effects significantly different in men vs women; associations independent of geographical location, alcohol consumption, diabetes, or HBV/HCV infections
Rui et al. (2012)	8 cohort studies in men and women 11 616	Liver	BMI 18.5–24.9 25–30 ≥ 30	 1.00 1.13 (1.05–1.21) 2.09 (1.72–2.45)	NR	Associations remained significant after excluding 3 studies on cirrhosis cohorts

Table 2.2.4c (continued)

Reference	Total number of studies Total number of cases	Organ site	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
Tanaka et al. (2012)	9 cohort studies and 3 case–control studies NR	Liver	BMI per 1 kg/m² increase	1.13 (1.07–1.20)	Different adjustment factors depending on study (hepatitis, alcohol consumption, diabetes, smoking)	Study restricted to Japanese populations Overweight/obese individuals showed a 74% increased risk compared with those with normal weight
Wang et al. (2012)	21 prospective cohort studies (11 in men and 5 in women) 17 624	Liver (primary cancer)	BMI per 5 kg/m² increase	All: 1.39 (1.25–1.55) Men: 1.26 (1.11–1.44) Women: 1.18 (1.08–1.29)	Age (all studies). Other covariates, depending on study	Significant heterogeneity among studies was observed. Non-linear association was reported, with a steeper increase in risk from BMI > 32 kg/m²
WCRF/AICR (2015)	12 studies Men and women Incidence and mortality 14 311	Liver	BMI per 5 kg/m²	1.30 (1.16–1.46)		Heterogeneity between studies; non-linear associations; similar risks in men and women; associations stronger for incidence than for mortality, and for European vs Asian studies
	8 studies Men and women Incidence 11 530	Liver	BMI per 5 kg/m²	1.43 (1.19–1.70)		
	4 studies Men and women Mortality 2543	Liver	BMI per 5 kg/m²	1.13 (1.00–1.28)		
	8 studies Men Incidence and mortality 11 180	Liver	BMI per 5 kg/m²	1.21 (1.02–1.44)		

Table 2.2.4c (continued)

Reference	Total number of studies Total number of cases	Organ site	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
WCRF/AICR (2015) (cont.)	4 studies Women Incidence and mortality 2337	Liver	BMI per 5 kg/m²	1.21 (1.10–1.33)		
	Meta-analysis of European studies: 4 studies Men and women Incidence and mortality 588	Liver	BMI per 5 kg/m²	1.59 (1.35–1.87)		
	Meta-analysis of Asian studies: 7 studies Men and women Incidence and mortality 12 520	Liver	BMI per 5 kg/m²	1.18 (1.04–1.34)		

BMI, body mass index (in kg/m²); CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; NR, not reported; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research

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2.2.5 Cancer of the gall bladder

Cancer of the gall bladder cancer is uncommon, and almost all gall bladder cancers are adenocarcinomas. In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and gall bladder cancer was *inadequate*. Since then, numberous individual studies and meta-analyses of anthropometric measures of body fatness and risk of gall bladder cancer have been published. Results are presented here for cohort studies with at least 50 cases (Table 2.2.5a) and for case–control studies (Table 2.2.5b) and meta-analyses (Table 2.2.5c).

(a) Cohort studies

There are at least 11 individual informative prospective studies of the associations of BMI or weight with gall bladder cancer incidence or mortality (Table 2.2.5a). No association was observed in three of these studies (Samanic et al., 2006; Ishiguro et al., 2008; Hemminki et al., 2011). Findings from the other eight prospective studies showed statistically significant positive association between BMI or weight and risk of gall bladder cancer (Calle et al., 2003; Samanic et al., 2004; Engeland et al., 2005; Kuriyama et al., 2005; Jee et al., 2008; Schlesinger et al., 2013; Bhaskaran et al., 2014; Borena et al., 2014), and in several of those studies there was a dose–response relationship. In a large study of nearly 1.2 million public servants in the Republic of Korea (Jee et al., 2008), the relative risk of gall bladder cancer incidence for BMI ≥ 30 kg/m^2 versus 23.0–24.9 kg/m^2 was 1.44 (95% CI, 0.98–2.12) in women (P_{trend} = 0.0007) and 1.65 (95% CI, 1.11–2.44) in men (P_{trend} = 0.0003). A large cohort study in the United Kingdom that included more than 5.2 million men and women also showed a statistically significant positive association between BMI and risk of gall bladder cancer (RR per 5 kg/m^2 increase, 1.31; 95% CI, 1.12–1.52; P_{trend} < 0.0001) (Bhaskaran et al., 2014). In a nationwide prospective study in the USA, there was evidence of a strong positive association between being obese (BMI ≥ 30 kg/m^2) and risk of gall bladder cancer mortality in both women (RR, 2.13; 95% CI, 1.56–2.90; P_{trend} < 0.001) and men (RR, 1.76; 95% CI, 1.06–2.95; P_{trend} = 0.02) (Calle et al., 2003).

In one study that assessed waist circumference in relation to risk of gall bladder cancer, each increase of 5 cm in waist circumference was associated with a 17% (95% CI, 1.06–1.30) higher risk in men and women combined (Schlesinger et al., 2013). [These results should be interpreted with caution because only 76 cases of gall bladder cancer were identified during follow-up in 359 156 men and women included in the analysis.]

The association between weight change and risk of gall bladder cancer was also examined in the EPIC cohort. Average annual weight change from age 20 years to the age at cohort enrolment was not associated with risk of gall bladder cancer (Schlesinger et al., 2013).

(b) Case–control studies

Of the case–control studies that examined the association between BMI and risk of gall bladder cancer (Table 2.2.5b), seven showed no association (Strom et al., 1995; Serra et al., 2002; Máchová et al., 2007; Grainge et al., 2009; Nakadaira et al., 2009; Alvi et al., 2011; Cha, 2015), whereas in three studies there was a statistically significant positive association between adult BMI and risk of gall bladder cancer, which appeared to be dose-related (Zatonski et al., 1997; Ahrens et al., 2007; Hsing et al., 2008).

(c) Pooled analyses and meta-analyses

There have been one pooled analysis (Whitlock et al., 2009; Table 2.2.5a) and several meta-analyses of cohort and case–control studies (Larsson & Wolk, 2007; Renehan et al., 2008; Tan et al., 2015; WCRF/AICR, 2015; Table 2.2.5c) that

examined the relationship between BMI and gall bladder cancer incidence or mortality.

All meta-results were significantly positive. In the largest and most recent meta-analysis (Tan et al., 2015), which included 12 prospective studies in Asia, Europe, and the USA, both overweight (RR, 1.15; 95% CI, 1.02–1.29) and obesity (RR, 1.62; 95% CI, 1.45–1.81) were statistically significantly positively associated with risk of gall bladder cancer. Similarly, results from the 2015 WCRF Continuous Update Project on BMI and risk of gall bladder cancer showed a statistically significant 25% (95% CI, 1.15–1.37) higher risk per 5 kg/m^2 increase reported in a dose–response analysis based on eight prospective studies (WCRF/AICR, 2015). In the WCRF analysis, associations were similar between cancer incidence and mortality, between men and women, and between studies in Asia and in Europe. In a meta-analysis of eight case–control studies, both overweight (RR, 1.16) and obesity (RR, 1.37) were associated with statistically significant higher risks of gall bladder cancer (Tan et al., 2015).

Table 2.2.5a Cohort studies of measures of body fatness and cancer of the gall bladder

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Calle et al. (2003) Cancer Prevention Study II (CPS II) USA 1982–1998	495 477 Women Mortality	Gall bladder and extrahepatic bile ducts ICD-9: 156.0–156.9	BMI 18.5–24.9 25–29.9 30–34 [P_{trend}]	 159 86 59	 1.00 1.12 (0.86–1.47) 2.13 (1.56–2.90) [< 0.001]	Age, education level, smoking, physical activity, alcohol consumption, marital status, race, aspirin use, fat consumption, vegetable consumption; for women, also adjusted for HRT use	
	404 576 Men Mortality		BMI 18.5–24.9 25–29.9 30–34 [P_{trend}]	 66 94 20	 1.00 1.34 (0.97–1.84) 1.76 (1.06–2.94) [0.02]		
Samanic et al. (2004) United States Veterans cohort USA 1969–1996	4 500 700 Men Incidence	Gall bladder and extrahepatic bile ducts ICD-9: 156	Obesity Non-obese Obese Non-obese Obese	 White men: 265 26 Black men: 45 2	 1.00 1.70 (1.13–2.57) 1.00 0.93 (0.23–3.86)	Age, calendar year	Obesity defined as discharge diagnosis of obesity: ICD-8: 277; ICD-9: 278.0
Engeland et al. (2005) Norwegian men and women Norway 1963–2002	1 037 892 Women Incidence	Gall bladder ICD-7: 155.1	BMI < 18.5 18.5–24.9 25.0–29.9 ≥ 30 [P_{trend}]	1087 total	 1.02 (0.54–1.91) 1.00 1.27 (1.10–1.47) 1.88 (1.60–2.21) [< 0.001]	Age, birth cohort, height	
	963 619 Men Incidence		BMI < 18.5 18.5–24.9 25.0–29.9 ≥ 30 [P_{trend}]	628 total	 0.31 (0.04–2.24) 1.00 1.00 (0.84–1.17) 1.38 (1.01–1.89) [0.2]		

Table 2.2.5a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Kuriyama et al. (2005) Japanese men and women Japan 1984–1992	15 054 Women Incidence	Gall bladder and extrahepatic bile ducts ICD-9: 156.0–156.9	BMI 18.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 [P_{trend}]	 12 3 5 4	 1.00 0.83 (0.23–2.98) 3.43 (1.19–9.94) 4.45 (1.39–14.23) [0.004]	Age, smoking, alcohol consumption, consumption of red meat, fruits and vegetables, and bean paste, type of health insurance; for women, also adjusted for menopausal status, parity, age at menarche, age at first pregnancy	
	12 485 Men Incidence		BMI 18.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 [P_{trend}]	 8 1 – – 	 1.00 0.46 (0.05–3.93) – – [0.48]		
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1958–1999	362 552 Men Incidence	Gall bladder ICD-7: 155.1	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 53 45 11 	 1.00 0.93 (0.62–1.39) 1.40 (0.73–2.70) [> 0.5]	Attained age, calendar year, smoking	
Ishiguro et al. (2008) Japan Public Health Center Japan 1990–2004	53 187 Women Incidence	Gall bladder ICD-O-3: C23.9, C24.0	BMI < 23 23.0–24.9 25.0–26.9 ≥ 27.0 [P_{trend}]	 35 9 8 11 	 1.00 0.47 (0.22–0.98) 0.62 (0.29–1.34) 0.94 (0.48–1.88) [0.50]	Age, study area, cholelithiasis, diabetes, smoking, alcohol consumption	
	48 681 Men Incidence		BMI < 23 23.0–24.9 25.0–26.9 ≥ 27.0 [P_{trend}]	 14 6 6 4 	 1.00 0.74 (0.28–1.92) 1.26 (0.48–3.33) 1.39 (0.45–4.34) [0.52]		

Table 2.2.5a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Ishiguro et al. (2008) (cont.)	101 868 Men and women Incidence		BMI < 23 23.0–24.9 25.0–26.9 ≥ 27.0 [P_{trend}]	 49 15 14 15	 1.00 0.55 (0.31–0.98) 0.80 (0.44–1.46) 1.06 (0.59–1.90) [0.82]		
Jee et al. (2008) Cohort from the National Health Insurance Corporation Republic of Korea 1992–2006	443 273 Women Incidence	Gall bladder (NOS)	BMI < 20.0 20.0–22.9 23.0–24.9 25.0–29.9 ≥ 30.0 [P_{trend}]	 121 302 262 341 36	 0.97 (0.78–1.21) 1.12 (0.90–1.41) 1.00 1.27 (1.02–2.12) 1.44 (0.98–2.12) [0.0007]	Age, smoking	Excluded first 2 yr of follow-up Update of study by Oh et al. (2005)
	770 556 Men Incidence		BMI < 20.0 20.0–22.9 23.0–24.9 25.0–29.9 ≥ 30.0 [P_{trend}]	 246 787 670 542 31	 0.80 (0.68–0.94) 0.86 (0.77–0.96) 1.00 0.97 (0.86–1.10) 1.65 (1.11–2.44) [0.0003]		
Whitlock et al. (2009) Pooled analysis of 57 cohort studies Europe, Japan, and USA Follow-up varied by cohort	894 576 Men and women Mortality	Gall bladder and extrahepatic bile ducts ICD-9: 156	BMI, per 5 kg/m^2	120	1.29 (0.90–1.85)	Age, sex, smoking status, study	
Hemminki et al. (2011) Swedish hospital patients Sweden 1964–2006	30 020 Men and women Incidence	Gall bladder ICD-7: 155.1	Obesity Observed vs expected rates	19	SIR 1.55 (0.93–2.43)	Age, sex, time period, region, SES	Overlap with study by Wolk et al. (2001) is unclear Obesity defined as hospital discharge diagnosis

Table 2.2.5a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Schlesinger et al. (2013) EPIC cohort 10 European countries 1992–2010	359 156 (191 856 for weight change) Men and women Incidence	Gall bladder ICD-10: C23.9	BMI, per 5 kg/m²	76 total	1.28 (0.99–1.65) 0.70 (0.43–1.15)*	Age, sex, study centre, education level, smoking, alcohol consumption, height *additional adjustment for WC **additional adjustment for BMI	
			Baseline weight, per 5 kg	76 total	1.11 (1.00–1.22)		
			Weight change (kg/year)	37 total	1.76 (0.59–5.29)		
			WC, per 5 cm	76 total	1.17 (1.06–1.30) 1.33 (1.10–1.62)**		
Bhaskaran et al. (2014) Clinical Practice Research Datalink United Kingdom 1987–2012	5 243 978 Men and women Incidence	Gall bladder ICD-10: C23	BMI per 5 kg/m² [P_{trend}]	303 total	HR (99% CI) 1.31 (1.12–1.52) [< 0.0001]	Age, sex, diabetes, smoking, alcohol consumption, SES, calendar year	
Borena et al. (2014) Metabolic Syndrome and Cancer Project (Me-Can) cohort Austria, Norway, and Sweden 1972–2006	578 700 Men and women Incidence	Gall bladder ICD-7: 155.1	BMI, quintiles (mean)			Smoking status, baseline age, cohort, sex, year of birth	
			Q1 (20.7)	20	1.00		
			Q2 (23.0)	26	1.12 (0.58–2.19)		
			Q3 (24.7)	38	1.49 (0.80–2.76)		
			Q4 (26.8)	47	1.70 (0.93–3.09)		
			Q5 (31.3)	53	1.94 (1.08–3.51)		
			[P_{trend}]		[0.08]		
			BMI				
			< 25	77	1.00		
			≥ 25	107	1.52 (1.12–2.10)		

BMI, body mass index (in kg/m²); CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; HRT, hormone replacement therapy; SES, socioeconomic status; SIR, standardized incidence ratio; WC, waist circumference

Table 2.2.5b Case–control studies of measures of body fatness and cancer of the gall bladder

Reference Study location Period	Total number of cases Total number of controls Source of controls	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding
Strom et al. (1995) Bolivia and Mexico 1984–1988	84 126 Men and women Hospital		BMI, most of adult life < 24 24–25.9 26–28 > 28 BMI, maximum ever < 24 24–25.9 26–28 > 28	 33 17 12 3 12 15 22 19	 1.0 1.5 (0.5–4.6) 2.2 (0.7–8.4) 1.6 (0.4–6.1) 1.0 1.6 (0.4–7.6) 1.3 (0.3–5.6) 2.6 (0.5–18.6)	Age, sex, country
Zatonski et al. (1997) Australia, Canada, The Netherlands, and Poland 1983–1988	Men: 44 815 Population Women: 152 700 Population		BMI, quartiles Q1 Q2 Q3 Q4 [P_{trend}] BMI, quatiles Q1 Q2 Q3 Q4 [P_{trend}]	Men: 9 11 13 11 Women: 30 37 22 56	 1.0 1.0 (0.3–3.0) 0.7 (0.3–2.0) 1.0 (0.3–2.8) [0.74] 1.0 1.7 (0.9–3.1) 1.5 (0.3–3.0) 2.1 (1.2–3.8) [0.02]	
Serra et al. (2002) Chile 1992–1995	114 114 Hospital		BMI < 25 25–29.9 ≥ 30	 53 42 19	 1.0 0.8 (0.4–1.4) 0.9 (0.4–1.8)	Age, sex
Ahrens et al. (2007) Europe 1995–1997	104 1401 (men only) Population	Gall bladder ICD-O: C23.9	BMI ≤ 25 25– < 27 27– < 30 ≥ 30	62 total	 1.0 1.8 (0.4–7.2) 11.0 (2.9–41.9) 13.3 (1.4–123)	Age, country, history of gallstones

Table 2.2.5b (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding
Máchová et al. (2007) Czech Republic 1987–2002	93 37 772 Population		BMI Men: 18.5–24.9 25–30 ≥ 30 Women: 18.5–24.9 25–30 ≥ 30	 14 total 79 total 	 1.00 1.01 (0.24–4.32) 0.76 (0.08–7.41) 1.00 1.07 (0.58–1.95) 0.73 (0.36–1.50)	Age, smoking, height, hypertension
Hsing et al. (2008) China 1997–2001	627 959 Population	Gall bladder, excluding extrahepatic bile ducts and ampulla of Vater	Usual adult BMI < 18.5 18.5–22.9 23.0–24.9 ≥ 25 [P_{trend}] Maximum adult BMI < 18.5 18.5–22.9 23.0–24.9 ≥ 25 [P_{trend}] BMI change in adulthood ≤ 0.74 0.75–2.77 2.78–5.21 > 5.21 [P_{trend}]	 17 30 73 145 6 74 83 185 74 62 86 93 	 0.62 (0.35–1.09) 1.0 1.20 (0.85–1.68) 1.56 (1.17–2.10) [< 0.001] 1.24 (0.47–3.29) 1.00 1.35 (0.94–1.95) 1.48 (1.08–2.03) [0.02] 1.00 0.93 (0.62–1.39) 1.45 (0.98–2.14) 1.47 (1.00–2.16) [0.01]	Age (continuous), sex (male, female), and education level (none/ primary, junior middle, senior, some college)
Grainge et al. (2009) United Kingdom 1987–2002	184 3007 Population	Gall bladder, excluding cholangiocarcinomas and unspecified biliary tract cancers	BMI < 25 25–29.9 ≥ 30	 36 31 19	 1.00 1.03 (0.62–1.72) 1.51 (0.83–2.75)	Smoking, alcohol consumption, NSAID use

Table 2.2.5b (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding
Nakadaira et al. (2009) Hungary 2003–2006	41 30 Hospital		BMI ≤ 24.9 25–29.9 ≥ 30	 13 9 19	 1.0 1.5 (0.4–5.0) 0.8 (0.3–1.8)	Age
Alvi et al. (2011) Pakistan 1988–2007	60 120 (70% of cases were women) Hospital		BMI < 23 > 23	 14 46	 1.00 1.98 (0.62–6.28)	Sex, hypertension, diabetes, smoking
Shebl et al. (2011) China 1997–2001	627 959 Population	Gall bladder, excluding extrahepatic bile ducts and ampulla of Vater	WC (cm) Low High (men: ≥ 90; women: ≥ 80)	 83 111	 1.00 0.98 (0.65–1.47)	Age, sex, BMI
Cha (2015) Republic of Korea 2008–2013	78 78 Population		BMI < 23 ≥ 23	 18 23	 1.00 0.74 (0.28–1.97)	Age, sex, hypertension, diabetes mellitus, vascular occlusive disease, alcohol consumption, smoking, polypoid lesions of gall bladder, gallstone disease

BMI, body mass index (in kg/m^2); CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug; WC, waist circumference

Table 2.2.5c Meta-analyses of measures of body fatness and cancer of the gall bladder

Reference Period	Number and type of studies	Population Incidence/mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates, comments
Larsson & Wolk (2007) 1966–2007	8 cohort studies	Men and women Incidence and mortality	Obese vs normal (definition varies by study)		1.69 (1.48–1.92)	See also Table 2.2.5b
	8 cohort studies, 4 case–control studies	Men and women Incidence and mortality	Obese vs normal (definition varies by study)	-	1.66 (1.47–1.88)	
Renehan et al. (2008) 1966–2007	2 cohort studies	Women Incidence	BMI, per 5 kg/m²	1111 total	1.59 (1.02–2.47)	Also split up by geographical region
	4 cohort studies	Men Incidence	BMI, per 5 kg/m²	928 total	1.09 (0.99–1.21)	
Tan et al. (2015) Cohort studies: 1964–2006	12 cohort studies	Men and women Incidence and mortality	Overweight Obese	5101 total	1.15 (1.02–1.29) 1.62 (1.45–1.81)	Normal BMI used as reference
Case–control studies: 1984–2007	8 case–control studies		Overweight Obese		1.16 (0.96–1.41) 1.37 (1.10–1.71)	
	12 cohort studies, 8 case–control studies		BMI Overall: 25–30 > 30 Men: 25–30 > 30 Women: 25–30 > 30		 1.14 (1.04–1.25) 1.56 (1.41–1.73) 1.06 (0.94–1.20) 1.42 (1.21–1.66) 1.26 (1.13–1.40) 1.67 (1.38–2.02)	
WCRF/AICR (2015) NR	8 cohort studies	Men and women Incidence and mortality	BMI, per 5 kg/m²	6004 total	1.25 (1.15–1.37)	

BMI, body mass index (in kg/m²); CI, confidence interval; ICD, International Classification of Diseases; NR, not reported; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research

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2.2.6 Cancers of the biliary tract

Intrahepatic bile duct cancers occur in the smaller bile duct branches within the liver and comprise about 10% of bile duct cancers. Extrahepatic bile duct cancers occur outside of the liver. Perihilar (also called hilar) extrahepatic bile duct cancers occur where the left and right hepatic ducts join and are the most common type of bile duct cancer, accounting for about two thirds of all bile duct cancers. Nearly all bile duct cancers are cholangiocarcinomas, of which most are adenocarcinomas. This section reviews studies of all subtypes of cancer of the biliary tract.

(a) Cohort studies

See Table 2.2.6a (web only; available at: http://publications.iarc.fr/570).

Only one prospective study (i.e. the EPIC cohort) assessed the association between body weight and intrahepatic bile duct cancer specifically; relative risk estimates for all measurements (BMI, weight, waist or hip circumference, waist-to-hip ratio, or weight change) as continuous measures were greater than 1, but none of the associations were statistically significant (Schlesinger et al., 2013).

The association between BMI and extrahepatic bile duct cancer specifically (excluding the gall bladder) was examined in the Japan Public Health Center Study. In that study, BMI was positively associated with risk in men and women combined, with a relative risk of 1.78 for BMI ≥ 27 kg/m^2 compared with < 23 kg/m^2 (P_{trend} = 0.03) (Ishiguro et al., 2008).

The association between BMI and intra- or extrahepatic bile duct cancer was examined in the Korea National Health Insurance Corporation Study, which included only men and found a statistically significant positive dose–response relationship (P_{trend} = 0.005) (Oh et al., 2005).

The association between BMI and cancer of the bile ducts and gall bladder combined was examined in two prospective studies. In the Japan Public Health Center Study, the relative risk estimates for the highest versus lowest categories of BMI in men and in women were greater than 1 but were not statistically significant (Ishiguro et al., 2008). In the EPIC study, in which cancers of the extrahepatic bile ducts included cancers of the gall bladder, associations of BMI and weight in men and women combined were not statistically significant. [The median BMI in the highest tertile was 29.9 kg/m^2 for men and 29.6 kg/m^2 for women, which includes people with a BMI in the overweight and obese category.] Similarly, no association was found with average annual weight change from age 20 years, or with waist circumference (Schlesinger et al., 2013).

In a meta-analysis of gall bladder or biliary tract cancer incidence or mortality that included seven studies, BMI was statistically significantly positively associated with risk in men and women combined (RR for highest vs lowest category of BMI, 1.40; 95% CI, 1.15–1.65) (Park et al., 2014).

(b) Case–control studies

See Table 2.2.6b (web only; available at: http://publications.iarc.fr/570).

The associations of BMI with cancers of the biliary tract system (including gall bladder or not) were examined in six population- or hospital-based case–control studies.

For extrahepatic bile duct cancer, two population-based case–control studies, one in Europe (Ahrens et al., 2007) and one in China (Hsing et al., 2008), showed a statistically significant higher risk for BMI > 25 kg/m^2 versus 18.5–25 kg/m^2, whereas a lower risk with high BMI was observed in one study in China (Kato et al., 1989). No association was observed in a study of cholangiocarcinoma (Grainge et al., 2009). No association was observed with waist circumference in the only study that examined such association (Shebl et al., 2011).

For overall biliary tract cancer, a 2.5-fold increase in risk was observed with BMI ≥ 30 kg/m^2 at age 35 years, but not with BMI 1–5 years before study entry (Ahrens et al., 2007).

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2.2.7 Cancer of the pancreas

Cancer of the pancreas is the seventh leading cause of cancer death worldwide (Ferlay et al., 2015). Even in developed countries, few individuals diagnosed with pancreatic cancer survive more than 5 years (Sirri et al., 2016). Pancreatic cancer incidence and mortality rates have been increasing both in the USA (Kohler et al., 2015) and in western Europe (Bosetti et al., 2013), despite declines in cigarette smoking, an established risk factor for pancreatic cancer. It has been suggested that these increases may be at least partly attributable to increases in the prevalence of obesity (Ma & Jemal, 2013). Notably, type 2 diabetes mellitus, which is caused by obesity, is also an established risk factor for pancreatic cancer, and the incidence of diabetes is also increasing.

The great majority (> 85%) of pancreatic tumours are ductal adenocarcinomas and derive from the exocrine component of the pancreas. Other pancreatic tumours are a more heterogeneous collection of different tumour types and include, among others, acinar cell carcinoma of the pancreas (about 5% of exocrine pancreatic cancers), cystadenocarcinomas, adenosquamous carcinomas, pancreatic mucinous cystic neoplasms, and pancreatic neuroendocrine (islet cell) tumours (1–2% of all pancreatic cancers).

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and pancreatic cancer was *inadequate*. Because of the high case fatality of pancreatic cancer, results from studies of pancreatic cancer incidence and mortality can be considered comparable. Results from individual cohort studies with more than 100 cases of pancreatic cancer (Table 2.2.7a), from case–control studies (Table 2.2.7b), and from meta-analyses or pooled analyses (Table 2.2.7c) are summarized in this section.

(a) Cohort studies

Since 2000, more than 30 individual cohort studies including pooled analyses have reported on the associations of excess body fatness with pancreatic cancer incidence or mortality (Table 2.2.7a). In addition, seven meta-analyses of cohort studies have been published since then (Table 2.2.7c).

BMI, usually ascertained at study enrolment at or after middle age, was by far the most common measure of excess body weight examined in these cohort studies. In a comprehensive meta-analysis by the WCRF Continuous Update Project that included 23 cohort studies of pancreatic cancer incidence and more than 9500 incident cases of pancreatic cancer, the summary relative risk for a continuous 5 kg/m^2 increase in BMI was 1.10 (95% CI, 1.07–1.14), with similar results in men and in women (WCRF/AICR, 2012). Other meta-analyses or pooled cohort studies, all with considerable overlap in study populations, have reported similar results per 5 kg/m^2 increase in BMI (Larsson et al., 2007; Renehan et al., 2008; Genkinger et al., 2011, 2015).

The largest study that presented categorical BMI results was an analysis that included nearly 6000 pancreatic cancer deaths in White men and women in the Cancer Prevention Study II (Arnold et al., 2009). In that analysis, obesity (i.e. BMI ≥ 30 kg/m^2) was associated on average with a 40% higher risk of pancreatic cancer mortality compared with normal BMI (18.5– < 25 kg/m^2), and results were similar in men and in women separately. [No associations were found in Black men and women, but the sample size was very small compared with the group of White men and women.]

Relatively few large studies of BMI and pancreatic cancer have been conducted in populations that were not predominantly of European descent. Relative risks from the largest study in

African Americans, a pooled analysis of seven cohorts (Bethea et al., 2014), and from a study in the Republic of Korea with 1860 cases (Jee et al., 2008), the largest in an Asian population, appear consistent with those observed in meta-analyses of populations of Caucasians. However, BMI was not associated with risk of pancreatic cancer in a pooled analysis of the Asia Cohort Consortium (Lin et al., 2013b).

Some evidence suggests that the association between BMI and pancreatic cancer may differ by smoking status. In the large NIH-AARP cohort, there was a statistically significant interaction between BMI and smoking status, with a positive association between BMI and risk of pancreatic cancer in never-smokers and in former smokers but not in current smokers (Stolzenberg-Solomon et al., 2013). Similarly, increased BMI was associated with higher risk of pancreatic cancer in never-smokers and in former smokers in other studies, although these interactions were not statistically significant (Genkinger et al., 2011; Aune et al., 2012).

A limited number of individual cohort studies have examined the association between BMI in early adulthood, usually defined as age 18–21 years, and pancreatic cancer incidence or mortality (Patel et al., 2005; Lin, et al., 2007; Verhage et al., 2007; Stolzenberg-Solomon et al., 2013), with mixed results. [These studies calculated BMI in early adulthood based on weight in young adulthood recalled by participants who were middle-aged or older.]

The largest analysis of BMI in early adulthood, as well as BMI change after early adulthood in relation to pancreatic cancer mortality, is a pooled analysis including more than 3000 pancreatic cancer deaths from 14 cohorts (Genkinger et al., 2015). In that pooled analysis, an increase of 5 kg/m^2 in BMI in early adulthood was associated with a relative risk of 1.18 (95% CI, 1.11–1.25), and BMI change after early adulthood was also significantly associated with increased risk (RR per 5 kg/m^2 increase, 1.05, 95% CI, 1.01–1.10).

Several other individual cohort studies examined associations of change in weight (Samanic et al., 2006, Lin et al., 2007, Luo et al., 2008, Johansen et al., 2009) or change in BMI (Verhage et al., 2007) with risk of pancreatic cancer. None of these studies reported statistically significant associations, except for a study in Sweden that found higher risk in a small group of men with a weight increase of 15% or more in 6 years (Samanic et al., 2006) and another study that reported significant positive associations in a small group of men with a BMI increase of 8 kg/m^2 or more since age 20 years (Verhage et al., 2007).

Several individual cohort studies have examined associations of waist circumference with risk of pancreatic cancer (Larsson et al., 2005; Berrington de González et al., 2006; Luo et al., 2008; Stolzenberg-Solomon et al., 2008). In the WCRF meta-analysis, the relative risk per 10 cm increase in waist circumference was 1.11 (95% CI, 1.05–1.18) (WCRF/AICR, 2012). In addition, waist circumference was examined in a large pooled analysis of pancreatic cancer mortality including data from 11 cohort studies (Genkinger et al., 2015); a higher waist circumference was associated with increased risk of pancreatic cancer mortality (RR per 10 cm increase, 1.07; 95% CI, 1.00–1.14), and no differences in risk were observed between men and women.

(b) Case–control studies

A total of 15 independent case–control studies, conducted in Canada, China, Europe, Japan, North Africa (Egypt), and the USA, reported on the association of BMI with cancer of the pancreas (Table 2.2.7b). In all studies, the assessment of BMI was based on self-reported height and usual body weight or body weight during a relatively recent time frame before cancer diagnosis. In a few studies, additional self-reports were also obtained for body weight

up to 20 years before cancer diagnosis, or body weight at various pre-specified ages in the more distant past. In all but two studies (Pezzilli et al., 2005; Lo et al., 2007), the estimated association of BMI with risk of pancreatic cancer was adjusted for smoking, as well as for various other potential confounding factors.

For usual BMI before disease onset, 7 of the 14 studies reported statistically significant increases in risk, either overall or in sex-stratified analyses (Silverman et al., 1998; Hanley et al., 2001; Eberle et al., 2005; Anderson et al., 2009; Li et al., 2009; Halfdanarson et al., 2014; Zheng et al., 2016).

Of the remaining studies, the majority showed odds ratios above 1.0. In studies presenting sex-stratified analyses, positive associations with BMI appeared to be somewhat stronger and more often significant for men than for women (Hanley et al., 2001; Silverman, 2001; Eberle et al., 2005; Fryzek et al. 2005; Li et al., 2009).

The study by Fryzek et al. (2005) in the USA showed inverse associations of current BMI (at diagnosis) and cancer of the pancreas and no association with BMI 5 years before interview. However, analyses based on recalled BMI 20 years before interview showed a statistically significant direct association with risk of pancreatic cancer, although in men only. In a similar type of analysis, a case–control study in the Czech Republic and Slovakia (Urayama et al., 2011) also showed a statistically significant association of pancreatic cancer with recalled BMI at age 20 years and at age 40 years, but not with BMI 2 years before interview (OR, 0.98; 95% CI, 0.85–1.13).

In two studies, associations of BMI with risk of pancreatic cancer were estimated separately for never-smokers and ever-smokers.

In the USA, Fryzek et al. (2005) reported a statistically significant and up to 3.3-fold increase in risk of pancreatic cancer (95% CI, 1.2–9.2) only in never-smokers in the highest category of BMI compared with those with low BMI, and no relationship was found in smokers. A second study, also in the USA (Li et al., 2009), reported a positive association of BMI with risk of pancreatic cancer both in ever-smokers (OR per 5 kg/m^2 increase, 1.75; 95% CI, 1.37–2.22) and in never-smokers (OR, 1.46; 95% CI, 1.16–1.84).

One case–control study in the USA (with 309 cases and 602 controls) specifically addressed the association of BMI with pancreatic neuroendocrine tumours, a rare pancreatic cancer tumour, and observed an increased risk in individuals who were obese (BMI ≥ 30 kg/m^2) compared with those with a lower BMI (OR, 1.65; 95% CI, 1.11–2.45) (Halfdanarson et al., 2014).

Table 2.2.7a Cohort studies of measures of body fatness and cancer of the pancreas

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Friedman & van den Eeden (1993) Nested case–control study within Kaiser Permanente USA 1964–1988	450 cases, 2687 controls Men and women Incidence	Pancreas	BMI, per 1 kg/m² increase Weight, per 5 kg	450	1.02 (1.00–1.04) 1.06 (1.01–1.11)	Age, cigarette smoking, race	
Gapstur et al. (2000) Chicago Heart Association Detection Project in Industry Cohort USA 1967–1995	20 475 Men Mortality 15 183 Women Mortality	Pancreas ICD-8: 157	BMI < 24.129 24.129–26.292 26.293–28.630 ≥ 28.631 BMI < 20.978 20.978–23.240 23.241–26.156 ≥ 26.157	 10 21 23 42 9 6 16 12	 1.00 1.76 (0.83–3.74) 1.68 (0.80–3.53) 3.04 (1.52–6.08) 1.00 0.48 (0.17–1.26) 1.09 (0.47–2.51) 0.73 (0.30–1.80)	Age Age	
Isaksson et al. (2002) Swedish Twin Registry Sweden 1969–1997	21 884 Men and women Incidence	Pancreas	BMI < 18.5 18.5–24.99 25–30 > 30	 5 84 70 4	 2.30 (0.93–5.71) 1.00 1.36 (0.99–1.88) 0.56 (0.20–1.52)	Age, sex, smoking	No associations were observed for adult weight gain (in kg)
Samanic et al. (2004) United States Veterans cohort USA 1969–1996	4 500 700 Men Incidence	Pancreas ICD-9: 157	Obesity Non-obese Obese Non-obese Obese	 White men: 5483 391 Black men: 1638 83	 1.00 1.20 (1.07–1.33) 1.00 1.07 (0.86–1.34)	Age, calendar year	Obesity defined as discharge diagnosis of obesity: ICD-8: 277; ICD-9: 278.0

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Batty et al. (2005) Whitehall Study United Kingdom 1967–2002	18 403 Men Mortality	Pancreas ICD-8/9: 157 ICD-10: C25	BMI 18.5–24.9 25.0–29.9 ≥ 30 [P_{trend}]	 75 69 3	 1.00 1.18 (0.83–1.68) 0.58 (0.18–1.91) [0.80]	Age, employment grade, physical activity, smoking, marital status, prevalent disease, weight loss in past year, BP medication, height, skinfold thickness, systolic BP, plasma cholesterol, glucose intolerance, diabetes	
Larsson et al. (2005) Swedish Mammography Cohort (SMC) Sweden 1987–2004 Cohort of Swedish Men (COSM) Sweden 1997–2004	83 053 Men and women Incidence	Pancreas ICD-9: 157, excluding 157.4	BMI < 20 20–24.9 25–29.9 ≥ 30 [P_{trend}] WC (cm), quartiles (sex-specific) Men: Women: < 90 < 76 90–94 76–81 95–101 82–89 ≥ 102 ≥ 90 [P_{trend}]	 5 50 54 19 16 20 34 36	 0.96 (0.38–2.46) 1.00 1.25 (0.84–1.86) 1.81 (1.04–3.15) [0.04] 1.00 1.15 (0.59–2.25) 1.59 (0.87–2.93) 1.72 (0.93–3.20) [0.05]	Age, education level, physical activity, smoking, alcohol consumption, sex	In stratified analyses, stronger associations with BMI in men than in women

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Patel et al. (2005) Cancer Prevention Study II (CPS II) Nutrition Cohort 1992–1999	145 627 Men and women Incidence and mortality	Pancreas ICD-9: 157.0–157.9 ICD-10: C25.0–25.9	BMI at baseline			Age, smoking, years since quitting smoking, education level, family history of pancreatic cancer, gall bladder disease, diabetes, height, energy intake, physical activity	In stratified analyses, association with BMI at baseline was stronger in men than in women
			< 25	50	1.00		
			25–29.9	33	1.03 (0.76–1.38)		
			≥ 30	22	2.08 (1.48–2.93)		
			[P_{trend}]		[0.0001]		
			BMI at age 18 yr				
			< 21	59	1.00		
			21–22.9	25	1.07 (0.77–1.49)		
			≥ 23	17	1.33 (0.95–1.85)		
			[P_{trend}]		[0.11]		
			Adult weight change (kg)				
			< –2.27	4	1.74 (0.94–3.22)		
			–2.27 to 4.54	20	1.00		
			4.55–9.07	18	1.12 (0.70–1.79)		
			9.08–13.61	21	0.97 (0.60–1.58)		
			≥ 13.62	38	0.96 (0.61–1.52)		
			[P_{trend}]		[0.16]		
Sinner et al. (2005) Iowa Women's Health Study USA 1986–2001	28 002 Women Incidence	Pancreas ICD-10: C25	BMI			Age, smoking status, multivitamin use	
			< 25	84	1.00		
			25–29.9	72	0.94 (0.69–1.29)		
			≥ 30	53	1.14 (0.81–1.62)		
Berrington de González et al. (2006) EPIC cohort 10 European countries 1991–2004	438 405 Men and women Incidence	Pancreas	BMI			Sex, smoking, diabetes Weight and WC estimates also adjusted for height	
			< 20	9	0.67 (0.33–1.37)		
			20–22.9	48	1.00		
			23–24.9	85	0.99 (0.69–1.41)		
			25–26.9	71	0.82 (0.56–1.19)		
			27–29.9	43	0.76 (0.50–1.16)		
			30–34.9	50	1.16 (0.77–1.76)		
			≥ 35	13	1.19 (0.64–2.23)		
			per 5 kg/m^2		1.09 (0.95–1.24)		
			[P_{trend}]		[0.24]		

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Berrington de González et al. (2006) (cont.)			Weight (kg), quartiles (sex-specific) Men: Women: < 73 < 58 73–79 58–63 80–87 64–71 ≥ 88 ≥ 72 per 5 kg [P_{trend}]	 66 65 85 103 	 1.00 0.90 (0.63–1.28) 1.02(0.73–1.44) 1.14 (0.82–1.61) 1.05 (0.99–1.10) [0.06]		
			WC (cm), quartiles (sex-specific) Men: Women: < 88 < 73 88–93 73–78 94–100 79–87 ≥ 101 ≥ 88 per 10 cm [P_{trend}]	 51 59 79 91 	 1.00 0.96 (0.65–1.41) 1.05(0.72–1.53) 1.33 (0.93–1.92) 1.24 (1.04–1.48) [0.03]		
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1958–1999	362 552 (107 815 in weight change analysis) Men Incidence	Pancreas ICD-7: 157	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}] 6-yr weight change –4% to +4.9% 5–9.9% 10–14.9% ≥ 15% [P_{trend}]	 352 289 57 86 41 13 7 	 1.00 0.95 (0.82–1.12) 1.16 (0.87–1.53) [> 0.5] 1.00 1.45 (1.00–2.11) 1.53 (0.85–2.77) 2.67 (1.22–5.84) [> 0.5]	Attained age, calendar year, smoking	

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Lin et al. (2007) JACC cohort Japan 1988–2003	43 579 Men Mortality	Pancreas ICD-10: C25	BMI at baseline			Age, smoking, diabetes, gall bladder disease	
			< 20	46	1.12 (0.76–1.63)		
			20–22.4	71	1.00		
			22.5–24.9	57	0.94 (0.66–1.34)		
			25–27.4	26	1.02 (0.65–1.62)		
			27.5–29.9	6	0.62 (0.23–1.70)		
			≥ 30	1	0.58 (0.08–4.16)		
			[P_{trend}]		[0.47]		
			BMI at age 20 yr				
			< 20	27	1.39 (0.86–2.24)		
			20–22.4	45	1.00		
			22.5–24.9	45	1.13 (0.75–1.71)		
			25–27.4	21	1.54 (0.92–2.58)		
			27.5–29.9	6	1.65 (0.70–3.86)		
			≥ 30	4	3.51 (1.26–9.78)		
			[P_{trend}]		[0.01]		
			Weight change (kg)				
			< –5	45	1.63 (1.05–2.53)		
			–5 to < 0	22	1.39 (0.82–2.33)		
			0	47	1.00		
			> 0–4.9	12	1.11 (0.58–2.12)		
			≥ 5	21	0.85 (0.49–1.47)		
	59 107 Women Mortality	Pancreas ICD-10: C25	BMI at baseline			Age, smoking, diabetes, gall bladder disease	
			< 20	33	1.15 (0.74–1.80)		
			20–22.4	50	1.00		
			22.5–24.9	62	1.33 (0.91–1.95)		
			25–27.4	30	1.21 (0.77–1.92)		
			27.5–29.9	16	1.57 (0.86–2.86)		
			≥ 30	4	1.04 (0.37–2.89)		
			[P_{trend}]		[0.28]		

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Lin et al. (2007) (cont.)			BMI at age 20 yr				
			< 20	25	0.81 (0.50–1.31)		
			20–22.4	51	1.00		
			22.5–24.9	48	1.08 (0.73–1.61)		
			25–27.4	15	0.69 (0.39–1.23)		
			27.5–29.9	3	0.46 (0.14–1.48)		
			≥ 30	1	0.43 (0.06–3.15)		
			[P_{trend}]		[0.09]		
			Weight change (kg)				
			< –5	14	0.41 (0.22–0.74)		
			–5 to < 0	14	0.61 (0.34–1.11)		
			0	59	1.00		
			> 0–4.9	13	0.70 (0.38–1.28)		
			≥ 5	43	0.93 (0.60–1.45)		
Luo et al. (2007) Japan Public Health Center Prospective Study Japan 1990–2003	47 499 Men Incidence	Pancreas ICD-10: C25	BMI			Smoking, diabetes, physical activity, study area, age, alcohol use, history of cholelithiasis	
			14–20.9	37	1.4 (0.8–2.5)		
			21–24.9	69	1.0		
			25–40	22	0.7 (0.4–1.1)		
			[P_{trend}]		[0.01]		
	52 161 Women Incidence		BMI				
			14–20.9	14	0.7 (0.4–1.3)		
			21–24.9	49	1.0		
			25–40	33	1.1 (0.7–1.6)		
			[P_{trend}]		[0.3]		
Máchová et al. (2007) National Cancer Registry, nested case–control study Czech Republic 1987–2002	17 110 Men Incidence	Pancreas ICD-10: C25	BMI	114 total		Age, smoking, hypertension, height	Nested case–control study, reporting odds ratios
			18.5–24.9		1.00		
			25–29.9		1.24 (0.74–2.07)		
			≥ 30		1.81 (0.98–3.31)		
	20 856 Women Incidence		BMI	80 total			
			18.5–24.9		1.00		
			25–29.9		0.68 (0.37–1.26)		
			≥ 30		0.95 (0.50–1.79)		

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Nöthlings et al. (2007) Multiethnic Cohort Study USA 1993–2002	77 255 Men Incidence	Pancreas ICD-10: C25.0–25.3, C25.7–25.9	BMI			Ethnicity, smoking, family history of pancreatic cancer, diabetes, age, energy intake, intake of red meat, intake of processed meat, physical activity	
			< 25	110	1.00		
			25–29.9	89	0.99 (0.74–1.33)		
			≥ 30	38	1.51 (1.02–2.26)		
			[P_{trend}]		[0.085]		
	90 175 Women Incidence		BMI				
			< 25	52	1		
			25–29.9	62	0.80 (0.59–1.09)		
			≥ 30	62	0.65 (0.43–0.99)		
			[P_{trend}]	61	[0.031]		
Verhage et al. (2007) Netherlands Cohort Study on Diet and Cancer The Netherlands 1986–1999	2366 Men Incidence	Pancreas ICD-10: C25	BMI at baseline			Age, smoking, diabetes, hypertension	When restricting to microscopically confirmed exocrine pancreatic cancer, significant positive associations were found with increased BMI and weight at baseline, and with BMI change since age 20 yr
			< 23	44	1.10 (0.72–1.69)		
			23–24.9	67	1.00		
			25–26.9	50	0.93 (0.61–1.39)		
			27–29.9	39	1.17 (0.75–1.81)		
			≥ 30	20	2.69 (1.47–4.92)		
			[P_{trend}]		[0.141]		
			per 1 kg/m²		1.05 (0.99–1.12)		
			BMI at age 20 yr				
			< 20	35	1.00		
			20–20.9	26	0.80 (0.46–1.40)		
			21–22.9	60	0.99 (0.62–1.59)		
			≥ 23	52	1.07 (0.67–1.73)		
			[P_{trend}]		[0.56]		
			per 1 kg/m²		1.03 (0.96–1.10)		
			BMI change since age 20 yr				
			< 0	14	0.99 (0.53–1.85)		
			0–3.9	84	1.00		
			4–7.9	60	1.34 (0.90–1.99)		
			≥ 8	15	2.21 (1.09–4.49)		
			[P_{trend}]		[0.052]		
			per 1 kg/m²		1.07 (0.99–1.15)		

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Verhage et al. (2007) (cont.)			Weight at baseline (kg)				
			< 65	74	1.00		
			65–69	47	1.16 (0.76–1.76)		
			70–74	46	1.13 (0.75–1.70)		
			75–79	21	0.92 (0.53–1.59)		
			≥ 80	36	1.55 (0.99–2.45)		
			[P_{trend}]		[0.18]		
			continuous per kg		1.01 (0.99–1.03)		
	2438 Women Incidence	Pancreas ICD-10: C25	BMI at baseline			Age, smoking, diabetes, hypertension	When restricting to microscopically confirmed exocrine pancreatic cancer, significant positive associations were found with increased weight at baseline and with BMI change since age 20 yr. A significant P_{trend} was also observed with increased BMI at baseline
			< 23	46	1.02 (0.66–1.58)		
			23–24.9	45	1.00		
			25–26.9	55	1.69 (1.11–2.58)		
			27–29.9	38	1.41 (0.89–2.25)		
			≥ 30	19	1.31 (0.74–2.31)		
			[P_{trend}]		[0.052]		
			per 1 kg/m²		1.04 (1.00–1.08)		
			BMI at age 20 yr				
			< 20	65	1.00		
			20–20.9	27	0.93 (0.58–1.51)		
			21–22.9	42	0.69 (0.46–1.04)		
			≥ 23	52	0.97 (0.66–1.44)		
			[P_{trend}]		[0.535]		
			per 1 kg/m²		1.02 (0.95–1.09)		
			BMI change since age 20 yr				
			< 0	15	0.67 (0.37–1.21)		
			0–3.9	76	1.00		
			4–7.9	63	1.08 (0.75–1.55)		
			≥ 8	31	1.72 (1.11–2.67)		
			[P_{trend}]	185	[0.004]		
			per 1 kg/m²		1.05 (1.01–1.10)		

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Verhage et al. (2007) (cont.)			Weight at baseline (kg) < 65 65–69 70–74 75–79 ≥ 80 [P_{trend}] continuous per kg	 59 42 39 31 39	 1.00 1.23 (0.81–1.88) 1.30 (0.84–1.99) 1.58 (0.99–2.52) 1.64 (1.07–2.52) [0.010] 1.02 (1.01–1.03)		
Jee et al. (2008) National Health Insurance Corporation Republic of Korea 1992–2006	770 556 Men Incidence	Pancreas	BMI < 20.0 20.0–22.9 23.0–24.9 25.0–29.9 ≥ 30.0 [P_{trend}]	 199 678 524 442 17	 0.87 (0.71–1.08) 1.01 (0.87–1.16) 1.00 1.06 (0.90–1.24) 1.34 (0.75–2.38) [0.1139]	Age, smoking	
	423 273 Women Incidence		BMI < 20.0 20.0–22.9 23.0–24.9 25.0–29.9 ≥ 30.0 [P_{trend}]	 80 246 178 253 34	 0.88 (0.62–1.24) 1.09 (0.84–1.40) 1.00 1.35 (1.05–1.74) 1.80 (1.14–2.86) [0.0014]	Age, smoking	
Luo et al. (2008) Women's Health Initiative USA 1993–2005	138 503 Women Incidence	Pancreas	BMI < 22.0 22.0–24.9 25.0–29.9 30.0–34.9 ≥ 35.0 [P_{trend}]	 25 62 84 56 24	 0.8 (0.5–1.2) 1.0 0.9 (0.6–1.2) 1.1 (0.7–1.5) 0.8 (0.5–1.3) [0.9]	Age, treatment assignments, cigarette smoking, diabetes	Study of postmenopausal women

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Luo et al. (2008) (cont.)			WC (cm), quintiles (range, median)				
			35.0–74.5, 70.5	41	1.0		
			74.6–81.0, 78.0	50	1.1 (0.7–1.7)		
			81.1–88.0, 85.0	46	1.0 (0.7–1.6)		
			88.1–97.4, 92.4	63	1.4 (0.9–2.0)		
			97.5–194.2, 105.0	51	1.1 (0.7–1.6)		
			[P_{trend}]		[0.6]		
			per 10 cm		1.05 (0.95–1.15)		
			Type of weight change:				
			Stable weight	85	1.0		
			Steady gain in weight	77	0.9 (0.6–1.2)		
			Lost weight and kept it off	5	0.6 (0.3–1.5)		
			Weight up and down (> 10 lb)	83	0.9 (0.7–1.2)		
Stolzenberg-Solomon et al. (2008) NIH-AARP cohort USA 1995–2000	293 562 Men Incidence	Pancreatic adenocarcinoma ICD-10: C25.0–25.9 Excludes endocrine tumours	BMI			Age, smoking, race, energy intake, energy-adjusted total fat intake, diabetes; for WC, also adjusted for BMI	
			18.5– < 25.0	110	1.00		
			25.0–29.9	227	1.22 (0.97–1.54)		
			30.0–34.9	66	1.09 (0.80–1.48)		
			≥ 35.0	26	1.61 (1.05–2.49)		
			[P_{trend}]		[0.07]		
			WC (cm)				
			< 88.9	40	1.00		
			88.9–93.3	35	1.00 (0.62–1.61)		
			93.3–98.4	39	0.81 (0.49–1.32)		
			98.4–106	46	0.96 (0.58–1.58)		
			≥ 106	52	0.95 (0.54–1.67)		
			[P_{trend}]		[0.91]		

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Stolzenberg-Solomon et al. (2008) (cont.)	201 473 Women Incidence		BMI 18.5– < 25.0 25.0–29.9 30.0–34.9 35.0 [P_{trend}] WC (cm) < 74.9 74.9–83.2 83.2–92.1 ≥ 92.1 [P_{trend}]	 84 84 38 19 14 24 28 34 	 1.00 1.33 (0.98–1.81) 1.40 (0.95–2.07) 1.29 (0.78–2.16) [0.09] 1.00 1.74 (0.89–3.41) 1.88 (0.92–3.85) 2.53 (1.13–5.65) [0.04]	Age, smoking, race, energy intake, energy-adjusted total fat intake, diabetes; for WC, also adjusted for BMI	
Arnold et al. (2009) Cancer Prevention Study II (CPS II) USA 1984–2004	48 525 Black men and women Mortality	Pancreas ICD-9: 157	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 2 122 136 80	 0.44 (0.11–1.77) 1.00 0.89 (0.70–1.40) 1.06 (0.80–1.42)	Age, diabetes, family history of pancreatic cancer, cholecystectomy, smoking status; analysis for men and women also adjusted for sex	
	17 602 Black men Mortality		BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 0 45 65 33	 – 1.00 1.02 (0.69–1.49) 1.66 (1.05–2.63)		
	30 923 Black women Mortality		BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 2 77 71 47	 0.60 (0.15, 2.44) 1.00 0.82 (0.59–1.14) 0.82 (0.56–1.18)		
	1 011 864 White men and women Mortality		BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 86 2644 2351 690	 0.93 (0.75–1.16) 1.00 1.15 (1.08–1.22) 1.40 (1.28–1.52)		

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Arnold et al. (2009) (cont.)	444 351 White men Mortality		BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 19 1080 1479 336	 0.83 (0.53–1.31) 1.00 1.11 (1.02–1.20) 1.42 (1.25–1.60)		
	567 513 White women Mortality		BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 67 1564 872 354	 0.97 (0.76–1.24) 1.00 1.20 (1.10–1.30) 1.37 (1.22–1.54)		
Johansen et al. (2009) Malmö Preventive Project Sweden 1974–2004	33 325 Men and women Incidence	Pancreas ICD-7: 157 ICD-10: C25	BMI < 20 20–24.9 25–29.9 ≥ 30 continuous Weight gain > 10 kg No Yes Missing	 10 101 54 18 118 52 13	 0.84 (0.44–1.61) 1.00 0.83 (0.60–1.16) 1.38 (0.83–2.28) 1.04 (0.995–1.08) 1.00 1.07 (0.77–1.48) 0.65 (0.34–1.27)	Age, sex, smoking, alcohol consumption	
Meinhold et al. (2009) ATBC subcohort of non-diabetics Finland 1985–2004	27 035 Men Incidence	Pancreas ICD-9: 157, excluding 157.4	BMI, quartiles Q1 Q2 Q3 Q4 continuous [P_{trend}]	 117 139 41 8	 1.00 0.97 (0.76–1.24) 1.03 (0.72–1.47) 1.42 (0.69–2.93) 1.01 (0.94–1.08) [0.80]	Age, smoking, energy intake, diabetes mellitus (self-reported)	
Stevens et al. (2009) Million Women Study USA 1996–2006	1.29 million Women Incidence	Pancreas ICD-10: C25	BMI < 22.5 22–24.9 25–27.4 27.5–29.9 30–32.4 ≥ 32.5	 246 311 260 188 119 152	RR (floating SE) 1.02 (0.07) 1.00 (0.06) 0.99 (0.06) 1.17 (0.09) 1.27 (0.12) 1.42 (0.12)	Age, region, SES, smoking, height	

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Stevens et al. (2009) (cont.)	1.29 million Women Mortality		BMI < 22.5 22–24.9 25–27.4 27.5–29.9 30–32.4 ≥ 32.5	 334 400 347 227 139 188	RR (floating SE) 1.08 (0.06) 1.00 (0.05) 1.03 (0.05) 1.09 (0.07) 1.14 (0.10) 1.36 (0.10)	Age, region, SES, smoking, height	
Whitlock et al. (2009) Pooled analysis of 57 cohort studies Europe, Japan, and USA Follow-up varied by cohort	894 576 Men and women Mortality	Pancreas ICD-9: 157	BMI, per 5 kg/m² For BMI 15–25 For BMI 25–50 For BMI 15–50	 470 520	 0.87 (0.65–1.17) 1.04 (0.86–1.25) 1.07 (0.97–1.19)	Study, sex, age, baseline smoking	
Arslan et al. (2010) Pancreatic Cancer Cohort Consortium (PanScan) pooled analysis, nested case–control Follow-up varies by cohort	2170 (men: 1059; women: 1111) Incidence	Pancreas	BMI < 18.5 ≥ 18.5– < 25.0 ≥ 25– < 30 ≥ 30– < 35 ≥ 35 [P_{trend}]	 19 759 868 325 124	 0.84 (0.44–1.59) 1.00 1.15 (1.00–1.33) 1.13 (0.93–1.37) 1.26 (0.93–1.71) [0.047]	Cohort, age, sex, anthropometry source, smoking, diabetes history	Non-significant positive associations were observed with WC (P_{trend} = 0.09)
Jiao et al. (2010) Pooled analysis of 7 cohort studies Follow-up varies by cohort	943 759 Men and women Incidence	Pancreatic adenocarcinoma ICD-10: C25 excluding C25.4 ICD-8/9: 157 excluding 157.4	BMI 16.5–18.4 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}] per 5 kg/m²	 17 855 1109 381 92	 0.89 (0.55–1.44) 1.00 1.13 (1.03–1.23) 1.19 (1.05–1.35) 1.19 (0.96–1.48) [0.001] 1.08 (1.03–1.14)	Age, sex, cohort, smoking	

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Jiao et al. (2010) (cont.)	458 070 Men Incidence		BMI 16.5–18.4 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}] per 5 kg/m²	 7 465 793 240 43	 0.88 (0.42–1.86) 1.00 1.11 (0.99–1.25) 1.11 (0.95–1.30) 1.34 (0.98–1.84) [0.03] 1.05 (0.98–1.12)		
	485 689 Women Incidence		BMI 16.5–18.4 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}] per 5 kg/m²	 10 390 316 141 49	 0.91 (0.48–1.70) 1.00 1.15 (0.99–1.34) 1.34 (1.11–1.64) 1.09 (0.81–1.47) [0.01] 1.12 (1.05–1.19)		
Parr et al. (2010) Pooled analysis of 39 cohort studies Asia, Australia, and New Zealand 1961–1999, median follow-up 4 yr	326 387 Men and women Mortality	Pancreas ICD-9: 157 ICD-10: C25	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 per 5 kg/m² [P_{trend}]	 11 114 65 90 21	 0.71 (0.38–1.31) 1.00 (0.86–1.16) 0.93 (0.75–1.15) 0.75 (0.48–1.18) 0.93 (0.78–1.11) [0.24]	Age, sex, smoking	
Genkinger et al. (2011) Pooling project of prospective studies of diet and cancer (14 cohort studies)	Women: 531 755 Men: 314 585 Incidence and mortality	Pancreas	BMI at baseline < 21 21–22.9 23–24.9 25–29.9 ≥ 30 [P_{trend}] per 5 kg/m²	All: 196 290 457 847 345	 1.16 (0.96–1.40) 1.00 1.07 (0.92–1.25) 1.18 (1.03–1.36) 1.47 (1.23–1.75) [< 0.001] 1.14 (1.07–1.21)	Smoking, diabetes, alcohol consumption, energy intake, age, baseline year	No statistically significant interaction by sex was found for BMI at baseline, BMI in early adulthood, or BMI change

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Genkinger et al. (2011) (cont.)	Women: 531 755 Men: 314 585 Incidence and mortality	Pancreas	BMI at baseline	Women:			
			< 21	148	1.15 (0.92–1.44)		
			21–22.9	177	1.00		
			23–24.9	221	1.08 (0.88–1.32)		
			25–29.9	378	1.29 (1.04–1.61)		
			≥ 30	192	1.46 (1.17–1.80)		
			[P_{trend}]		[0.002]		
			per 5 kg/m²		1.13 (1.06–1.21)		
			BMI at baseline	Men:			
			< 21	48	1.19 (0.85–1.68)		
			21–22.9	113	1.00		
			23–24.9	236	1.07 (0.85–1.34)		
			25–29.9	469	1.09 (0.88–1.34)		
			≥ 30	153	1.50 (1.07–2.11)		
			[P_{trend}]		[0.06]		
			per 5 kg/m²		1.14 (1.01–1.29)		
			BMI in early adulthood	All:			
			< 18.5	163	0.95 (0.79–1.15)		
			18.5–20.9	519	0.99 (0.87–1.13)		
			21–22.9	426	1.00		
			23–24.9	276	1.09 (0.92–1.29)		
			≥ 25	214	1.21 (1.01–1.45)		
			[P_{trend}]		[0.03]		
			per 5 kg/m²		1.20 (1.10–1.30)		
			BMI in early adulthood	Women:			
			< 18.5	121	0.92 (0.70–1.21)		
			18.5–20.9	351	0.96 (0.81–1.14)		
			21–22.9	239	1.00		
			23–24.9	113	0.98 (0.78–1.24)		
			≥ 25	94	1.16 (0.90–1.50)		
			[P_{trend}]		[0.18]		
			per 5 kg/m²		1.14 (1.02–1.28)		

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Genkinger et al. (2011) (cont.)	Women: 531 755 Men: 314 585 Incidence and mortality	Pancreas	BMI in early adulthood < 18.5 18.5–20.9 21–22.9 23–24.9 ≥ 25 [P_{trend}] per 5 kg/m^2 BMI change < –2 –2 to +2 2–5 5–10 > 10 [P_{trend}]	Men: 42 168 187 163 120 All: 79 391 493 491 144	 1.02 (0.72–1.45) 1.03 (0.78–1.35) 1.00 1.19 (0.87–1.62) 1.21 (0.88–1.68) [0.06] 1.27 (1.12–1.44) 1.44 (1.13–1.85) 1 0.98 (0.85–1.12) 1.13 (0.98–1.30) 1.40 (1.13–1.72) [0.04]		
Klein et al. (2013) Pancreatic Cancer Cohort Consortium (PanScan)	3349 Men and women Incidence	Pancreas	BMI < 18.5 18.5–24.9 25–30 > 30	NR	 0.91 (0.54–1.53) 1.00 1.08 (0.96–1.22) 1.26 (1.09–1.45)	Sex, age, study	
Lin et al. (2013b) Pooled analysis of 16 cohort studies from Asia Cohort Consortium Follow-up varies by cohort	799 542 Men and women Mortality	Pancreas	BMI < 18.5 18.5–19.9 20–22.4 22.5–24.9 25–27.4 27.5–29.9 ≥ 30	All: 116 130 432 454 232 89 36	 1.04 (0.84–1.30) 0.82 (0.67–1.00) 0.91 (0.80–1.05) 1.00 0.95 (0.80–1.11) 1.01 (0.80–1.29) 0.96 (0.67–1.37)	Age, sex, cohort, smoking, type 2 diabetes	No associations were observed when results were stratified by Asian region (i.e. East Asia vs South Asia)

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Lin et al. (2013b) (cont.)			BMI	Women:			
			< 18.5	53	0.89 (0.64–1.24)		
			18.5–19.9	59	0.85 (0.63–1.15)		
			20–22.4	174	0.78 (0.63–0.96)		
			22.5–24.9	213	1.00		
			25–27.4	129	1.01 (0.81–1.27)		
			27.5–29.9	52	1.02 (0.74–1.39)		
			≥ 30	28	1.09 (0.72–1.65		
			BMI	Men:			
			< 18.5	63	1.20 (0.90–1.61)		
			18.5–19.9	71	0.80 (0.61–1.05)		
			20–22.4	258	1.03 (0.86–1.24)		
			22.5–24.9	241	1.00		
			25–27.4	103	0.87 (0.69–1.10)		
			27.5–29.9	37	0.99 (0.69–1.42)		
			≥ 30	8	0.64 (0.30–1.35)		
Stolzenberg-Solomon et al. (2013) NIH-AARP cohort USA 1995–2006	501 698 Men and women Incidence	Pancreatic adenocarcinoma ICD-10: C25.0–25.9	BMI at age 18 yr			Smoking, total fat consumption, energy intake, sex	
			< 18.5	188	1.08 (0.92–1.27)		
			18.5–22.4	652	1.00		
			22.5–24.9	216	1.07 (0.92–1.25)		
			25–27.4	91	1.11 (0.89–1.39)		
			≥ 27.5	59	1.56 (1.19–2.03)		
			[P_{trend}]		[0.005]		
			BMI at age 35 yr				
			< 18.5	34	1.04 (0.73–1.48)		
			18.5–22.4	405	1.00		
			22.5–24.9	350	1.08 (0.94–1.25)		
			25–29.9	346	1.22 (1.05–1.41)		
			≥ 30	71	1.37 (1.06–1.79)		
			[P_{trend}]		[0.001]		

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Stolzenberg-Solomon et al. (2013) (cont.)			BMI at age 50 yr				
			< 18.5	27	1.26 (0.85–1.85)		
			18.5–24.9	532	1.00		
			25–29.9	499	1.13 (1.00–1.29)		
			≥ 30	148	1.22 (1.02–1.47)		
			[P_{trend}]		[0.01]		
			BMI at age > 50 yr				
			< 18.5	25	1.18 (0.79–1.75)		
			18.5–24.9	689	1.00		
			25–29.9	934	1.09 (0.98–1.20)		
			30–34.9	340	1.14 (1.00–1.30)		
			≥ 35	134	1.29 (1.07–1.55)		
			[P_{trend}]		[0.01]		
Bhaskaran et al. (2014) Clinical Practice Research Datalink United Kingdom 1987–2012	5 243 978 Men and women Incidence	Pancreas ICD-10: C25	BMI, per 5 kg/m²	3851 total	1.05 (1.00–1.10)	Age, diabetes, smoking, alcohol consumption, SES, calendar year, sex	A 11% significant risk was observed when restricting to non-smokers only
Bethea et al. (2014) Pooled study of African Americans (7 cohorts) USA Follow-up times differ across cohorts (at least 5 yr)	239 597 Men and women Mortality	Pancreas ICD-10: C25 ICD-9: 157	BMI			Age, smoking, education level, marital status, alcohol consumption, physical activity; analysis for men and women also adjusted for sex	
			18.5–24.9	187	1.00		
			25–29.9	270	1.08 (0.90–1.31)		
			30–34.9	128	1.25 (0.99–1.57)		
			≥ 35	60	1.31 (0.97–1.77)		
			[P_{trend}]		[0.03]		
	NR Men Mortality		BMI				
			18.5–24.9	68	1.00		
			25–29.9	123	1.15 (0.85–1.55)		
			30–34.9	45	1.36 (0.93–2.00)		
			≥ 35	10	1.14 (0.58–2.24)		
			[P_{trend}]		[0.20]		

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Bethea et al. (2014) (cont.)	NR Women Mortality		BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 119 147 83 50	 1.00 1.03 (0.80–1.31) 1.16 (0.87–1.55) 1.34 (0.95–1.89) [0.08]		
Untawale et al. (2014) Singapore Chinese Health Study China 1993–2011	51 251 Men and women Incidence	Pancreas	BMI < 18.5 18.5–21.4 21.5–24.4 24.5–27.4 ≥ 27.5 [P_{trend}]	 23 55 53 47 16	 1.89 (1.15–3.09) 1.34 (0.92–1.96) 1.00 1.46 (0.99–2.17) 1.02 (0.58–1.79) [0.08]	Age, sex, enrolment year, dialect, education level, diabetes, smoking history, alcohol consumption, diet, physical activity, sleep duration, energy intake	
Genkinger et al. (2015) National Cancer Institute BMI and Mortality Cohort Consortium (pooled analysis of 20 cohort studies) Follow-up varies by cohort	1 564 218 for BMI at baseline 1 096 492 for BMI in early adulthood 647 478 for WC Men and women Mortality	Pancreas ICD-9: 157 ICD-10: C25	BMI at baseline 15–18.4 18.5–21 21–22.9 23–24.9 25–27.4 27.5–29.9 30–34.9 35– < 60 continuous	 51 296 574 908 1134 653 617 212	 1.10 (0.83–1.47) 1.01 (0.87–1.16) 1.00 1.12 (1.01–1.24) 1.14 (1.03–1.26) 1.14 (1.01–1.27) 1.27 (1.13–1.43) 1.34 (1.14–1.57) 1.09 (1.05–1.12)	Age, race, education level, marital status, alcohol consumption, physical activity, smoking status	The positive association of WC with increased risk of pancreatic cancer mortality remained significant when additionally adjusting for BMI No differences between men and women in associations with BMI at baseline and in early adulthood, or with WC Stronger positive associations of pancreatic cancer risk with BMI change in women than in men

Table 2.2.7a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or cancer type (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Genkinger et al. (2015) (cont.)			BMI in early adulthood				
			15–18.4	376	1.01 (0.89–1.14)		
			18.5–21	1036	0.98 (0.89–1.08)		
			21–22.9	814	1.00		
			23–24.9	510	1.13 (1.01–1.26)		
			25–27.4	331	1.36 (1.20–1.55)		
			27.5–29.9	93	1.48 (1.20–1.84)		
			30–39.9	61	1.43 (1.11–1.85)		
			per 5 kg/m^2		1.18 (1.11–1.25)		
			BMI change				
			< –2.5	117	1.24 (1.01–1.53)		
			–2.5 to 0	269	1.12 (0.97–1.29)		
			0–2.4	658	1.00		
			2.5–4.9	828	1.07 (0.97–1.19)		
			5–7.4	640	1.11 (0.99–1.24)		
			7.5–9.9	357	1.11 (0.98–1.27)		
			≥ 10	354	1.28 (1.12–1.47)		
			per 5 kg/m^2		1.05 (1.01–1.10)		
			WC (cm), quartiles (sex-specific)				
			Men: Women:				
			< 90 < 70	385	1.00		
			90–99 70–79	660	1.11 (0.98–1.27)		
			110–109 80–89	531	1.26 (1.10–1.45)		
			≥ 110 ≥ 90	371	1.31 (1.12–1.54)		
			per 10 cm		1.09 (1.04–1.13)		
			[P_{trend}]		[< 0.0001]		
Meyer et al. (2015) Swiss cohort study Switzerland 1977–2008	35 703 Men and women Mortality	Pancreas ICD-8: 157 ICD-10: C25	BMI < 25 25–29.9 ≥ 30	127 total	 1.00 1.20 (0.81–1.78) 1.60 (0.93–2.75)	Sex, age, survey, alcohol consumption, physical activity, civil status, years of education, nationality, diet	

ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; BMI, body mass index (in kg/m^2); BP, blood pressure; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; ICD, International Classification of Diseases; JACC, Japan Collaborative Cohort Study for Evaluation of Cancer Risk; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; NR, not reported; SE, standard error; SES, socioeconomic status; WC, waist circumference; yr, year or years

Table 2.2.7b Case–control studies of measures of body fatness and cancer of the pancreas

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Bueno de Mesquita et al. (1990) The Netherlands 1984–1988	Men: 89 Women: 79 Population	BMI 2 yr before diagnosis < 23 > 27.9 [P_{trend}] BMI 2 yr before diagnosis < 21.6 > 28.7 [P_{trend}]	Men: 20 20 Women: 15 12 	 1.00 0.88 (0.40–1.90) [> 0.50] 1.00 1.10 (0.46–2.80) [> 0.90]	10-yr age group, response status, total smoking	
Ghadirian et al. (1991) Canada 1984–1988	179 Population	BMI < 21.1 > 26.5	 42 40	 1.00 0.88 (0.42–1.80)	Age, sex, response status, cigarette smoking	
Ji et al. (1996) China 1990–1993	Men: 255 Women: 183 Population	BMI < 19.4 > 22.5 [P_{trend}] BMI < 19.4 > 23.2 [P_{trend}]	Men: 72 59 Women: 43 54 	 1.0 1.40 (0.91–2.10) [0.14] 1.00 1.50 (0.85–2.50) [0.57]	Age, income, smoking, physical activity, response status, diabetes, vitamin C, total energy In women only: green tea drinking	
Hanley et al. (2001) Canada (7 Canadian provinces) 1994–1997	312 Population	BMI 2 yr before interview < 23.7 23.7– < 25.8 25.8– < 28.3 ≥ 28.3 [P_{trend}]	Men: 31 44 40 57 	 1.0 1.79 (1.01–3.19) 1.36 (0.74–2.49) 1.90 (1.08–3.35) [0.03]	Age, province, percentage weight change, energy intake, composite index of physical activity	Men who reported a 2.9% or greater decrease in weight from their maximum lifetime weight were at significantly reduced risk of pancreatic cancer
		BMI 2 yr before interview < 22.1 22.1– < 24.5 24.5– < 27.4 ≥ 27.4 [P_{trend}]	Women: 32 22 34 51 	 1.0 0.64 (0.35–1.18) 0.78 (0.44–1.40) 1.21 (0.70–2.06) [0.39]	Age, province, energy intake, age at first menstruation, cigarette smoking	Women who reported a 12.5% or greater decrease in weight from their maximum lifetime weight were at significantly reduced risk of pancreatic cancer

Table 2.2.7b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Silverman (2001) USA (Atlanta, Detroit, New Jersey) 1986–1989	Men: 218 Women: 213 Population	BMI	Men:		Age at diagnosis/interview, race, area, diabetes mellitus, gall bladder disease, cigarette smoking, alcohol consumption, income (men), marital status (women), energy intake from food	An interaction was observed between BMI and total energy intake in relation to pancreatic cancer risk; those with high BMI and high energy intake were at 60% increased risk.
		17.35–23.13	51	1.0		
		23.17–25.07	39	0.8 (0.5–1.3)		
		25.09–27.18	55	1.1 (0.7–1.7)		
		≥ 27.2	73	1.5 (1.0–2.3)		
		[P_{trend}]		[0.019]		
		BMI	Women:			
		20.49–27.54	40	1.0		
		27.56–30.25	54	1.4 (0.9–2.3)		
		30.30–34.21	57	1.5 (0.9–2.4)		
		≥ 34.43	62	1.5 (0.9–2.5)		
		[P_{trend}]		[0.129]		
Eberle et al. (2005) USA 1995–1999	Men: 291 Women: 241 Population	Adult BMI	Men:		Age, cigarette smoking only for usual BMI in men	
		< 23.1	48	1.0		
		23.1– < 25.1	70	1.6 (1.04–2.5)		
		25.1– < 27.1	75	1.6 (1.1–2.5)		
		≥ 27.1	95	2.1 (1.4–3.2)		
		[P_{trend}]		[0.0007]		
		Adult BMI	Women:			
		< 21.5	67	1.0		
		21.5– < 23.4	51	0.72 (0.47–1.1)		
		23.4– < 25.8	62	0.86 (0.58–1.3)		
		≥ 25.8	61	0.91 (0.61–1.4)		
		[P_{trend}]		[NS]		
		BMI at age 25 yr	Men:			
		< 20.9	44	1.0		
		20.9– < 22.8	76	1.7 (1.1–2.6)		
		22.8– < 24.7	79	1.8 (1.2–2.8)		
		≥ 24.7	91	2.0 (1.4–3.1)		
		[P_{trend}]		[0.001]		
		BMI at age 25 yr	Women:			
		< 19.7	54	1.0		
		19.7– < 21.0	50	0.88 (0.57–1.4)		
		21.0– < 22.5	64	1.2 (0.77–1.7)		
		≥ 22.5	72	1.3 (0.84–1.9)		
		[P_{trend}]		[0.13]		

Table 2.2.7b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Fryzek et al. (2005) USA (South-eastern Michigan) 1996–1999	Men: 119 Women: 112 Population	Current BMI, quartiles			Age, sex, race, county group, smoking, relative with pancreatic cancer, income, medical history of diabetes	
		Q1: ≤ 24.4	33	1.0		
		Q2: 24.5–27.3	59	0.4 (0.3–0.7)		
		Q3: 27.4–31.5	22	0.2 (0.1–0.3)		
		Q4: 31.5–67.8	17	0.1 (0.0–0.2)		
		[P_{trend}]		[< 0.0001]		
		BMI 5 yr before interview, quartiles				
		Q1: ≤ 24.1	46	1.0		
		Q2: 24.2–26.5	56	1.1 (0.6–1.8)		
		Q3: 26.6–30.3	68	1.3 (0.8–2.2)		
		Q4: 30.4–68.5	61	1.0 (0.6–1.8)		
		[P_{trend}]		[0.77]		
		BMI 20 yr before interview, quartiles				
			All:			
		Q1: 0.0–22.2	43	1.0		
		Q2: 22.3–24.4	48	1.1 (0.6–1.9)		
		Q3: 24.5–27.4	71	1.6 (0.9–2.6)		
		Q4: 27.5–43.0	69	1.4 (0.8–2.5)		
		[P_{trend}]		[0.15]		
			Men:			
		Q1: 0.0–22.2	8	1.0		
		Q2: 22.3–24.4	25	1.6 (0.6–4.1)		
		Q3: 24.5–27.4	43	2.6 (1.0–6.4)		
		Q4: 27.5–43.0	43	2.4 (1.0–6.2)		
		[P_{trend}]		[0.048]		
			Women:			
		Q1: 0.0–22.2	35	1.0		
		Q2: 22.3–24.4	23	1.2 (0.6–2.5)		
		Q3: 24.5–27.4	28	1.5 (0.7–3.0)		
		Q4: 27.5–43.0	26	1.4 (0.7–3.0)		
		[P_{trend}]		[0.37]		

Table 2.2.7b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Fryzek et al. (2005) (cont.)		BMI, ever-smokers				
		≤ 22.2	34	1.0		
		22.3–24.4	32	1.0 (0.5–1.8)		
		24.5–27.4	52	1.7 (0.9–3.1)		
		27.5–43.0	36	0.9 (0.5–1.8)		
		[P_{trend}]		[0.94]		
		BMI, never-smokers				
		≤ 22.2	9	1.0		
		22.3–24.4	16	1.6 (0.6–0.46)		
		24.5–27.4	19	1.5 (0.5–4.0)		
		27.5–43.0	33	3.3 (1.2–9.2)		
		[P_{trend}]		[0.014]		
Pezzilli et al. (2005) Italy	400 Hospital	BMI before diagnosis			Matched for sex, age (± 5 yr), social class, geographical region	
		< 23	110	1.01 (0.72–1.41)		
		23–29.9	246	1.00		
		≥ 30	44	0.96 (0.60–1.53)		
Lo et al. (2007) Egypt 2001–2004	194 Hospital	BMI 1 yr before			Age, sex, residence	
		< 27	99	1.0		
		27–31	59	1.4 (0.9–2.2)		
		≥ 32	28	1.5 (0.8–2.9)		
Anderson et al. (2009) Canada (Ontario) 2003–2007	422 Population	BMI 1 yr before			Age, education level, smoking status, family history of pancreatic cancer, weekly fruit servings, alcohol consumption, caffeinated beverages, allergies	
		< 25	148	1.00		
		25–29.9	183	1.77 (1.19–2.62)		
		≥ 30	83	3.51 (1.92–6.39)		

Table 2.2.7b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Li et al. (2009) USA (Texas) 2004–2008	841 (men: 496; women: 282) Population (proxy controls)	Mean lifetime BMI, per 5 kg/m² increase	All: 841 Men: 496 Women: 345	 1.55 (1.32–1.84) 1.80 (1.45–2.23) 1.32 (1.02–1.70)	Age, race, sex, smoking, alcohol consumption, history of diabetes, family history of cancer	Associations were somewhat stronger in ever-smokers than in never-smokers (1.75 vs 1.46) When stratifying BMI by age ranges, the greatest risk of pancreatic cancer was found at the ages of onset of overweight and/or obesity between 14–19 yr and 20–29 yr
Urayama et al. (2011) Czech Republic and Slovakia 2004–2009	574 Population	BMI at age 20 yr 18.5–21.1 21.2–22.8 22.9–24.5 > 24.5 per 5 kg/m² BMI at age 40 yr 18.5–23.0 23.1–24.8 24.9–27.3 > 27.3 per 5 kg/m² BMI 2 yr before interview 18.5–24.3 24.4–27.1 27.2–30.4 > 30.4 per 5 kg/m²	 101 113 161 164 106 114 154 173 131 151 153 130 	 1.00 1.15 (0.79–1.69) 1.81 (1.24–2.63) 1.79 (1.23–2.61) 1.45 (1.15–1.84) 1.00 1.04 (0.72–1.52) 1.40 (0.97–2.03) 1.57 (1.09–2.27) 1.24 (1.04–1.47) 1.00 1.07 (0.75–1.52) 1.04 (0.73–1.47) 0.91 (0.63–1.30) 0.98 (0.85–1.13)	Centre, age at interview, sex, diabetes mellitus, chronic pancreatitis, smoking, alcohol consumption	
Lin et al. (2013a) Japan 2010–2012	360 (men: 145; women: 215) Hospital	BMI in the yr before study entry < 25 25.0–29.9 ≥ 30	 278 64 16	 1.00 0.96 (0.65–1.43) 1.21 (0.53–2.77)	Age, sex, history of diabetes, cigarette smoking	

Table 2.2.7b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Zheng et al. (2016) China 2011–2013	323 Population (family members of other inpatients)	Current BMI < 24.0 ≥ 24.0	 197 126	 1.00 1.77 (1.22–2.57)	Age, sex, race, residential areas, smoking, tea drinking, mental pressure, family history of pancreatic cancer, diabetes, gallstone, intake of pickles and vegetables	
Pancreatic neuroendocrine tumours						
Halfdanarson et al. (2014) USA (Mayo Clinic Rochester 2004–2011	309 Hospital	Current BMI < 30 ≥ 30	 141 61	 1.00 1.65 (1.11–2.45)		

BMI, body mass index (in kg/m^2); CI, confidence interval; NS, not significant; yr, year or years

Table 2.2.7c Meta-analyses of measures of body fatness and cancer of the pancreas

Reference	Total number of studies Total number of cases	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
Michaud et al. (2001)	2 cohort studies 350	BMI < 23 23–24.9 25.0–26.9 27.0–39.9 ≥ 30 [P_{trend}]	 1.00 1.09 (0.79–1.49) 1.29 (0.92–1.80) 1.30 (0.91–1.87) 1.72 (1.19–2.48) [0.003]	Height, BMI at baseline, age, smoking, history of diabetes mellitus, cholecystectomy	
Berrington de Gonzalez et al. (2003)	6 case–control studies 8 cohort studies 6391	BMI, per 1 kg/m² increase	1.02 (1.01–1.03)	Age (all), smoking and diabetes (not all studies)	No differences were observed between men and women or when stratifying by study design (cohort vs case–control)
Larsson et al. (2007)	21 prospective studies (13 in men and 10 in women) 8062	BMI, per 5 kg/m² increase	All: 1.12 (1.06–1.17) Men: 1.16 (1.05–1.28) Women: 1.10 (1.02–1.19)	All studies adjusted for age, cigarette smoking; 13 studies also adjusted for diabetes	
Renehan et al. (2008)	12 prospective studies All studies: Men: 2390 Women: 2053 Studies with both sexes: Men: 839 Women: 778	BMI, per 5 kg/m² increase	Men: 1.07 (0.93–1.23) Women: 1.12 (1.03–1.23) Men: 1.07 (0.83–1.39) Women: 1.12 (0.95–1.33)	Method of BMI determination, extent of cancer site-specific risk factor adjustment, geographical region	When stratifying by region, the highest risk ratios were reported in North America (n = 2 studies)
Guh et al. (2009)	10 prospective studies (4 in men and 6 in women) NR	BMI Normal Overweight Obesity BMI Normal Overweight Obesity	Men: 1.00 1.28 (0.94–1.75) 2.29 (1.65–3.19) Women: 1.00 1.24 (0.98–1.56) 1.60 (1.17–2.20)		

Table 2.2.7c (continued)

Reference	Total number of studies Total number of cases	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
Aune et al. (2012)	23 prospective studies 9504	BMI, per 5 kg/m^2 increase	All (23 studies): 1.10 (1.07–1.14) Men (14 studies): 1.13 (1.04–1.22) Women (15 studies): 1.10 (1.04–1.16) Never-smoker (5 studies): 1.11 (1.04–1.17) Ever-smoker (4 studies): 1.03 (0.95–1.10)		Non-linear association between BMI and pancreatic cancer risk, with the most pronounced increase in risk in those with BMI > 35
WCRF/AICR (2012)	23 cohort studies 9504	BMI, per 5 kg/m^2 increase	Incidence: 1.10 (1.07–1.14)	NR	No differences were observed between men and women. Some evidence for a non-linear dose–response with an increase in risk from BMI ≥ 25
		BMI, per 5 kg/m^2 increase	Mortality: 1.10 (1.02–1.19)		
	5 cohort studies 949	WC, per 10 cm increase	1.11 (1.05–1.18)	NR	
	4 cohort studies 900	BMI at age 20 yr, per 5 kg/m^2 increase	1.12 (0.97–1.29)	NR	

BMI, body mass index (in kg/m^2); CI, confidence interval; NR, not reported; WC, waist circumference; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research; yr, year or years

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2.2.8 Cancer of the lung

The lung is the leading cancer site for deaths, accounting for about 19% of all deaths from cancer. Most (80–90%) cases of lung cancer can be attributed to long-term smoking. Because of the large influence of tobacco smoking, any errors in estimating tobacco exposure could lead to errors in attribution of risk to any other factor known to be associated with tobacco use, including adiposity, resulting in residual confounding, even after statistical adjustment for tobacco exposure, as measured.

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and lung cancer was *inadequate*. The 2007 WCRF review concluded that there was "limited evidence suggesting that low body fatness (underweight) is a cause of lung cancer" (WCRF/AICR, 2007).

(a) Cohort studies

The evidence from cohort studies published since 2000 includes 18 reports (excluding analyses that were later updated and analyses based on fewer than 100 incident cases) and is summarized in Table 2.2.8a (web only; available at: http://publications.iarc.fr/570).

In general, studies consistently showed an inverse association between BMI and risk of lung cancer. The inverse association is linear across categories of BMI, with about 20–30% lower risk for those with BMI ≥ 30 kg/m^2. The association is generally stronger for current smokers than for never-smokers (Samanic et al., 2006; Kabat et al., 2008; Koh et al., 2010; Smith et al., 2012; Bhaskaran et al., 2014). A meta-analysis of 29 cohort studies found consistency of the association by sex and region of the world, with a relative risk estimate for obesity (compared with normal weight) of 0.78 (95% CI, 0.74–0.83) (Duan et al., 2015).

Few investigators have explored weight across the life-course as related to lung cancer risk. In general, BMI at cohort baseline (recruitment into the cohort) seems to be more strongly (inversely) associated with lung cancer risk than is BMI earlier in life (Olson et al., 2002; Fujino et al., 2007; Kabat et al., 2008; Lam et al., 2013).

Several cohorts have included measurements of waist and hip circumferences (Olson et al., 2002; Kabat et al., 2008; Bethea et al., 2013). In general, waist circumference and waist-to-hip ratio were less associated with lung cancer risk than was BMI.

(b) Case–control studies

There were a total of 11 independent reports from case–control studies on the association of BMI with lung cancer, conducted in Europe, Japan, and the USA (Table 2.2.8b, web only; available at: http://publications.iarc.fr/570). The studies were highly variable in size, some including fewer than 200 lung cancer cases, whereas others included about 1000 (El-Zein et al., 2013), more than 2000 (Brennan et al., 2009; ICARE study, France, Tarnaud et al., 2012), and more than 3000 (NECSS study, Canada, Pan et al., 2004; Kabat & Wynder, 1992). In all studies except those of Kubík et al. (2004) and Kanashiki et al. (2005), BMI was assessed on the basis of self-reported height and body weight referring to a recent period (mostly 1 year or 2 years) before disease diagnosis. Several studies collected recalled body weight in the more distant past, for example at age 20–30 years (Goodman & Wilkens, 1993; Tarleton et al., 2012; Tarnaud et al., 2012; El-Zein et al., 2013). In addition to various other adjustments for potential confounding factors, all studies except one (Heck et al., 2009) adjusted for smoking, although the degree of the adjustment varied from smoking status only (current, former, never) to lifetime cumulative exposure to tobacco smoke. The large studies by Kabat & Wynder (1992) in the USA, Pan et al. (2004) in Canada, Kanashiki et al. (2005) in Japan, and

Tarnaud et al. (2012) in France also provided estimates within separate strata of current smokers, former smokers, and never-smokers. Furthermore, one study in the USA, by Rauscher et al. (2000), provided odds ratio estimates only for former smokers and never-smokers (244 and 188 case–control pairs, respectively).

Among the studies for which the reference time frames for BMI assessment were within 5 years before lung cancer diagnosis, all studies except that of Rauscher et al. (2000), which included only former smokers and never-smokers, showed inverse associations of BMI with lung cancer risk. Several studies showed an increased risk of lung cancer particularly in individuals with low BMI, compared with individuals with BMI in the normal mid-range or higher (Tarnaud et al., 2012: OR, 2.7; 95% CI, 1.2–6.2 for BMI < 18.5 vs 18.5– < 25 kg/m^2 as reference category; El-Zein et al., 2013: OR, 2.30; 95% CI, 1.30–4.10 for BMI < 18.5 vs 18.5– < 25 kg/m^2 as reference category; and Kanashiki et al., 2005: OR, 2.0; 95% CI, 1.2–3.4 for BMI categories < 22.9 vs 22.9– < 25 kg/m^2 as reference category). However, other studies showed a more linear inverse relationship between BMI and relative risk over a wider range of BMI values, from < 18.5 kg/m^2 to > 30 kg/m^2.

In several larger studies that stratified the analysis by current smokers, former smokers, and never–smokers, an increased risk in underweight individuals, and more generally an inverse relationship between BMI and lung cancer risk, was observed only in current smokers and former smokers (Kabat & Wynder, 1992; Pan et al., 2004; Kanashiki et al., 2005; Tarleton et al., 2012; Tarnaud et al., 2012; El-Zein et al., 2013), whereas in never-smokers there was no significant association. The study of Rauscher et al. (2000), which included only former smokers and never-smokers, showed an increase in lung cancer risk with increasing BMI.

In studies that collected information about weight at ages 20–30 years, BMI in early adulthood showed no significant association (Goodman & Wilkens, 1993; Tarleton et al., 2012; El-Zein et al., 2013) with lung cancer risk or a weaker (inverse) association than that reported for BMI shortly before diagnosis (Tarnaud et al., 2012). In all four studies, cases tended to gain less weight during adult life than did controls. In one study that analysed lung cancer risk according to weight gained since early adulthood (Tarleton et al., 2012), weight gain was significantly inversely related to lung cancer risk, and more so in current smokers than in never-smokers or former smokers.

(c) Mendelian randomization studies

Two studies have applied Mendelian randomization in the context of lung cancer (Table 2.2.8c, web only; available at: http://publications.iarc.fr/570). Brennan et al. (2009) used the *FTO* rs9939609 SNP, which is robustly associated with BMI (Frayling et al., 2007; Scuteri et al., 2007; Peeters et al., 2008), as an instrument for BMI. Mendelian randomization analyses showed that each 1 kg/m^2 increase in BMI was associated with a reduced risk of lung cancer (OR, 0.85; 95% CI, 0.72–0.99; P = 0.04), including adenocarcinoma (OR, 0.51; 95% CI, 0.33–0.82; P = 0.004) and squamous cell carcinoma (OR, 0.72; 95% CI, 0.57–0.90; P = 0.01). An inverse association was observed in never-smokers (OR, 0.57; 95% CI, 0.35–0.94; P = 0.03) but not in former smokers or current smokers.

Gao et al. (2016) used genetic risk scores comprising 15 SNPs for childhood BMI and 77 SNPs for adult BMI in Mendelian randomization analyses to assess association between these measures of adiposity and all lung cancer and lung cancer subtypes. Each 1 kg/m^2 increase in adult BMI was associated with a 5% increased risk of all lung cancer (95% CI, 1.02–1.09; $P = 2.9 \times 10^{-3}$) and a 10% increased risk of squamous cell carcinoma (95% CI, 1.04–1.16; $P = 6.6 \times 10^{-4}$) (assuming that a standard deviation was equivalent to 4.5 kg/m^2). There was no association with

childhood BMI. There was minimal evidence for a positive directional pleiotropy from Mendelian randomization Egger regression, and results were null, suggesting that the positive association between adult BMI and both all lung cancer and squamous cell lung cancer may be overestimated. [The Working Group noted that interpretation of this finding is limited because individual-level data were not available on smoking status, which may be an important effect modifier. In addition, there is a potential violation of the Mendelian randomization assumptions in this analysis.]

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2.2.9 Cancer of the breast in women

In women, cancer of the breast constitutes about 25% of all incident cancers and about 15% of all cancer deaths worldwide. There are several established risk factors for breast cancer, including age at menarche, age at menopause, age at first birth, parity, breastfeeding, alcohol consumption, physical activity, and use of exogenous estrogens. Breast cancer diagnosed before menopause differs from breast cancer diagnosed after menopause in both risk factors and clinical characteristics. There are several molecular subtypes of breast cancer; the most important aspect is the presence or absence of estrogen receptors in the tumour, because this substantially affects treatment options and prognosis.

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that there was *sufficient evidence* for a cancer-preventive effect of avoidance of weight gain for postmenopausal breast cancer.

(a) Cohort studies

The evidence published since 2000 includes about 30 publications from cohort studies (excluding analyses that were later updated and analyses based on fewer than 100 incident cases). These findings are displayed for BMI at baseline in Table 2.2.9a for postmenopausal women and Table 2.2.9b (web only; available at: http://publications.iarc.fr/570) for premenopausal women, with comments on findings according to other measures of body fatness, such as weight changes over the life-course.

(i) BMI

In general, the findings are quite consistent across the studies, showing an inverse association between baseline BMI and premenopausal breast cancer risk and a positive association between baseline BMI and postmenopausal breast cancer risk.

For premenopausal breast cancer, the risk diminishes with increasing BMI on an approximately linear scale, and for postmenopausal breast cancer the risk increases on an approximately linear scale. Two large meta-analyses estimated a 7–8% decrease in premenopausal breast cancer risk and a 12–13% increase in postmenopausal breast cancer risk per 5 kg/m^2 (Renehan et al., 2008; WCRF/AICR, 2010).

Among those studies that have assessed the association between BMI and breast cancer risk by estrogen receptor (ER) status (for postmenopausal and premenopausal breast cancer combined), the association was most robust for women with ER-positive tumours (MacInnis et al., 2004; Suzuki et al., 2006; Vrieling et al., 2010; Canchola et al., 2012; Bandera et al., 2015; Neuhouser et al., 2015).

Among postmenopausal women, the majority of studies that have assessed the interaction between obesity and use of HRT have found the association between BMI and breast cancer risk to be apparent only among non-users of HRT (Feigelson et al., 2004; Lahmann et al., 2004; Eliassen et al., 2006; Mellemkjaer et al., 2006; Ahn et al., 2007; White et al., 2012). Similar conclusions were reported by several meta-analyses and systematic literature reviews (WCRF/AICR, 2010).

(ii) BMI or weight at earlier time points and weight change

Several investigators have assessed the association of BMI or weight at earlier time points and weight change with subsequent breast cancer risk.

For postmenopausal breast cancer, BMI in middle adulthood (ages 35–50 years) is associated with a risk similar to that with baseline BMI (Ahn et al., 2007), but BMI in early adulthood (generally reported at age 18 years) is either not associated or modestly inversely associated with postmenopausal breast cancer risk (Sweeney

et al., 2004; Ahn et al., 2007; Canchola et al., 2012; Bandera et al., 2015).

Weight gain since age 18 years has been shown to be associated with postmenopausal breast cancer risk (Sweeney et al., 2004; Eliassen et al., 2006). Also, weight gain after age 50 years is positively associated with postmenopausal breast cancer risk (Eng et al., 2005).

Weight loss in adulthood has been examined in six studies (Eliassen et al., 2006; Ahn et al., 2007; Teras et al., 2011; Emaus et al., 2014; Neuhouser et al., 2015; Rosner et al., 2015). Across these studies, there is not consistent evidence that weight loss from about age 50 years to the baseline of entry into the cohort affects postmenopausal breast cancer risk.

(iii) Waist circumference

Seven cohort studies have included measurements of waist circumference (Lahmann et al., 2004; Sweeney et al., 2004; Krebs et al., 2006; Ahn et al., 2007; Canchola et al., 2012; Fourkala et al., 2014; Kabat et al., 2015). Waist circumference (either as measured or as indicated by skirt size) or waist-to-hip ratio was generally positively associated with postmenopausal breast cancer risk, and the strengths of those associations are approximately equivalent to those reported for BMI.

(b) Case–control studies

For the current evaluation, data from more than 400 case–control studies published after 2000 were reviewed. Only studies with more than 100 cases are summarized.

(i) BMI

In postmenopausal women, case–control studies yielded consistent results, with increased risk of breast cancer with higher BMI (Table 2.2.9c).

In premenopausal women, the results are less consistent despite the substantial number of studies; they mostly indicate an inverse association (Table 2.2.9d; web only; available at: http://publications.iarc.fr/570).

Studies that assessed weight gave similar results to those with BMI for both postmenopausal women (Table 2.2.9e; web only; available at: http://publications.iarc.fr/570) and premenopausal women (Table 2.2.9f; web only; available at: http://publications.iarc.fr/570).

Comparable associations were observed for tumours that are both ER-positive and progesterone receptor (PR)-positive, especially for postmenopausal women; see Table 2.2.9g for postmenopausal women and Table 2.2.9h (web only; available at: http://publications.iarc.fr/570) for premenopausal women.

A meta-analysis based on 35 case–control studies involving 71 216 subjects showed an increased risk of postmenopausal breast cancer (OR, 1.15; 95% CI, 1.07–1.24) but not of premenopausal breast cancer, for which the estimates were suggestive of an inverse association with higher BMI (overweight and obese subjects) (OR, 0.93; 95% CI, 0.86–1.02) (Cheraghi et al., 2012).

(ii) BMI and ethnicity

More than 20 studies were carried out in Caucasian women in North America and western Europe (Wenten et al., 2002; Magnusson et al., 2005; Tsakountakis et al., 2005; Verla-Tebit & Chang-Claude, 2005; Dinger et al., 2006; Rosenberg et al., 2006; Kruk, 2007; Slattery et al., 2007; Justenhoven et al., 2008; Berstad et al., 2010; Healy et al., 2010; Barnes et al., 2011; Cerne et al., 2011; John et al., 2011; Rosato et al., 2011; Attner et al., 2012; Bandera et al., 2013a; Robinson et al., 2014; John et al., 2015a, b; Sanderson et al., 2015), 16 studies in women in East Asia (Hirose et al., 2001, 2003; Shu et al., 2001; Yoo et al., 2001; Adegoke et al., 2004; Chow et al., 2005; Nichols et al., 2005; Tian et al., 2007; Wu et al., 2006; Gao et al., 2009; Shin et al., 2009; Shi et al., 2010; Bao et al., 2011; Kawai et al., 2013; Noh et al., 2013; Sangrajrang et al., 2013; Minatoya et al., 2014), 12 studies in Hispanic or Latina women

(de Vasconcelos et al., 2001; Wenten et al., 2002; Ibarluzea et al., 2004; Ziv et al., 2006; Garmendia et al., 2007; Slattery et al., 2007; Justenhoven et al., 2008; John et al., 2011, 2015a, b; Ronco et al., 2012; Amadou et al., 2014), 8 studies in women in South Asia (Gilani & Kamal, 2004; Mathew et al., 2008; Montazeri et al., 2008; Dey et al., 2009; Dogan et al., 2011; Lodha et al., 2011; Ghiasvand et al., 2012; Singh & Jangra, 2013), and 4 studies in Arab women (Alothaimeen et al., 2004; Dogan et al., 2011; Msolly et al., 2011; Elkum et al., 2014).

Except for Asian populations, there are not clear differences in risk estimates between ethnic groups for either postmenopausal women (Table 2.2.9i; web only; available at: http://publications.iarc.fr/570) or premenopausal women (Table 2.2.9j; web only; available at: http://publications.iarc.fr/570).

The incidence of breast cancer in Hispanic Whites is lower than that in non-Hispanic Whites. In the case–control studies that have evaluated the associations of BMI (or other anthropometric measures) or weight change with breast cancer risk and compared Hispanic Whites with non-Hispanic Whites (Wenten et al., 2002; Slattery et al., 2007; John et al., 2015b), the positive association observed in postmenopausal women was generally stronger in non-Hispanic Whites than in Hispanic Whites.

Most studies in Asian women observed an increased risk of breast cancer with higher BMI, especially for postmenopausal women (Table 2.2.9i; web only; available at: http://publications.iarc.fr/570) and/or tumours that were hormone receptor-positive (ER-positive and/or PR-positive). However, the associations between BMI and breast cancer risk in postmenopausal women are observed at lower BMI levels in Asian populations than in Caucasian populations. Some studies in East Asian women (Bao et al., 2011; Kawai et al., 2013) used BMI < 21 kg/m^2 or BMI < 18.5 kg/m^2 as a reference and categories of lower BMI for overweight and obesity, and observed a positive association in both categories. Such lower BMI categories were not specifically examined in most studies in South Asian women.

(iii) Waist circumference

As for BMI, results from case–control studies using waist circumference as an indicator of body fatness yielded consistent results in postmenopausal women, with mostly positive associations (Table 2.2.9k).

In premenopausal women, the results of the 11 available studies were not consistent (Table 2.2.9l; web only; available at: http://publications.iarc.fr/570); two studies (Bandera et al., 2013b; Robinson et al., 2014) showed significant positive associations, whereas two studies showed an inverse association (John et al., 2011 in ER-positive, PR-positive tumours only; Amadou et al., 2014). Interestingly, the significant positive associations were observed in women of African ancestry.

Evidence is scarce about waist circumference and risk of breast cancer by hormone receptor status. The three studies in postmenopausal women (John et al., 2011, 2013; Bandera et al., 2013b; Table 2.2.9k) provided conflicting results.

(iv) Change in BMI or weight

Changes in BMI or weight were mostly studied as an increase from the value at age 18, 21, 25, or 30 years to the value at the reference date or 1 year before the reference date.

In postmenopausal women (Table 2.2.9m), 12 of the 20 studies found a positive association between weight gain and risk of breast cancer (Li et al., 2000; Trentham-Dietz et al., 2000; Shu et al., 2001; Friedenreich et al., 2002; Carpenter et al., 2003, Eng et al., 2005; Han et al., 2006; Wu et al., 2006; Shin et al., 2009), in three studies in non-Hispanic White women only (Wenten et al., 2002; Slattery et al., 2007; John et al., 2013). One of the two studies of BMI gain also found a positive association (Hirose et al., 2001). The remaining studies found no significant association.

In the two studies that assessed weight gain specifically after menopause (weight gain after age 50 years or in the past 10 years) (Shu et al., 2001; Eng et al., 2005), the association was still significant but was slightly weaker than that with weight change since early adulthood.

When premenopausal women were considered (Table 2.2.9n; web only; available at: http://publications.iarc.fr/570), BMI change was consistently not associated with risk of breast cancer in all four available studies (Hirose et al., 2001; Verla-Tebit & Chang-Claude, 2005; Kawai et al., 2014; Robinson et al., 2014). Of 16 studies, 10 confirmed no association between body weight gain and breast cancer risk (Shu et al., 2001; Friedenreich et al., 2002; Wenten et al., 2002; Slattery et al., 2007; Wu et al., 2006; Berstad et al., 2010; Bandera et al., 2013a; Troisi et al., 2013; Robinson et al., 2014; Sanderson et al., 2015). The remaining studies were inconsistent; two found an increased risk with increasing body weight gain (Shin et al., 2009; Cribb et al., 2011), and three found a protective effect of body weight gain in at least one measure of exposure (Verla-Tebit & Chang-Claude, 2005; John et al., 2011; Sangaramoorthy et al., 2011).

(v) Weight loss

When assessing weight change during adulthood, several studies also assessed the impact of weight loss on breast cancer risk (Trentham-Dietz et al., 2000; de Vasconcelos et al., 2001; Eliassen et al., 2006). The results were inconsistent, probably because of heterogeneity of ethnicity and current BMI between studies.

(c) Mendelian randomization studies

One Mendelian randomization study has been conducted to assess the association of childhood and adult BMI with all and ER-negative breast cancer risk (Gao et al., 2016; Table 2.2.9o). In this study, each unit increase in adult BMI was associated with a 9% decrease in risk (95% CI, 6–12%; $P = 2.5 \times 10^{-7}$) in all breast cancers, and an 11% decrease in risk (95% CI, 6–16%; $P = 2.0 \times 10^{-5}$) in ER-negative tumours (assuming that a standard deviation [SD] was equivalent to 4.5 kg/m^2; Locke et al., 2015). Childhood BMI was inversely associated with all (OR per SD increase, 0.71; 95% CI, 0.60–0.80; $P = 6.5 \times 10^{-5}$) and ER-negative breast cancer risk (OR per SD increase, 0.69; 95% CI, 0.53–0.98; $P = 5.8 \times 10^{-3}$), where each SD increase was equivalent to 0.073 kg/m^2 (Felix et al., 2016). [There was minimal evidence for positive directional pleiotropy in the associations with childhood BMI, suggesting that estimates may be underestimated.]

[Although the inverse association observed between adult BMI and breast cancer risk in this study is inconsistent with the positive associations observed for postmenopausal women in observational studies, Mendelian randomization analyses represent a lifelong predisposition to increased BMI (especially because there is a high correlation between the otherwise independent childhood and adult BMI genetic risk scores). The results may suggest that the positive association between adult BMI and breast cancer risk may be driven by adult weight gain, as a result of environmental factors not captured by genetic risk scores.]

Table 2.2.9a Cohort studies of body mass index and cancer of the breast in postmenopausal women

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Feigelson et al. (2004) CPS2 cohort USA 1992–2001	62 756 Incidence	BMI		Non-HRT users	Age, race, age at menarche, age at menopause, parity, OC use, family history of BC in first-degree relative, benign breast disease, mammography, height, education level, physical activity, alcohol consumption	Positive association also with adult weight gain
		< 22	187	1.00		
		22–24.9	304	1.06 (0.88–1.27)		
		25–26.9	182	1.11 (0.91–1.36)		
		27–29.9	233	1.41 (1.16–1.71)		
		30–34.9	204	1.74 (1.42–2.13)		
		≥ 35	72	1.61 (1.22–2.12)		
		[P_{trend}]		[< 0.0001]		
		BMI		Current HRT users		No association with adult weight gain
		< 22	223	1.0		
		22–24.9	253	0.89 (0.74–1.06)		
		25–26.9	102	0.74 (0.59–0.94)		
		27–29.9	101	0.86 (0.68–1.09)		
		30–34.9	51	0.72 (0.53–0.98)		
		≥ 35	22	1.09 (0.70–1.69)		
		[P_{trend}]		[0.12]		
Lahmann et al. (2004) EPIC cohort Europe 1992–2002	103 334 Incidence	BMI, quintiles		Non-HRT users	Age, centre, education level, smoking, alcohol consumption, parity, age at first pregnancy, age at menarche	WC and WHR both showed no association
		Q1	98	1.00		
		Q2	127	1.02 (0.78–1.33)		
		Q3	206	1.35 (1.06–1.73)		
		Q4	241	1.38 (1.08–1.76)		
		Q5	239	1.36 (1.06–1.75)		
		[P_{trend}]		[0.002]		
		BMI, quintiles		HRT users		
		Q1	122	1.0		
		Q2	116	0.90 (0.69–1.17)		
		Q3	113	0.91 (0.70–1.19)		
		Q4	92	0.85 (0.64–1.13)		
		Q5	51	0.71 (0.50–1.10)		
		[P_{trend}]		[0.07]		
MacInnis et al. (2004) Population-based cohort Australia 1990–2003	13 598 Incidence	BMI, quartiles	357 total		Age, education level, country of birth, HRT use	Association limited to ER+ cases
		Q1		1.0		
		Q2		1.2 (0.9–1.5)		
		Q3		1.4 (1.0–1.9)		
		Q4		–		
		[P_{trend}]		[0.02]		

Table 2.2.9a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Sweeney et al. (2004) Iowa women's cohort USA 1986–2001	36 658 Incidence	BMI		55–64 yr	Age, education level, age at first birth, age at menarche, family history of BC, height	Associations with WHR and weight change since age 18 yr similar to those for BMI
		< 23.5	101	1.00		
		23.5–26	78	0.86 (0.64–1.16)		
		26–29.5	119	1.26 (0.96–1.64)		
		≥ 29.5	130	1.34 (1.03–1.75)		
		[P_{trend}]		[0.004]		
		BMI		65–74 yr		
		< 23.5	274	1.00		
		23.5–26	306	1.21 (1.03–1.42)		
		26–29.5	335	1.26 (1.08–1.49)		
		≥ 29.5	382	1.48 (1.26–1.73)		
		[P_{trend}]		[< 0.0001]		
		BMI		75–84 yr		
		< 23.5	112	1.00		
		23.5–26	129	1.19 (0.92–1.53)		
		26–29.5	167	1.45 (1.14–1.85)		
		≥ 29.5	153	1.44 (1.12–1.84)		
		[P_{trend}]		[0.001]		
Kuriyama et al. (2005) Population-based cohort Japan 1984–1992	15 054 Incidence	BMI			Age, smoking, alcohol consumption, diet, age at menopause, age at menarche, age at first pregnancy	
		< 18.5–24.9	73	1.00		
		25–27.4	23	1.20 (0.75–1.93)		
		27.5–29.9	12	1.55 (0.84–2.87)		
		≥ 30	7	1.90 (0.87–4.15)		
		[P_{trend}]		[0.04]		
Rapp et al. (2005) Population-based cohort Austria 1985–2002	78 484 Incidence	BMI	NR		Age, smoking, occupation	
		18.5–24.9		1.00		
		30–34.9		1.48 (1.12–1.95)		
		≥ 35		1.29 (0.79–2.11)		
		[P_{trend}]		[0.02]		
Chang et al. (2006) USA PLCO cohort 1993–2003	38 660 Incidence	BMI			Age, study centre, race, family history of BC in first-degree relative, age at menarche, age at menopause, HRT use, education level	
		< 22.4	139	1.00		
		22.5–24.9	177	1.20 (0.96–1.51)		
		25–27.4	168	1.24 (0.99–1.56)		
		27.5–29.9	114	1.42 (1.11–1.83)		
		≥ 30	166	1.35 (1.06–1.70)		
		[P_{trend}]		[0.014]		

Table 2.2.9a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Eliassen et al. (2006) NHS1 and NHS2 USA	87 143 Incidence	Weight change (kg), age 18 yr to baseline			Age, age at menarche, parity, age at first birth, height, weight at age 18 yr, first-degree family history of BC, benign breast disease, alcohol consumption, use of HRT, age at menopause	Weight change since menopause associated more weakly. Association was much weaker among users of HRT
		loss ≥ 10	22	1.05 (0.64–1.70)		
		loss 5–9.9	35	1.14 (0.76–1.70)		
		loss 2–4.9	33	0.77 (0.51–1.15)		
		stable	85	1.00		
		gain 2–4.9	108	1.02 (0.77–1.36)		
		gain 5–9.9	204	1.08 (0.83–1.39)		
		gain 10–19.9	435	1.34 (1.06–1.69)		
		gain 20–24.9	159	1.55 (1.18–2.02)		
		gain ≥ 25	313	1.98 (1.55–2.53)		
		[P_{trend}]		[< 0.001]		
Krebs et al. (2006) Cohort of older women for osteoporosis USA 1986 Average follow-up, 11.3 yr	7523 Incidence	BMI, quartiles	350 total		Age, HRT use, bone density, family history of BC, exercise, education level, parity, age at menarche, age at menopause, smoking	WC and WHR both showed no association
		Q1		1.00		
		Q2		0.82 (0.58–1.15)		
		Q3		1.01 (0.72–1.41)		
		Q4		1.29 (0.92–1.81)		
		[P_{trend}]		[0.06]		
Lukanova et al. (2006) Population-based cohort Sweden 1994–2004	35 362 Incidence	BMI			Age, tobacco use	
		18.5–24.9	213	1.00		
		25–29.9	140	0.92 (0.74–1.14)		
		≥ 30	69	1.09 (0.83–1.43)		
		[P_{trend}]		[0.70]		
Mellemkjaer et al. (2006) Population-based cohort Denmark 1993–2002	11 992 Incidence	BMI			Parity, age at first birth, education level, benign breast disease, alcohol consumption	WC and WHR both showed no association
		< 18.5	7	1.23 (0.58–2.63)		
		18.5–24.9	237	1.00		
		25–29.9	130	0.88 (0.71–1.09)		
		≥ 30	42	0.94 (0.67–1.31)		
		[P_{trend}]		[0.74]		
	11 796 Incidence	BMI			Parity, age at first birth, education level, benign breast disease, alcohol consumption	WC and WHR both showed no association
		< 18.5	1	–		
		18.5–24.9	96	1.00		
		25–29.9	85	1.34 (1.00–1.80)		
		≥ 30	35	1.17 (0.79–1.73)		
		[P_{trend}]		[0.28]		

Table 2.2.9a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Silvera et al. (2006) Canadian mammography screening cohort Canada 1980–2000	40 318 Incidence	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	662 total	 1.00 1.12 (0.91–1.38) 1.26 (0.95–1.67) [0.08]	Age, alcohol consumption, smoking, HRT use, age at menarche, age at first birth, family history of BC	
Suzuki et al. (2006) Swedish mammography cohort Sweden 1987–2003	51 823 Incidence	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}] BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 11 345 249 111 2 83 52 6 	ER+PR+: 1.03 (0.55–1.95) 1.00 1.23 (1.05–1.46) 1.67 (1.34–2.07) [< 0.0001] ER–PR–: 0.80 (0.20–3.27) 1.00 0.96 (0.67–1.38) 0.52 (0.26–1.04) [0.017]	Age, family history of BC, age at menarche, parity, age at first birth, education level, OC use, HRT use, diet, alcohol consumption	
Ahn et al. (2007) NIH-AARP USA 1995–2000	99 039 Incidence	BMI 15–18.4 18.5–22.4 22.5–24.9 25.0–27.4 27.5–29.9 30–34.9 35–39.9 ≥ 40 [P_{trend}]	 6 134 179 197 136 175 77 44 	Non-HRT users: 0.64 (0.28–1.45) 1.00 1.19 (0.95–1.49) 1.35 (1.08–1.68) 1.52 (1.29–1.94) 1.55 (1.22–1.96) 1.89 (1.40–2.55) 2.08 (1.44–2.99) [< 0.001]	Age, age at first pregnancy, age at menopause, age at first birth, parity, smoking, education level, race, family history of BC, alcohol consumption, diet, physical activity, oophorectomy	Associations with BMI at age 50 yr similar to BMI at baseline. Association null at age 35 yr, inverse at age 18 yr. Both WC and WHR positively associated with risk

Table 2.2.9a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Ahn et al. (2007) (cont.)	99 039 Incidence	BMI 15–18.4 18.5–22.4 22.5–24.9 25.0–27.4 27.5–29.9 30–34.9 35–39.9 ≥ 40 [P_{trend}]	 11 280 313 257 117 129 40 15	HRT users: 0.79 (0.43–1.44) 1.00 1.13 (0.96–1.33) 1.19 (1.00–1.42) 1.04 (0.83–1.30) 1.14 (0.91–1.42) 1.13 (0.80–1.61) 1.10 (0.64–1.88) [0.22]	Age, age at first pregnancy, age at menopause, age at first birth, parity, smoking, education level, race, family history of BC, alcohol consumption, diet, physical activity, oophorectomy	
Ericson et al. (2007) Malmö cohort Sweden 1991–2003	11 699 Incidence	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 183 147 62	 1.00 1.20 (0.96–1.49) 1.19 (0.89–1.59) [0.41]	Age	
Lundqvist et al. (2007) Twin cohort studies Sweden and Finland 1961–2004	14 058 older twins (mean age at baseline, 56 yr) Incidence	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 12 411 274 59	 0.9 (0.5–1.5) 1.0 1.2 (1.0–1.4) 1.3 (1.0–1.7) [< 0.007]	Smoking, physical activity, education level, diabetes	
Reeves et al. (2007) Population-based cohort United Kingdom 1996–2001	1.2 million Incidence	BMI < 22.5 22.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 per 10 kg/m^2	 879 1336 1262 878 1274	 0.85 (0.80–0.91) 1.00 1.10 (1.04–1.16) 1.21 (1.13–1.29) 1.29 (1.22–1.36) 1.40 (1.21–1.49)	Age, region, SES, reproductive history, smoking, alcohol consumption, physical activity, HRT use	
Reinier et al. (2007) Mammography screening cohort in Vermont USA 1996–2002	32 607 Incidence	BMI < 22.0 22–24.9 25.0–27.4 27.5–29.9 ≥ 30	572 total	 1.0 1.2 (0.9–1.6) 1.4 (1.0–1.8) 1.6 (1.1–2.1) 1.9 (1.4–2.5)	Age, family history of BC, age at first birth, breast density	

Table 2.2.9a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Song et al. (2008) Korean medial insurance cohort Republic of Korea 1994–2003	107 481 Incidence	BMI < 18.5 18.5–20.9 21.0–22.9 23.0–24.9 25.0–26.7 27.0–29.9 ≥ 30 per 1 kg/m^2	 11 59 132 186 159 130 36	 0.54 (0.17–1.73) 0.87 (0.54–1.41) 1.00 1.27 (0.90–1.80) 1.52 (1.07–2.15) 1.97 (1.37–2.83) 1.64 (0.91–2.97) 1.08 (1.04–1.12)	Age, smoking, alcohol consumption, exercise	
Andreotti et al. (2010) Agricultural workers USA 1993–2005	28 319 Incidence	BMI < 18.5 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 5 186 156 93 24 	 – 1.00 1.22 (0.93–1.60) 1.62 (1.17–2.24) 1.07 (0.61–1.87) [0.02]	Age, race, smoking, vegetable intake, exercise, family history of cancer	
Parr et al. (2010) 39 cohorts Asia, Australia, and New Zealand 1961–NR	130 946 Mortality	BMI < 12–18.4 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	324 total	 0.71 (0.22–2.24) 1.00 1.13 (0.85–1.50) 1.63 (1.13–2.35) [0.03]	Age, sex, tobacco use	
Canchola et al. (2012) California Teachers Study USA 1995–2008	52 642 Incidence	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 740 413 218 	ER+PR+: 1.00 1.13 (1.00–1.28) 1.20 (1.03–1.40) [0.01]	Age, race, parity, age at menarche, age at first birth, family history of BC, alcohol consumption, HRT use	No association with BMI at age 18 yr. WC positively associated with risk
		BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 156 91 33 	ER–PR–: 1.00 1.13 (0.87–1.47) 0.77 (0.53–1.12) [0.36]		No association with BMI at age 18 yr. WC not associated with risk

Table 2.2.9a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
White et al. (2012) Population-based Multiethnic Cohort USA 1993–2004	35 495 Incidence	BMI < 20 20–24.9 25–29.9 ≥ 30 [P_{trend}]	 63 316 396 329	Never HRT users: 0.90 (0.69–1.18) 1.00 1.35 (1.17–1.57) 1.60 (1.36–1.87) [< 0.0001]	Age, family history of BC, age at first birth, age at menarche, parity, smoking, physical activity, alcohol consumption, height	Analyses available by race/ ethnicity: non-Hispanic White, Latina, Japanese, Native Hawaiian, African American
	28 200 Incidence	BMI < 20 20–24.9 25–29.9 ≥ 30 [P_{trend}]	 132 610 376 190	Current HRT users: 1.02 (0.84–1.23) 1.00 1.04 (0.91–1.18) 1.14 (0.97–1.35) [0.18]	Age, family history of BC, age at first birth, age at menarche, parity, smoking, physical activity, alcohol consumption, height	
Fourkala et al. (2014) Ovarian cancer screening cohort United Kingdom 2001–2012	1.2 million Incidence	BMI per 1 kg/m²	1090	1.06 (1.01–1.12)	Age, age at menarche, age at menopause	
	1.2 million Incidence	Skirt size per 1 unit	1090	1.05 (1.01–1.08)		Skirt size remained significant after adjustment for BMI
Gaudet et al. (2014) CPS2 cohort USA 1997–2006	28 965 Incidence	BMI < 25 25–29.9 ≥ 30 per 1 kg/m²	 441 401 246	 1.00 1.34 (1.17–1.54) 1.60 (1.36–1.89) 1.04 (1.02–1.06)	Age, family history of BC, education level, height, age at menopause, tobacco use, diabetes, race, age at first birth, physical activity, alcohol consumption, OC use, HRT use	Similar association with WC , but in multivariate adjustment, the BMI association persisted but the WC association did not. Cases overlap with Feigelson et al. (2004)
Bandera et al. (2015) Pooled data on African American women in 4 cohorts USA 1995–2013	15 234 Incidence	BMI < 25 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 254 469 361 329	ER+: 1.00 1.10 (0.93–1.30) 1.21 (1.01–1.45) 1.32 (1.09–1.60) [0.002]	Age, education level, study, family history of BC, age at menarche, parity, breastfeeding, age at first birth, HRT use, OC use	Inverse association with BMI in young adulthood and risk. WHR positively associated with risk

Table 2.2.9a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Bandera et al. (2015) (cont.)		BMI < 25 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 130 200 156 126	ER–: 1.00 0.87 (0.69–1.11) 0.90 (0.70–1.17) 0.82 (0.63–1.08) [0.23]	Age, education level, study, family history of BC, age at menarche, parity, breastfeeding, age at first birth, HRT use, OC use	Inverse association with BMI in young adulthood and risk. WHR positively associated with risk
Kabat et al. (2015) Women's Health Initiative cohort USA 1992–2013	143 901 Incidence	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	7039 total	 1.00 1.09 (1.01–1.18) 1.12 (1.04–1.21) 1.23 (1.14–1.33) 1.41 (1.31–1.53) [< 0.0001]	Age, alcohol consumption, smoking, physical activity, age at menarche, age at first birth, parity, HRT use, family history of BC, ethnicity, education level	WC, WHR not associated any more strongly than BMI
Dartois et al. (2016) E3N cohort France 1990–2008	67 634 Incidence	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30	 84 2310 610 134	 – 1.00 1.19 (1.10–1.30) 1.25 (1.07–1.46)	Age, family history of BC, education level, height, age at menarche, age at menopause, tobacco use, parity, physical activity, alcohol consumption, OC use, HRT use	Earlier study by Tehard & Clavel-Chapelon (2006) showed similar association between WC and risk, but no associations with WHR

BC, breast cancer; BMI, body mass index (in kg/m^2); CI, confidence interval; CPS, Cancer Prevention Study; EPIC, European Prospective Investigation into Cancer and Nutrition; HRT, hormone replacement therapy; NHS, Nurses' Health Study; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; NR, not reported; OC, oral contraceptive; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SES, socioeconomic status; WC, waist circumference; WHR, waist-to-hip ratio; yr, year or years

Table 2.2.9c Case–control studies of body mass index and cancer of the breast in postmenopausal women

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Li et al. (2000) USA 1988–1990	479 435 Population; Caucasian women	BMI at age 50–64 yr ≤ 21.5 21.6–24.1 24.2–27.5 ≥ 27.6	 111 126 120 122	 1.00 1.2 (0.9–1.8) 1.1 (0.8–1.6) 1.5 (1.1–2.3)	Age, family history of BC, parity
Trentham-Dietz et al. (2000) USA January 1992–December 1994	Postmenopausal women aged 50–79 yr 5031 5255 Population; matched by age	BMI 11.62–21.94 21.95–24.02 24.03–26.44 26.45–29.44 29.45–54.87 [P_{trend}]	 841 920 971 1013 1286	 1.0 1.0 (0.9–1.2) 1.1 (1.0–1.3) 1.2 (1.1–1.4) 1.6 (1.4–1.9) [< 0.001]	Logistic conditional models on age and state. Parity, age at FFTP, family history of BC, recent alcohol consumption, education level, age at menopause
de Vasconcelos et al. (2001) Brazil May 1995–February 1996	177 377 Hospital/population; visitors at hospital; 27 relatives of BC patients	Current BMI < 24.55 24.55–27.64 27.65–30.79 ≥ 30.80 [P_{trend}]	 38 29 35 29	 1.00 0.61 (0.33–1.14) 0.84 (0.46–1.53) 0.61 (0.33–1.14) [0.24]	Age, parity, family history of BC, education level
Shu et al. (2001) China August 1996–March 1998	1459 aged 25–64 yr enrolled from Shanghai Cancer Registry 1556 Population; randomly selected from female residents of Shanghai (Shanghai Resident Registry), matched to cases by age, 5-yr interval	BMI at diagnosis < 20.70 20.70–22.79 22.80–25.09 25.10–27.90 ≥ 28.0 [P_{trend}]	 63 95 134 125 83	 1.0 1.4 (0.9–2.1) 1.5 (1.0–2.3) 1.7 (1.1–2.6) 2.0 (1.2–3.2) [0.003]	Age, education level, family history of BC, ever had fibroadenoma, age at menarche, age at first live birth, exercise, age at menopause
Yoo et al. (2001) Japan 1988–1992	1154 aged ≥ 25 yr, with no previous history of cancer 21 714 Hospital	BMI per 1 kg/m^2		1.07 (1.04–1.10)	Age at interview, occupation, family history of BC, age at menarche, age at menopause, age at FFTP, number of FTPs, months of breastfeeding, alcohol consumption, cigarette smoking, weight, height

Table 2.2.9c (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Friedenreich et al. (2002) Canada, Alberta 1995–1997	1233 1241 Population; frequency-matched to cases by age, 5-yr interval, and place of residence (urban/rural)	BMI < 24.1 ≥ 24.1– < 27.3 ≥ 27.3– < 31.3 ≥ 31.3 [P_{trend}]	 206 179 187 199	 1.00 0.93 (0.69–1.24) 0.94 (0.70–1.26) 0.99 (0.74–1.32) [0.55]	Current age, total energy intake, total lifetime physical activity, education level, ever use of HRT, ever diagnosed with benign breast disease, first-degree family history of BC, ever alcohol consumption, current smoking
Adebamowo et al. (2003) Nigeria, urban 1998–2000	234 273 Population	BMI ≥ 30 vs < 30	 31	 1.82 (0.78–4.31)	Age, age at menarche, regularity of periods; only natural menopause
Carpenter et al. (2003) Canada, USA, and western Europe Group I: March 1987–December 1989 Group II: January 1992–December 1992 Group III: September 1995–April 1996	1883 Caucasian (including Hispanic), born in Canada, USA, or western Europe, diagnosed at age ≥ 55 yr 1628 Population; matched to cases by neighbourhood	BMI, 1 yr before diagnosis < 21.7 21.7–23.6 23.7–27.0 ≥ 27.1 [P_{trend}]	 366 379 497 641	 1.00 1.10 (0.88–1.37) 1.18 (0.95–1.46) 1.34 (1.09–1.66) [0.005]	Age at FFTP, age at menarche, age at menopause, family history of BC, interviewer, average MET hours per week of lifetime exercise activity
Li et al. (2003) USA 1997–1999	975 1007 Population	BMI at age 65–79 yr < 23.32 23.33–26.20 26.21–30.11 ≥ 30.12	 209 240 245 245	 1.00 1.3 (1.0–1.7) 1.4 (1.1–1.9) 1.4 (1.0–1.8)	Age, income
Pan et al. (2004) Canada 1994–1997	1449 postmenopausal 2492 Population	BMI < 25 25–30 ≥ 30 [P_{trend}]	1449	 1.00 1.17 (1.00–1.39) 1.66 (1.33–2.06) [< 0.0001]	
Chow et al. (2005) Hong Kong Special Administrative Region 1995–2000	Chinese women aged 24–85 yr 198 353 Hospital; followed up for benign breast disease; no BC	BMI at diagnosis < 19 19–23 23–27 27–31 > 31 [P_{trend}]	 10 38 42 20 10	 1.00 1.78 (0.79–4.04) 1.73 (1.04–2.86) 2.06 (1.08–3.93) 3.82 (1.03–14.27) [< 0.001]	

Table 2.2.9c (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Zhu et al. (2005) USA 1995–1998	African American, aged 20–64 yr 304, without previous cancer history, interviewed 1–3 yr after diagnosis 305 Population; no history of BC, matched to cases by age (5-yr intervals) and county; women were offered money to participate	BMI at diagnosis < 25 25– < 30 ≥ 30 [P_{trend}]	 45 55 61	 1.00 1.50 (0.70–3.21) 2.32 (1.04–5.19) [0.039]	Family history of BC, history of benign breast disease, alcohol consumption, smoking, menstrual status, age at menarche, menstrual cycle length, parity, age at first birth, miscarriages, history of radiotherapy, use of estrogen other than for birth control, history of losing weight, history of taking iron pills, age at first sexual intercourse, daily energy intake, physical activity, use of electric bedding devices, history of infertility, demographic variables
Okobia et al. (2006) Nigeria September 2002–April 2004	250 250 Hospital; patients recruited from the same hospitals as cases, treated for non-malignant and non-hormonal surgical disorders	BMI, mean (± SD) Cases, 24.74 (± 6.89) Controls, 25.03 (± 5.33)	108	0.76 (0.44–1.32)	Age
Wu et al. (2006) USA 1995–2001	Asian American (Chinese, Japanese and Filipino) women aged 25–74 yr 1277 1160 Population; neighbourhood controls, frequency-matched by ethnicity and 5-yr age groups	BMI, recent ≤ 20.43 > 20.43–22.32 > 22.32–24.60 > 24.60 [P_{trend}]	 139 138 187 241	 1.00 0.94 (0.65–1.36) 1.13 (0.79–1.62) 1.35 (0.95–1.93) [0.045]	Age, ethnicity, duration of residence in the USA, education level, age at menarche, number of live births, age at menopause, intake of tea and soy during adolescence and adult life, years of physical activity, height
Garmendia et al. (2007) Chile, Santiago 2005	170 diagnosed within 2 mo before recruitment, aged 33–86 yr 170 Population; mammography service of the same hospitals	BMI ≥ 30	 122	 0.66 (0.39–1.14)	Crude OR; controls matched to cases by 5-yr age interval and place of residence
Kruk (2007) Poland 2003–2007	858 1085 Hospital; controls frequency-matched by 5-yr age group and place of residence (urban/rural)	Current BMI < 22.5 22.6– < 25.0 25.0– < 30.0 ≥ 30.0 [P_{trend}]	 78 127 221 122	 1.00 1.85 (0.98–2.84) 2.13 (1.45–3.13) 2.62 (1.66–4.11) [< 0.0001]	Age, recreational activity, breastfeeding, stress, passive smoking $P_{interaction}$ = 0.002

Table 2.2.9c (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Tian et al. (2007) Taiwan, China January 2004–December 2005	244 aged 22–87 yr 244 Hospital; recruited from health examination clinics at the same hospital and time, no history of cancer, matched by menopausal status, date of enrolment, and duration of fasting	BMI ≤ 24.45 > 24.45	 54 49	 1.00 2.94 (1.53–5.68)	Age at enrolment, fasting status, levels of adiponectin
Mathew et al. (2008) India 2002–2005	1866 1873 Accompanying persons to cancer cases; matched by age ± 5 yr and residence type (urban/rural)	BMI < 25 25–29.9 ≥ 30	 559 297 76	 1.00 1.29 (1.00–1.66) 1.00 (0.64–1.54)	Age, centre, religion, marital status, education level, SES, residence status, parity, age at first birth, duration of breastfeeding, physical activity
Montazeri et al. (2008) Islamic Republic of Iran 1996–2000	116 in situ and invasive cancers 116 Hospital; women presenting for clinical breast examination	BMI 18.5–24.9 25–29.9 ≥ 30	 23 51 42	 1.00 2.53 (1.20–5.35) 3.21 (1.15–8.47)	Age, age at menopause, family history of BC, parity
Nemesure et al. (2009) Barbados July 2002–March 2006	Women of African descent aged ≥ 21 yr 222 454 Population; Barbados Statistical Services; frequency-matched by 5-yr age group	BMI at age ≥ 50 yr < 25 25–30 ≥ 30	 51 42 49	 1.00 0.67 (0.36–1.24) 0.70 (0.38–1.28)	Age, HRT use, parity, family history of BC, history of benign breast disease, age at first pregnancy, age at menarche, physical activity, other body size variable
Shin et al. (2009) China 1996–1998 (phase 1), 2002–2005 (phase 2)	3452 aged 20–64 yr (phase 1), 20–70 yr (phase 2) 3474 Population; controls frequency-matched to cases by age	Current BMI ≤ 20.9 21–22.9 23–24.9 ≥ 25 [P_{trend}]	 192 285 348 543	 1.0 1.3 (1.0–1.7) 1.5 (1.2–1.9) 1.8 (1.4–2.2) [< 0.001]	

Table 2.2.9c (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Berstad et al. (2010) USA 1994–1998	4575 4682 Caucasian: 2953 3021 African American: 1622 1661 Population	BMI, 5 yr before reference date < 25 25–29 30–34 ≥ 35 [P_{trend}]	 918 579 254 149	 1.00 0.98 (0.84–1.14) 1.02 (0.82–1.26) 1.09 (0.83–1.43) [0.67]	Age, race, education level, study site, first-degree family history of BC, parity, age at menopause, HRT use, BMI at age 18 yr
Healy et al. (2010) Ireland NR	200 519 (age-matched) healthy women	BMI, quartiles Q4 vs Q1 > 30 vs 20–25		 2.2 (1.3–3.7) 2.04 (1.3–3.3)	 $P = 0.002$ $P = 0.004$
Ogundiran et al. (2010) Nigeria 1998–2009	1233 1101 Population; community register of Ibadan	BMI < 21 21–23.9 24–27.9 ≥ 28 [P_{trend}]	 100 115 139 151	 1.00 1.04 (0.63–1.71) 0.88 (0.55–1.41) 0.76 (0.48–1.21) [0.15]	Age at diagnosis or interview, ethnicity, education level, age at menarche, number of live births, age at first live birth, duration of breastfeeding, age at menopause, family history of BC, benign breast disease, OC use, alcohol consumption, height $P_{interaction} = 0.85$
Barnes et al. (2011) Germany 2001 (Hamburg); 2002 (Rhein-Neckar-Karlsruhe) to 2005	3074 6386 Population; frequency-matched by year of birth and study region	BMI at age 50–74 yr ≤ 22.4 22.5–24.9 25–29.9 ≥ 30	 1354 993 622 105	 1.00 1.06 (0.95–1.17) 1.04 (0.92–1.18) 0.93 (0.73–1.19)	Family history of BC, benign breast disease, age at menarche, OC use, breastfeeding, parity, cause of menopause, age at menopause, alcohol consumption, HRT use, recent physical activity, occupational status, year of birth, study region, lifetime number of mammograms
Cerne et al. (2011) Slovenia January 2006–December 2008	Caucasian women 784, aged 50–69 yr at diagnosis 709 Hospital; no history of BC	BMI < 25 25–30 ≥ 30	 267 327 190	 1.00 1.34 (1.04–1.73) 1.89 (1.36–2.63)	

Table 2.2.9c (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Cribb et al. (2011) Canada, Prince Edward Island 1999–2002	207 621 Population; women presenting for routine mammography screening; matched by age, menopausal status, and family history of BC	BMI > 25 vs ≤ 25	61%	1.71 (1.08–2.70)	
Rosato et al. (2011) Pooled analysis of 2 studies in Italy and Switzerland 1983–1994 (1st study), 1991–2007 (2nd study)	3869, postmenopausal 4082 Hospital; admitted for acute, non-neoplastic diseases, not related to gynaecological or hormonal conditions, matched by age and study centre	BMI < 30 ≥ 30	3292 578	1.00 1.26 (1.11–1.44)	Age, study centre, study period, education level, alcohol consumption, age at menarche, age at first birth, age at menopause, HRT use, family history of BC
Attner et al. (2012) Sweden, County of Scania 2005–2007	2613 19 898 Registry: Population Registry of Scania	Obesity	2.1%	0.79 (0.52–1.19)	90–1461 days (4 yr) before diagnosis Obesity defined as comorbidity diagnosis of obesity (ICD-10: E66)
Ghiasvand et al. (2012) Islamic Republic of Iran September 2005–December 2008 (cases), May–August 2009 (controls)	493 women aged ≥ 50 yr enrolled within 6 mo after diagnosis 493 Hospital; frequency-matched to cases by 5-yr age groups and province of residence; no history of BC	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 4 129 208 141	 0.60 (0.17–2.11) 1.00 1.39 (1.02–1.94) 1.61 (1.18–2.30) [0.01]	Age, parity, age at menarche, education level, occupation, height, family history of BC
Ronco et al. (2012) Uruguay 2004–2009	367 545 Hospital; non-hospitalized women aged 23–69 yr; age-matched, with normal mammography	BMI < 25 25–30 ≥ 30	165	 3.60 (0.33–39.8) 5.40 (1.77–16.6) 0.84 (0.33–2.12)	Age, residence, first-degree family history of BC, age at menarche, number of live births, age at first delivery, months of breastfeeding
Bandera et al. (2013a) USA, New York City and New Jersey NR	978 postmenopausal women of African ancestry 958 Population; random-digit dialling	Current BMI < 25 25–29.99 ≥ 30 [P_{trend}]	 74 131 304	 1.00 0.93 (0.60–1.44) 0.98 (0.66–1.45) [0.94]	Age, ethnicity, country of origin, education level, family history of BC, history of benign breast disease, age at menarche, age at menopause, parity, breastfeeding, age at first birth, HRT use, OC use

Table 2.2.9c (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
John et al. (2013) USA Hispanic cases: 1995–2002 African American cases: 1995–1999 Non-Hispanic White cases: 1995–1999	1389 of 2571 1644 of 2706 Hispanic: 1119 1462 African American: 543 598 Non-Hispanic White: 596 646 Population; controls randomly selected and frequency-matched by race/ethnicity and expected 5-yr age distribution of cases	Current BMI < 25.0 25.0–29.9 ≥ 30 [P_{trend}]	 208 278 312	 1.00 0.95 (0.74–1.21) 0.94 (0.74–1.20) [0.64]	All non-users of HRT
Noh et al. (2013) Republic of Korea 1995–2011	270 540 Population; women attending routine health examination, with no evidence of malignant disease; matched by age, menopausal status, and time of visit to Health Promotion Center	BMI < 25 ≥ 25	106 69 37	 1.00 2.24 (1.22–4.10)	Number of live births, family history of BC, age at menarche, smoking, alcohol consumption, physical activity, use of HRT
Sangrajrang et al. (2013) Thailand May 2002–March 2004; August 2005–August 2006	1126 1135 Hospital/population; visitors of hospital patients admitted for conditions other than BC or ovarian cancer	Current BMI < 18.5 18.5–24.9 ≥ 25.0	 27 248 203	 1.94 (0.98–3.85) 1.00 1.67 (1.24–2.25)	
Singh & Jangra (2013) India August 2009–July 2010	128 aged 20–80 yr 128 Hospital; enrolled from the general surgical ward, without history of any type of cancer, matched to cases within 2-yr age interval	BMI < 18.5 18.5–23.0 23.0–25.0 25.0–30.0 > 30.0 [P_{trend}]	 4 34 14 21 6	 0.217 1.00 1.647 1.647 2.118 [0.016]	[No CIs provided]

Table 2.2.9c (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Troisi et al. (2013) USA 1974–2009	Women aged < 85 yr 22 646 with primary in situ or invasive cancer 224 721 Population; frequency-matched to cases by parity, age, calendar year of delivery, and race/ethnicity	Pre-pregnancy BMI (after 1992)			Age at delivery, race/ethnicity, parity at index birth, year of index birth
		Aged ≥ 50 yr at diagnosis:	144		
		< 18.5	3	0.62 (0.19–2.06)	
		18.5– < 25	105	1.00	
		25– < 30	19	0.60 (0.36–1.01)	
		≥ 30	17	0.84 (0.48–1.46)	
		[P_{trend}]		[0.33]	
Amadou et al. (2014) Mexico (Mexico City, Monterrey, Veracruz) 2004–2007	1000 1074 Population	BMI			Age, health-care system, region, SES, breastfeeding, family history of BC, alcohol consumption, physical activity, total energy intake, height, current BMI
		< 25	89	1.00	
		25–29.0	239	0.96 (0.64–1.44)	
		≥ 30	257	0.75 (0.51–1.12)	
		[P_{trend}]		[0.068]	
Elkum et al. (2014) Saudi Arabia 2007–2012	Arab women 534 638 Population; unmatched, randomly selected from primary health care visitors; free of BC	BMI			None
		18.5–24.9	60	1.00	
		25–29.9	70	1.25 (0.73–2.15)	
		≥ 30	137	1.66 (1.02–2.70)	
		BMI			Age, BMI, marital status, HRT use, age at menarche, breastfeeding, education level
		18.5–24.9		1.00	
		≥ 25		2.22 (1.32–3.72)	
Minatoya et al. (2014) Japan September 2012–July 2013	66 66 Hospital; hospitalized for CVD, hypertension, arrhythmia, nephritis, nephrosis; no BC or diabetes; matched by age ± 3 yr and menopausal status	BMI			Age at menarche, smoking, alcohol consumption, parity, OC/HRT use P_{trend} based on χ^2 test of log-transformed continuous variables
		< 19.1	4	0.28 (0.07–1.11)	
		≥ 19.1– < 22.3	15	1.00	
		≥ 22.5	25	1.39 (0.50–3.86)	
		[P_{trend}]		[0.043]	
Trentham-Dietz et al. (2014) USA Pooled analysis of 5 case–control studies 1988–2008	Women aged < 75 yr 23 959 28 304 Population	BMI	16 517		Age, state of residence, study period, family history of BC, alcohol consumption, age at menarche, parity, age at first pregnancy, OC use, smoking status
		< 18.5		0.75 (0.64–0.88)	
		18.5–24.9		1.00	
		25–29.9		1.11 (1.06–1.17)	
		≥ 30		1.32 (1.24–1.40)	

BC, breast cancer; BMI, body mass index (in kg/m^2); CI, confidence interval; CVD, cardiovascular diseases; FFTP, first full-term pregnancy; FTP, full-term pregnancy; HRT, hormone replacement therapy; MET, metabolic equivalent; mo, month or months; NR, not reported; OC, oral contraceptive; OR, odds ratio; SES, socioeconomic status; yr, year or years

[a] In this table, the study population describes the population of the entire study, and the numbers of cases and controls refer to the number of women in the study, not necessarily the number of postmenopausal women.

Table 2.2.9g Case–control studies of body mass index and cancer of the breast in postmenopausal women, by hormone receptor status

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Enger et al. (2000) USA 1997–1989	760 1091 Population; matched by age, race (Hispanic/non-Hispanic), parity, and residential neighbourhood	BMI ER+PR+: < 21.7 21.7–23.6 23.7–27.0 ≥ 27.1 [P_{trend}] ER+PR–: < 21.7 21.7–23.6 23.7–27.0 ≥ 27.1 [P_{trend}] ER–PR–: < 21.7 21.7–23.6 23.7–27.0 ≥ 27.1 [P_{trend}]	 71 101 127 151 34 38 46 41 31 36 25 35	 1.00 1.36 (0.96–1.94) 1.78 (1.26–2.51) 2.45 (1.73–3.47) [0.0001] 1.00 1.12 (0.68–1.85) 1.35 (0.83–2.20) 1.29 (0.78–2.15) [0.24] 1.00 1.19 (0.71–1.99) 0.80 (0.45–1.40) 1.20 (0.70–2.05) [0.85]	Age at reference year, SES, number of FTPs, months of breastfeeding, age at menopause, HRT use, family history of BC, alcohol consumption, physical activity Results available for BMI at age 18 yr
Huang et al. (2000) USA 1993–1996	862 790 Population	BMI ER+PR+: < 23 23–31 > 31 ER–PR–: < 23 23–31 > 31	213 111 	 1.0 1.1 (0.7–1.8) 1.6 (0.9–3.0) 1.0 1.0 (0.6–1.9) 0.8 (0.4–1.7)	Age at selection, race, age at menarche, nulliparity/age at FFTP, breastfeeding, abortion or miscarriage, WHR, OC use, HRT use, first-degree family history of BC, medical radiation to the chest, cigarette smoking, alcohol consumption, education level, and the offset term
Yoo et al. (2001) Japan 1988–1992	Women aged ≥ 25 yr 1154, no previous history of cancer 21 714 Hospital	BMI per 1 kg/m^2 ER+ ER– PR+ PR–		 1.09 (1.05–1.13) 1.05 (0.99–1.12) 1.09 (1.04–1.14) 1.07 (1.02–1.11)	

Table 2.2.9g (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Cotterchio et al. (2003) Canada ECSS study: April 1995–March 1996 WHS study: July 1996–September 1998	1867 2452 Population; frequency-matched to cases within 5-yr age groups	BMI			$P_{heterogeneity}$ = 0.29
		ER+PR+:			
		< 20	45	0.72 (0.43–1.21)	
		20–25	489	1.00	
		25.1–27	208	1.10 (0.84–1.43)	
		> 27	631	1.61 (1.32–1.98)	
		ER–PR–:			
		< 20	25	1.34 (0.72–2.49)	
		20–25	172	1.00	
		25.1–27	72	1.09 (0.74–1.61)	
		> 27	190	1.48 (1.09–1.99)	
Rusiecki et al. (2005) USA January 1994–December 1997	Women aged 40–80 yr 420, no prior BC or benign breast disease 406 Hospital; no BC or benign breast disease or incident fibroadenoma, or atypical hyperplasia, no previous cancer disease except for non-melanoma of the skin, frequency-matched by age within 5-yr intervals	BMI			
		ER+PR+:	104		Age, age at menarche, parity (nulliparous treated separately), age at FFTP, lifetime lactation, ever use of estrogen, alcohol consumption, smoking, family history of BC, race
		< 25.0		1.0	
		25.0–29.99		0.7 (0.4–1.2)	
		≥ 30.0		1.0 (0.6–1.9)	
		ER+PR–:	65		
		< 25.0		1.0	
		25.0–29.99		0.7 (0.4–1.4)	
		≥ 30.0		0.8 (0.4–1.8)	
		ER–PR+:	41		
		< 25.0		1.0	
		25.0–29.99		1.3 (0.6–2.8)	
		≥ 30.0		0.9 (0.3–2.3)	
		ER–PR–:	107		
		< 25.0		1.0	
		25.0–29.99		1.3 (0.7–2.1)	
		≥ 30.0		1.3 (0.7–2.3)	
		ER+PR+ vs ER–PR–:	104		*P* for four categories (ER+PR+, ER+PR–, ER–PR+, ER–PR–), 0.54
		< 25.0		1.0	
		25.0–29.99		0.7 (0.3–1.4)	
		≥ 30.0		0.7 (0.3–1.4)	

Table 2.2.9g (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Tsakountakis et al. (2005) Greece 1996–2002	384 women with primary invasive BC 566 Hospital; women referred for breast screening and who did not develop cancer	BMI > 29 vs ≤ 29: HER2/neu+ HER2/neu– Ratio HER2/neu+ to HER2/neu– ER+ cases: HER2/neu+ HER2/neu– Ratio HER2/neu+ to HER2/neu– ER– cases: HER2/neu+ HER2/neu– Ratio HER2/neu+ to HER2/neu–	 180 total 197 total 	 4.83 (2.75–8.49) 2.67 (1.56–4.55) 2.23 (1.20–4.15) 5.59 (2.58–12.13) 2.48 (1.52–5.32) NS 5.33 (2.59–10.94) 2.41 (1.15–5.04) 2.46 (0.97–6.21)	Age, residence, menopausal age, OC use, HRT use, first-degree family history of BC, age at FFTP, parity, abortion, lactation, medication to suppress lactation, radiation to the chest, BMI, benign breast disease
Li et al. (2006) USA 1997–1999	975 1007 Population	BMI, 65–79 yr ER+PR+: ≤ 24.9 25.0–29.9 ≥ 30.0 ER+PR–: ≤ 24.9 25.0–29.9 ≥ 30.0 ER–PR–: ≤ 24.9 25.0–29.9 ≥ 30.0	 615 218 223 174 139 55 48 36 95 38 35 22	 1.0 1.3 (1.0–1.6) 1.3 (1.0–1.7) 1.0 1.1 (0.7–1.7) 1.1 (0.7–1.7) 1.0 1.1 (0.7–1.8) 0.9 (0.5–1.6)	Age at diagnosis, reference year, type of menopause
Rosenberg et al. (2006) Sweden October 1993–March 1995	Women aged 50–74 yr 2643 3065 Population: frequency-matched to cases, with no history of invasive cancer other than non-melanoma of the skin	Recent BMI ER+PR+: < 22.2 22.2–24.0 24.1–25.8 25.9–28.2 ≥ 28.3	 105 128 135 176 228	 1.0 1.3 (1.0–1.7) 1.3 (1.0–1.8) 1.7 (1.3–2.3) 2.2 (1.7–2.8)	*P* for ER+PR+ vs ER–PR–, 0.48 Exclusion: women who are ever-users of HRT Adjusted for age, age at first birth

Table 2.2.9g (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Rosenberg et al. (2006) (cont.)		ER+PR–:			
		< 22.2	45	1.0	
		22.2–24.0	35	0.8 (0.5–1.3)	
		24.1–25.8	40	0.9 (0.6–1.5)	
		25.9–28.2	37	0.9 (0.5–1.3)	
		≥ 28.3	45	1.0 (0.7–1.6)	
		ER–PR+:			
		< 22.2	7	1.0	
		22.2–24.0	2	0.3 (0.1–1.5)	
		24.1–25.8	11	1.7 (0.7–4.5)	
		25.9–28.2	7	1.1 (0.4–3.1)	
		≥ 28.3	14	2.2 (0.9–5.6)	
		ER–PR–:			
		< 22.2	35	1.0	
		22.2–24.0	41	1.3 (0.8–2.0)	
		24.1–25.8	45	1.4 (0.9–2.2)	
		25.9–28.2	50	1.5 (0.9–2.3)	
		≥ 28.3	55	1.6 (1.0–2.5)	
Phipps et al. (2008) USA Study 1: April 1997–May 1999 Study 2: January 2000–March 2004	1233 (ductal only), aged 65–79 yr at diagnosis (study 1), and 55–74 yr at diagnosis (study 2) (study 1: 975; study 2: 1044) 1447 (study 1: 1007; study 2: 469) Population; from Health Care Financing Administration records, frequency-matched to cases by age	BMI			Age, reference year
		HER2-overexpressing cases:			
		< 25.0	15	1.0	
		25.0–29.0	11	0.8 (0.4–1.8)	
		≥ 30.0	13	1.1 (0.5–2.4)	
		[P_{trend}]		[0.78]	
		Triple-negative cases:			
		< 25.0	24	1.0	
		25.0–29.0	26	1.2 (0.7–2.1)	
		≥ 30.0	27	1.4 (0.8–2.5)	
		[P_{trend}]		[0.26]	
		BMI at age 30 yr			
		HER2-overexpressing cases:			
		< 20.8	11	1.0	
		20.8–22.3	9	0.8 (0.3–2.0)	
		22.4–24.3	6	0.6 (0.2–1.6)	
		> 24.3	13	1.2 (0.5–2.8)	
		[P_{trend}]		[0.74]	

Table 2.2.9g (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Phipps et al. (2008) (cont.)		Triple-negative cases:			
		< 20.8	21	1.0	
		20.8–22.3	18	0.9 (0.5–1.7)	
		22.4–24.3	11	0.6 (0.3–1.2)	
		> 24.3	27	1.4 (0.8–2.5)	
		[P_{trend}]		[0.41]	
Dey et al. (2009) South India 2002–2005	431 387 Population; visitors of non-BC patients, matched to cases by age (5-yr groups) and residence type (urban/rural)	BMI			Age, religion, education level, SES, age at menarche, parity, age at marriage, total duration of breastfeeding, physical activity per day
		ER+:	170		
		≤ 21.4		1.00	
		21.4–25.1		1.72 (1.04–2.84)	
		> 25.1		1.34 (0.81–2.23)	
		[P_{trend}]		[0.32]	
		ER–:	261		
		≤ 21.4		1.00	
		21.4–25.1		1.35 (0.88–2.07)	
		> 25.1		1.51 (0.98–2.30)	
		[P_{trend}]		[0.07]	
Bao et al. (2011) China Phase I: 1996–1998, Phase II: 2002–2005	1045 1508 Population; randomly selected, Shanghai Resident Registry; frequency-matched by 5-yr age groups ER+PR+: 522 ER–PR–: 299	BMI			Age, education, history of breast fibroadenoma, first-degree family history of BC, regular exercise, years of menstruation, history of live birth, parity, study phase (I or II)
		ER+PR+:			
		< 21.00	54	1.00	
		21.00–23.02	100	1.59 (1.09–2.33)	
		23.03–25.15	152	1.93 (1.34–2.79)	
		≥ 25.16	215	2.40 (1.65–3.47)	
		[P_{trend}]		[< 0.01]	
		ER–PR–:			
		< 21.00	46	1.00	
		21.00–23.02	67	1.10 (0.72–1.68)	
		23.03–25.15	87	1.06 (0.70–1.60)	
		≥ 25.16	99	1.00 (0.66–1.53)	
		[P_{trend}]		[0.88]	

Table 2.2.9g (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Barnes et al. (2011) Germany 2001–2005	3074 6386 Population; frequency-matched by year of birth and study region	BMI ER+PR+: ≤ 22.4 22.5–24.9 25–29.9 ≥ 30 ER+PR–: ≤ 22.4 22.5–24.9 25–29.9 ≥ 30 ER–PR–: ≤ 22.4 22.5–24.9 25–29.9 ≥ 30	 831 653 402 70 226 152 90 12 252 156 110 22	 1.00 1.15 (1.02–1.30) 1.13 (0.97–1.31) 1.06 (0.80–1.42) 1.00 0.96 (0.78–1.20) 0.90 (0.69–1.18) 0.63 (0.34–1.16) 1.00 0.87 (0.70–1.07) 0.92 (0.72–1.18) 0.94 (0.59–1.50)	Family history of BC, benign breast disease, age at menarche, duration of OC use, duration of breastfeeding, parity, cause of menopause, age at menopause, alcohol consumption, HRT use, recent physical activity, occupational status, year of birth, study region, lifetime number of mammograms
Dogan et al. (2011) Turkey NR	250 250 Hospital	BMI, mean ER+ PR+ Luminal		 1.144 (1.063–1.746) 1.053 (1.095–1.756) 1.245 (1.023–1.456)	Mostly postmenopausal women, but not clearly stated
Gaudet et al. (2011) USA December 1980–December 1982	890 3432 Population; frequency-matched, aged ≤ 56 yr	BMI treated as ordinal variable Underweight, < 18.5 Normal weight, 18.5– < 25.0 Overweight, 25.0– < 30.0 Obese, ≥ 30.0 Luminal A (n = 455) Luminal B (n = 72) HER2/neu+ (n = 117) Triple-negative (n = 246)	 151 18 57 86	 1.16 (0.87–1.54) 0.83 (0.36–1.93) 0.93 (0.57–1.52) 1.02 (0.70–1.48)	Age at diagnosis, age at menarche, nulliparity, age at first birth per 5-yr interval, duration of breastfeeding, ever use of OC, benign breast disease, family history of BC *P* for subtype vs luminal A: 0.58 0.53 0.72
Bandera et al. (2013b) USA NR	Postmenopausal women of African ancestry 978 958 Population; random-digit dialling	Current BMI ER+PR+: < 25 25–29.99 ≥ 30 [P_{trend}]	 26 49 131 	 1.00 1.05 (0.55–1.98) 1.04 (0.50–2.18) [0.95]	Age, ethnicity, country of origin, education level, family history of BC, history of benign breast disease, age at menarche, parity, breastfeeding, age at first birth, HRT use, OC use

Table 2.2.9g (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Bandera et al. (2013b) (cont.)		ER–PR–: < 25 25–29.99 ≥ 30 [P_{trend}]	 20 34 47	 1.00 0.77 (0.38–1.59) 0.37 (0.15–0.96) [0.03]	
John et al. (2013) USA Hispanic cases: 1995–2002 African American cases: 1995–1999 Non-Hispanic White cases: 1995–1999	1389 of 2571 1644 of 2706 Hispanic: 1119 1462 African American: 543 598 Non-Hispanic White: 596 646 Population; controls randomly selected and frequency-matched by race/ethnicity and expected 5-yr age distribution of cases	Current BMI ER+PR+: < 25.0 25.0–29.9 ≥ 30 [P_{trend}] ER–PR–: < 25.0 25.0–29.9 ≥ 30 [P_{trend}]	 98 141 175 34 46 54 	 1.00 1.09 (0.80–1.49) 1.30 (0.95–1.78) [0.09] 1.00 0.75 (0.46–1.22) 0.72 (0.45–1.16) [0.21]	All non-users of HRT Results available for Hispanic, African American, and non-Hispanic White women separately
		BMI in young adulthood ER+PR+: T1: ≤ 21.2 T2: 21.3–23.7 T3: > 23.7 [P_{trend}] ER–PR–: T1: ≤ 21.2 T2: 21.3–23.7 T3: > 23.7 [P_{trend}]	 147 133 116 46 43 37 	 1.00 0.87 (0.65–1.15) 0.73 (0.54–0.98) [0.04] 1.00 0.82 (0.52–1.29) 0.61 (0.38–0.97) [0.04]	All non-users of HRT Results available for Hispanic, African American, and non-Hispanic White women separately
Kawai et al. (2013) Japan 1997–2009	1017 2902 Hospital; female non-cancer patients = benign tumours, cardiovascular diseases, digestive tract diseases, respiratory tract disease, urological–gynaecological disease	BMI ER+PR+: < 18.5 18.5–22.1 22.1–25.0 25.0–30.0 ≥ 30.0 [P_{trend}]	 277 10 54 84 95 34 	 1.00 0.88 (0.41–1.87) 1.29 (0.61–2.72) 1.72 (0.82–3.60) 6.24 (2.68–14.53) [< 0.0001]	Age, smoking, alcohol consumption, family history of BC, occupation, age at menarche, age at first birth, parity, use of exogenous female hormones or OC, year of recruitment, area, referral base (screening, other), height, time spent exercising

Table 2.2.9g (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Kawai et al. (2013) (cont.)		ER–PR–:	142		$P_{heterogeneity}$ = 0.0002
		< 18.5	5	1.00	
		18.5–22.1	45	1.49 (0.56–3.96)	
		22.1–25.0	47	1.43 (0.53–3.80)	
		25.0–30.0	36	1.19 (0.44–3.21)	
		≥ 30.0	9	2.43 (0.74–7.95)	
		[P_{trend}]		[0.86]	

BC, breast cancer; BMI, body mass index (in kg/m^2); CI, confidence interval; ER, estrogen receptor; FFTP, first full-term pregnancy; HER2, human epidermal growth factor receptor 2; HRT, hormone replacement therapy; NR, not reported; NS, not significant; OC, oral contraceptive; PR, progesterone receptor; SES, socioeconomic status; WHR, waist-to-hip ratio; yr, year or years

[a] In this table, the study population describes the population of the entire study, and the numbers of cases and controls refer to the number of women in the study, not necessarily the number of postmenopausal women.

Table 2.2.9i Case–control studies of body mass index and cancer of the breast in postmenopausal women, by ethnicity

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Wenten et al. (2002) USA January 1992–December 1994	Women aged 30–70 yr 712 diagnosed with invasive or in situ breast cancer 1039 Hispanic: 332 511 Non-Hispanic White: 380 528 Population	Usual BMI Hispanic: < 22 22– < 25 25– < 30 ≥ 30 [P_{trend}] Non-Hispanic White: < 22 22– < 25 25– < 30 ≥ 30 [P_{trend}]	NR	 1.00 1.53 (0.67–3.50) 1.60 (0.67–3.82) 1.32 (0.47–3.72) [0.58] 1.00 0.90 (0.51–1.61) 1.15 (0.53–2.47) 2.77 (0.86–8.89) [0.16]	Age, first-degree family history of BC, total METs, parity, OC use, months of breastfeeding, age at first full-term birth, HRT use, weight at age 18 yr Results also reported for BMI at age 18 yr
Ziv et al. (2006) USA 1995–2002	Hispanic/Latina women 357 diagnosed 1997–1999 479 Completed interview: 324 421 Provided blood sample: 241 333 Population; matched to cases by ethnicity and 5-yr age groups	BMI All Latinas: < 25 25–29.9 ≥ 30 Latinas born in USA: < 25 25–29.9 ≥ 30 Foreign-born Latinas: < 25 25–29.9 ≥ 30	 48 71 115 106 total 128 total 	 1.00 1.93 (1.38–2.69) 1.51 (1.12–2.04) 1.00 1.25 (0.79–1.96) 1.26 (0.83–1.92) 1.00 3.44 (1.97–5.99) 1.95 (1.24–3.06)	Age, case–control status, grandparents' place of birth, age at migration, education level, place of birth (born in USA vs foreign-born) Age, case–control status, grandparents' place of birth, education level Age, case–control status, grandparents' place of birth, age at migration, education level

Table 2.2.9i (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Slattery et al. (2007) USA 1999–2004	Hispanic women living in non-reservations and non-Hispanic White women 2325 2525 Non-Hispanic White: 1527 1601 Hispanic: 798 924 Population; matched by ethnicity, age in 5-yr classes, random selection	BMI in reference year, no recent hormone exposure			Age, height, physical activity, energy intake, parity, alcohol consumption, age at first pregnancy, age at menopause, centre Analyses of BMI at age 18 yr also reported
		Non-Hispanic White:			
		< 25	146	1.00	
		25–29.9	122	1.60 (1.06–2.40)	
		≥ 30	112	1.61 (1.05–2.45)	
		[P_{trend}]		[0.03]	
		Hispanic:			
		< 25	43	1.00	
		25–29.9	91	0.68 (0.38–1.24)	
		≥ 30	104	0.80 (0.44–1.45)	
		[P_{trend}]		[0.61]	
		BMI in reference year, recent hormone exposure			
		Non-Hispanic White:			
		< 25	306	1.00	
		25–29.9	194	1.02 (0.79–1.32)	
		≥ 30	202	0.72 (0.54–0.96)	
		[P_{trend}]		[0.04]	
		Hispanic:			
		< 25	92	1.00	
		25–29.9	120	0.91 (0.60–1.38)	
		≥ 30	114	0.74 (0.47–1.15)	
		[P_{trend}]		[0.17]	
Berstad et al. (2010) USA: Atlanta (Georgia), Seattle (Washington), Detroit (Michigan), Philadelphia (Pennsylvania), Los Angeles (California); July 1994–April 1998	4575 4682 Caucasian: 2953 3021 African American: 1622 1661 Population	BMI at age 18 yr			Age, race, education level, study site, first-degree family history of BC, parity, age at menopause, HRT use, BMI at the other time point Results available by hormonal status for BMI by age 18 yr and 5 yr before reference date, for each ethnic group
		Caucasian:	1261		
		< 20	682	1.00	
		20–24	517	0.89 (0.75–1.05)	
		≥ 25	62	0.70 (0.49–1.00)	
		[P_{trend}]		[0.03]	
		African American:	639		
		< 20	297	1.00	
		20–24	286	0.91 (0.72–1.14)	
		≥ 25	56	0.80 (0.54–1.19)	
		[P_{trend}]		[0.22]	

Table 2.2.9i (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Berstad et al. (2010) (cont.)		BMI 5 yr before reference date			
		Caucasian:			
		< 25	733	1.00	
		25–29	333	0.93 (0.77–1.12)	
		30–34	127	0.94 (0.72–1.24)	
		≥ 35	68	0.75 (0.53–1.06)	
		[P_{trend}]		[0.13]	
		African American:			
		< 25	185	1.00	
		25–29	246	1.05 (0.80–1.37)	
		30–34	127	0.98 (0.71–1.35)	
		≥ 35	81	1.26 (0.85–1.85)	
		[P_{trend}]		[0.44]	
Bandera et al. (2013a) USA New York City: 2002–2008 New Jersey: 2006–2012	Postmenopausal women of African and Caucasian ancestry 1751 1673 African American: 979 958 European American: 772 715 Population	BMI at age 20 yr			Age, ethnicity (Hispanic/non-Hispanic), country of origin, family history of BC, history of benign breast disease, age at menarche, parity, breastfeeding status, age at first birth, HRT use, OC use, height and weight at menarche
		African American:			
		< 25	392	1.00	
		25–29.9	52	1.01 (0.65–1.58)	
		≥ 30	17	0.88 (0.43–1.81)	
		[P_{trend}]		[0.82]	
		European American:			
		< 25	342	1.00	
		25–29.9	17	0.82 (0.38–1.77)	
		≥ 30	4	0.15 (0.04–0.60)	
		[P_{trend}]		[0.01]	

Table 2.2.9i (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
John et al. (2013) USA Hispanic cases: 1995–2002 African American cases: 1995–1999 Non-Hispanic White cases: 1995–1999	1389 of 2571 1644 of 2706 Hispanic: 1119 1462 African American: 543 598 Non-Hispanic White: 596 646 Population; controls randomly selected and frequency-matched by race/ethnicity and expected 5-yr age distribution of cases	Current BMI			Non-users of HRT Results available for ER+PR+ tumours (for both current BMI and BMI in young adulthood, separated by race)
		Hispanic:			
		< 25.0	81	1.00	
		25.0–29.9	133	0.78 (0.54–1.14)	
		≥ 30	161	0.77 (0.53–1.12)	
		[P_{trend}]		[0.24]	
		African American:			
		< 25.0	51	1.00	
		25.0–29.9	90	1.19 (0.74–1.94)	
		≥ 30	101	1.07 (0.66–1.73)	
		[P_{trend}]		[0.88]	
		Non-Hispanic White:			
		< 25.0	76	1.00	
		25.0–29.9	55	0.90 (0.56–1.43)	
		≥ 30	50	1.19 (0.72–1.99)	
		[P_{trend}]		[0.58]	
		BMI in young adulthood			
		Hispanic:			
		T1: ≤ 21.2	109	1.00	
		T2: 21.3–23.7	122	0.85 (0.60–1.20)	
		T3: > 23.7	115	0.63 (0.45–0.90)	
		[P_{trend}]		[0.01]	
		African American:			
		T1: ≤ 21.2	93	1.00	
		T2: 21.3–23.7	77	1.17 (0.76–1.79)	
		T3: > 23.7	67	0.93 (0.59–1.45)	
		[P_{trend}]		[0.80]	
		Non-Hispanic White:			
		T1: ≤ 21.2	84	1.00	
		T2: 21.3–23.7	60	0.65 (0.41–1.02)	
		T3: > 23.7	34	0.52 (0.30–0.90)	
		[P_{trend}]		[0.01]	

Table 2.2.9i (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Robinson et al. (2014) USA 1993–2001	Women aged 20–74 yr 1783 1536 Black: 788 718 White: 995 818 Population; frequency-matched to cases by 5-yr age group	Measured BMI Black: < 25 25–30 30–35 ≥ 35 [P_{trend}] White: < 25 25–30 30–35 ≥ 35 [P_{trend}]	 74 121 118 113 212 165 69 30 	 1.00 0.61 (0.38–0.98) 0.77 (0.47–1.28) 0.58 (0.35–0.94) [0.11] 1.00 0.91 (0.67–1.25) 0.83 (0.55–1.25) 0.61 (0.35–1.06) [0.08]	Age, age squared, family history of BC, alcohol consumption, menarche, parity, age at FFTP composite, lactation, education level, smoking Data also reported for BMI at age 18 yr, 35 yr, and one yr before interview, by ethnicity; all of these associations were null
John et al. (2015b) USA 2 population-based case–control studies San Francisco Bay Area Study 4-Corners Breast Cancer Study Hispanic: 1995–2002 Non-Hispanic White: 1995–2004	4271 4713 Population	ER+PR+: Current BMI Hispanic: per 5 kg/m^2 Non-Hispanic White: per 5 kg/m^2 ER–PR–: Current BMI Hispanic: per 5 kg/m^2 Non-Hispanic White: per 5 kg/m^2	 294 292 153 	 0.81 (0.65–1.01) 0.94 (0.74–1.19) 0.76 (0.57–1.01) 0.63 (0.43–0.92)	Age, study, ethnicity/English language acculturation, education level, first-degree family history of BC, age at menarche, number of FTPs, age at FFTP, lifetime months of breastfeeding, average alcohol consumption Age, study, ethnicity, education level, first-degree family history of BC, age at menarche, number of FTPs, age at FFTP, lifetime months of breastfeeding, average alcohol consumption Age, study, ethnicity/English language acculturation, first-degree family history of BC, age at menarche, HRT use Age, study, ethnicity, first-degree family history of BC, age at menarche, HRT use

Table 2.2.9i (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Sanderson et al. (2015) USA 2001–2011	Women aged 25–75 yr 2614 with primary ductal carcinoma in situ or invasive breast cancer 2306 Population; matched by 5-yr age groups, race, and county of residence	BMI Black: < 25.0 25.0–29.9 30.0–34.9 ≥ 35 [P_{trend}] White: < 25.0 25.0–29.9 30.0–34.9 ≥ 35 [P_{trend}]	 75 129 123 113 493 433 223 121 	 1.0 1.0 (0.6–1.7) 1.2 (0.7–2.0) 1.0 (0.6–1.7) [0.90] 1.0 1.1 (0.9–1.3) 1.1 (0.9–1.4) 0.8 (0.6–1.1) [0.67]	Age, education level, first-degree family history of BC, OC use, age at menarche $P_{interaction}$ = 0.43

BC, breast cancer; BMI, body mass index (in kg/m^2); CI, confidence interval; ER, estrogen receptor; HRT, hormone replacement therapy; MET, metabolic equivalent; NR, not reported; OC, oral contraceptive; PR, progesterone receptor; yr, year or years

[a] In this table, the study population describes the population of the entire study, and the numbers of cases and controls refer to the number of women in the study, not necessarily the number of postmenopausal women.

Table 2.2.9k Case–control studies of waist circumference and cancer of the breast in postmenopausal women

Reference, study location and period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories (cm, unless otherwise stated)	Exposed cases	Relative risk (95% CI)	Covariates
Friedenreich et al. (2002) Canada 1995–1997	771 762 Population-based using Waksberg method; frequency-matched to cases by age, 5-yr intervals, and place of residence (urban/rural)	< 75.6 ≥ 75.6– < 82.8 ≥ 82.8– < 91.5 ≥ 91.5 [P_{trend}]	1533 175 159 187 242	1.00 0.89 (0.66–1.20) 1.06 (0.79–1.42) 1.30 (0.97–1.73) [0.07]	Current age, total energy intake, total lifetime physical activity, education level, ever use of HRT, ever diagnosed with benign breast disease, first-degree family history of BC, ever alcohol consumption, current smoking
Slattery et al. (2007) USA 1999–2004	Hispanic women living in non-reservations and non-Hispanic White women Non-Hispanic White: 858 1008 Hispanic: 399 522 Population; matched by ethnicity, age in 5-yr classes, random selection	WC (in), no recent hormone exposure Non-Hispanic White: < 35 35–40 > 40 [P_{trend}] Hispanic: < 35 35–40 > 40 [P_{trend}] WC (in), recent hormone exposure Non-Hispanic White: < 35 35–40 > 40 [P_{trend}] Hispanic: < 35 35–40 > 40 [P_{trend}]	 197 95 83 80 83 71 393 180 115 148 108 65 	 1.00 1.73 (1.16–2.58) 1.29 (0.83–1.99) [0.11] 1.00 0.98 (0.59–1.63) 0.81 (1.47–1.39) [0.45] 1.00 0.99 (0.76–1.28) 0.88 (0.64–1.21) [0.48] 1.00 1.18 (0.80–1.75) 0.86 (0.53–1.38) [0.74]	Age, height, physical activity, energy intake, parity, alcohol consumption, age at first pregnancy, age at menopause, centre

Table 2.2.9k (continued)

Reference, study location and period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories (cm, unless otherwise stated)	Exposed cases	Relative risk (95% CI)	Covariates
Tian et al. (2007) Taiwan 2004–2005	102 aged 22–87 yr 103 Hospital; recruited from health examination clinics at the same hospital and time, free for cancer history, matched by menopausal status, date of enrolment, duration of fasting	≤ 81.00 > 81.00	54 48	1.00 2.02 (1.05–3.91)	Age at enrolment, fasting status, levels of adiponectin
Mathew et al. (2008) India 2002–2005	968 691 Accompanying persons to cancer cases; matched by age ± 5 yr and residence type (urban/rural)	≤ 85 > 85 Unknown	57 380 31	1.00 1.61 (1.22–2.12) 2.88 (0.76–10.90)	Age, centre, religion, marital status, education level, SES, residence status, parity, age at first birth, duration of breastfeeding, physical activity
Nemesure et al. (2009) Barbados 2002–2006	Women of African descent aged ≥ 21 yr 222 454 Population; Barbados Statistical Services; frequency-matched by 5-yr age group	Aged ≥ 50 yr: < 80 80–101 ≥ 101	 18 88 38	 1.00 1.35 (0.57–3.18) 2.98 (0.91–9.71)	Current age, HRT use, parity, family history of BC, history of benign breast disease, age at first pregnancy, age at menarche, physical activity, other body size variable
Rosato et al. (2011) Italy, Switzerland 1983–1994 (Italy), 1991–2007 (Switzerland)	Postmenopausal women 1747 1935 Hospital; admitted for acute, non-neoplastic diseases, not related to gynaecological or hormonal conditions, matched by age and study centre	< 88 ≥ 88	869 878	1.00 1.17 (1.02–1.35)	Age, study centre, study period, education level, alcohol consumption, age at menarche, age at first birth, age at menopause, HRT use, family history of BC

Table 2.2.9k (continued)

Reference, study location and period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories (cm, unless otherwise stated)	Exposed cases	Relative risk (95% CI)	Covariates
Bandera et al. (2013b) USA NR	Postmenopausal women of African ancestry 978 958 Population; random-digit dialling	≤ 87.88	87	1.00	BMI, age, ethnicity, country of origin, education level, family history of BC, history of benign breast disease, age at menarche, age at menopause, parity, breastfeeding, age at first birth, HRT use, OC use
		87.89–97.75	119	1.13 (0.73–1.76)	
		97.76–110.25	154	1.51 (0.92–2.48)	
		> 110.25	140	1.23 (0.64–2.34)	
		[P_{trend}]		[0.48]	
		ER+PR+:			
		≤ 87.88	36	1.00	
		87.89–97.75	39	0.88 (0.48–1.60)	
		97.76–110.25	56	1.30 (0.68–2.48)	
		> 110.25	74	1.55 (0.68–3.55)	
		[P_{trend}]		[0.20]	
		ER–PR–:			
		≤ 87.88	23	1.00	
		87.89–97.75	25	0.93 (0.45–1.92)	
		97.76–110.25	25	1.11 (0.48–2.57)	
		> 110.25	27	1.08 (0.35–3.31)	
		[P_{trend}]		[0.83]	
John et al. (2013) USA 1995–2002	1389 postmenopausal women 1644 Population; controls randomly selected and frequency-matched by race/ethnicity and expected 5-yr age distribution of cases	All:			All non-users of HRT
		≤ 85.0	198	1.00	
		85.1–96.4	214	0.99 (0.77–1.27)	
		> 96.4	293	1.32 (1.03–1.69)	
		[P_{trend}]		[0.02]	
		ER+PR+:			
		≤ 85.0	95	1.00	
		85.1–96.4	106	1.11 (0.80–1.54)	
		> 96.4	162	1.76 (1.28–2.41)	
		[P_{trend}]		[< 0.01]	
		ER–PR–:			
		≤ 85.0	28	1.00	
		85.1–96.4	40	1.13 (0.67–1.89)	
		> 96.4	48	1.24 (0.75–2.06)	
		[P_{trend}]		[0.41]	

Table 2.2.9k (continued)

Reference, study location and period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories (cm, unless otherwise stated)	Exposed cases	Relative risk (95% CI)	Covariates
Sangrajrang et al. (2013) Thailand May 2002–March 2004; August 2005–August 2006	470 385 Hospital/population; female visitors of hospital patients admitted for conditions other than BC or ovarian cancer	< 80 ≥ 80	199 271	1.00 1.18 (0.89–1.57)	
Amadou et al. (2014) Mexico 2004–2007	585 598 Population	< 93 93–103 ≥ 103 [P_{trend}]	187 218 180	1.00 0.96 (0.70–1.32) 0.62 (0.44–0.85) [0.003]	Age, health care system, region, SES, breastfeeding, family history of BC, alcohol consumption, physical activity, total energy intake, height, current BMI
Robinson et al. (2014) USA 1993–2001	Women aged 20–74 yr 911 825 Black: 434 380 White: 477 445 Population; frequency-matched to cases by 5-yr age group	Black: ≤ 88 > 88 [P_{trend}] White: ≤ 88 > 88 [P_{trend}]	 113 321 314 163	 1.00 1.39 (0.92–2.10) [0.11] 1.00 1.31 (0.88–1.95) [0.18]	Age, age squared, family history of BC, alcohol consumption, menarche, parity, age at FFTP composite, lactation, education level, smoking, reference BMI

BC, breast cancer; BMI, body mass index (in kg/m^2); CI, confidence interval; ER, estrogen receptor; FFTP, first full-term pregnancy; HRT, hormone replacement therapy; NR, not reported; OC, oral contraceptive; PR, progesterone receptor; SES, socioeconomic status; WC, waist circumference (in cm); yr, year or years

[a] In this table, the study population describes the population of the entire study, and the numbers of cases and controls refer to the number of women in the study, not necessarily the number of postmenopausal women.

Table 2.2.9m Case–control studies of change in body mass index or weight and cancer of the breast in postmenopausal women

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
BMI change					
Hirose et al. (2001) Japan 1988–1997	1584 15 331 First visit outpatients (screening) without any previous diagnosis of cancer	BMI change from age 20 yr, without family history of BC			Age, age at menarche, menstrual regularity in the 20s, age at first birth, parity
		< 0	127	0.69 (0.52–0.92)	
		0–1.24	89	1.00	
		1.25–2.99	137	1.02 (0.77–1.40)	
		≥ 3	238	1.34 (1.00–1.70)	
		[P_{trend}]		[< 0.001]	
		BMI change from age 20 yr, with family history of BC			
		< 0	9	1.56 (0.44–5.60)	
		0–1.24	4	1.00	
		1.25–2.99	13	2.74 (0.82–9.10)	
		≥ 3	17	2.19 (0.68–7.00)	
		[P_{trend}]		[0.26]	
Robinson et al. (2014) USA 1993–2001	1783 women aged 20–74 yr 1536 Black: 788 718 White: 995 818 Population; frequency-matched to cases by 5-yr age group	BMI change, ages 18–35 yr			Age, age squared, family history of BC, alcohol consumption, menarche, parity, age at FFTP composite, lactation, education level, smoking, reference BMI
		Black:			
		< 1.77	103	1.0	
		1.77–4.44	151	1.47 (0.98–2.18)	
		≥ 4.44	161	1.14 (0.76–1.70)	
		[P_{trend}]		[0.63]	
		White:			
		< 1.77	194	1.0	
		1.77–4.44	172	1.17 (0.85–1.60)	
		≥ 4.44	98	1.33 (0.88–2.02)	
		[P_{trend}]		[0.16]	
Weight change					
Li et al. (2000) USA January 1988–June 1990	479 435 Population; Caucasian women	Weight change (lb), age 18 yr to reference date, 50–64 yr			Age, height, weight at age 18 yr, family history of BC, parity, HRT use, OC use
		< –10	14	0.9 (0.4–1.9)	
		–10 to 10	113	1.0	
		11–30	153	1.1 (0.7–1.5)	
		31–50	100	1.2 (0.8–1.7)	
		51–70	43	1.3 (0.7–2.1)	
		> 70	55	2.7 (1.5–4.9)	

Table 2.2.9m (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Trentham-Dietz et al. (2000) USA January 1992–December 1994	Postmenopausal women aged 50–79 yr 5031 5255 Population; matched by age and state	Weight loss (kg), overall			Parity, age at FFTP, family history of BC, recent alcohol consumption, education level, age at menopause, height, highest weight and age at highest weight Analyses of weight loss since age 11–45 yr and since age > 45 yr gave similar results to weight loss overall
		0.0	1690	1.0	
		0.1–4.9	1637	1.1 (1.0–1.2)	
		5.0–9.9	809	1.0 (0.9–1.2)	
		≥ 10.0	668	1.0 (0.9–1.2)	
		[P_{trend}]		[0.1]	
		Weight gain (kg), overall			Parity, age at FFTP, family history of BC, recent alcohol consumption, education level, age at menopause, height, lowest weight and time since lowest weight Analyses of weight gain since age 20, since age 21–30 yr and since age > 30 yr gave similar results to weight gain overall
		0–5.0	730	1.0	
		5.1–10.0	853	1.1 (0.9–1.3)	
		10.1–15.0	872	1.1 (1.0–1.3)	
		15.1–25.0	1409	1.4 (1.2–1.6)	
		> 25.0	1008	1.7 (1.5–2.0)	
		[P_{trend}]		[< 0.001]	
de Vasconcelos et al. (2001) Brazil May 1995–February 1996	177 377 Hospital/population; visitors at hospital; 27 relatives of breast cancer patients	Weight change (kg) since age 18 yr			Age, parity, age at menarche, family history of BC, weight and height at 18 yr Analyses of weight change from age 18 yr to age 30 yr and weight change since age 30 yr gave similar results
		> 22.3	31	1.00	
		13.11–22.3	38	1.39 (0.75–2.59)	
		0–13.10	28	1.24 (0.62–2.50)	
		Weight loss	12	2.05 (0.75–5.59)	
		[P_{trend}]		[0.24]	

Table 2.2.9m (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Shu et al. (2001) China August 1996–March 1998	Women aged 25–64 yr 1459 of 1602 1556 of 1724 Population; randomly selected from female residents of Shanghai (Shanghai Resident Registry), matched to cases by age, 5-yr interval	Weight gain (kg) since age 20 yr			Age, education level, family history of BC, ever had fibroadenoma, age at menarche, age at first live birth, exercise, age at menopause
		< 1.15	20.4%	1.0	
		1.15–3.41	31.7%	1.4 (1.0–2.1)	
		3.42–5.64	26.6%	1.3 (0.9–1.9)	
		≥ 5.65	21.3%	2.7 (1.7–4.2)	
		[P_{trend}]		[< 0.001]	
		Weight gain (kg) during past 10 yr			
		< 1.15	37.1%	1.0	
		1.15–3.41	19.8%	1.6 (1.1–2.2)	
		3.42–5.64	14.3%	1.2 (0.8–1.8)	
		≥ 5.65	28.8%	1.5 (1.1–2.1)	
		[P_{trend}]		[0.03]	
Friedenreich et al. (2002) Canada 1995–1997	1233 1241 Population-based using Waksberg method; frequency-matched to cases by age, 5-yr interval, and place of residence (urban/rural)	Weight gain (kg) since age 20 yr			Current age, total energy intake, total lifetime physical activity, education level, ever use of HRT, ever diagnosed with benign breast disease, first-degree family history of BC, ever alcohol consumption, current smoking
		< 7.80	181	1.00	
		≥ 7.80– < 15.7	173	1.02 (0.75–1.37)	
		≥ 15.7– < 25.0	182	1.08 (0.80–1.45)	
		≥ 25.0	231	1.35 (1.01–1.81)	
		[P_{trend}]		[0.05]	
		Difference, maximum − minimum weight (kg) over adult lifetime			
		< 9.07	161	1.00	
		≥ 9.07– < 15.4	161	0.94 (0.69–1.28)	
		≥ 15.4– < 22.7	184	1.21 (0.89–1.64)	
		≥ 22.7	265	1.56 (1.16–2.08)	
		[P_{trend}]		[0.0007]	

Table 2.2.9m (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Wenten et al. (2002) USA January 1992–December 1994	712 women aged 30–70 yr diagnosed with invasive or in situ breast cancer 1039 Hispanic: 332 511 Non-Hispanic White: 380 528 Population	Weight change (kg), age 18 yr to usual adult weight			Age, first-degree family history of BC, total METs, parity, OC use, months of breastfeeding, age at first full-term birth, HRT use, weight at age 18 yr
		Hispanic:			
		< 4		1.00	
		4–7		2.48 (0.89–6.93)	
		8–14		2.04 (0.73–5.68)	
		> 14		2.46 (0.98–6.17)	
		[P_{trend}]		[0.14]	
		Non-Hispanic White:			
		< 4		1.00	
		4–7		1.34 (0.66–2.74)	
		8–14		1.33 (0.63–2.77)	
		> 14		2.27 (1.09–4.73)	
		[P_{trend}]		[0.04]	
Carpenter et al. (2003) Canada, USA, western Europe Group I: March 1987–December 1989 Group II: January 1992–December 1992 Group III: September 1995–April 1996	Caucasian (including Hispanic), born in Canada, USA, or western Europe 1883 diagnosed at age 55–64 yr (Group I), age 55–69 yr (Group II), or age 55–72 yr (Group III) 1628 Population; matched to cases by neighbourhood	Weight change (%), age 18 yr to reference date (1 yr before diagnosis)			Age at FFTP, ages at menarche and menopause, family history of BC, interviewer, average MET hours per week of lifetime exercise activity
		Negative change to no change	229	1.00	
		> 0–16.9%	573	1.16 (0.92–1.47)	
		17.0–29.1%	404	1.13 (0.88–1.45)	
		≥ 29.2%	677	1.36 (1.08–1.73)	
		[P_{trend}]		[0.01]	
Eng et al. (2005) USA August 1996–July 1997	1006 990 Population; frequency-matched by 5-yr age group	Weight change (kg), age 20 yr to 1 yr before reference date			Age at reference date, number of pregnancies, months of HRT use, history of BC in a first-degree relative, history of benign breast disease, BMI at age 20 yr
		–44.91 to –3.01	36	0.55 (0.32–0.96)	
		–3.00 to 3.00	103	1.00	
		3.01–7.71	141	1.03 (0.70–1.50)	
		7.71–8.15	241	1.18 (0.84–1.74)	
		8.16–14.96	209	1.21 (0.84–1.74)	
		14.97–87.09	256	1.58 (1.11–2.26)	
		[P_{trend}]		[0.0001]	

Table 2.2.9m (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Eng et al. (2005) (cont.)		Weight change (kg), age 50 yr to 1 yr before reference date			Age at reference date, number of pregnancies, months of HRT use, history of BC in a first-degree relative, history of benign breast disease, BMI at age 50 yr
		−68.04 to −0.01	157	1.19 (0.85–1.67)	
		0.00	167	1.00	
		0.01–2.71	133	1.19 (0.84–1.69)	
		2.72–4.98	124	0.96 (0.68–1.37)	
		4.99–11.33	195	1.58 (1.14–2.23)	
		11.34–62.14	171	1.62 (1.14–2.30)	
		[P_{trend}]		[0.003]	
Han et al. (2006) USA 1996–2001	1166 2105 Population; frequency-matched by age, race, and county of residence	Weight change (kg), age 20 yr to 1 yr before study enrolment			Age, education level, previous benign disease, age at menarche, age at first birth, family history of BC, age at menopause, HRT use, BMI residuals Weight change (kg) from age at first pregnancy to age at menopause also showed a positive association with breast cancer risk (P_{trend} = 0.01)
		≤ 0	841	0.90 (0.56–1.45)	
		0–9.1	47	1.00	
		9.1–17.7	137	1.45 (1.06–1.96)	
		17.7–27.3	208	1.53 (1.12–2.08)	
		> 27.3	227	1.71 (1.23–2.37)	
		[P_{trend}]	222	[0.05]	
Wu et al. (2006) USA 1995–2001	Asian American women 1277 aged 25–74 yr at diagnosis 1160 Chinese: 450 486 Japanese: 352 311 Filipino: 475 363 Population; neighbourhood controls; frequency-matched by ethnicity and 5-yr age group	Weight gain (kg) since age 18 yr (recent weight − weight at age 18 yr)			Age, ethnicity, duration of residence in the USA, education level, age at menarche, number of live births, age at menopause, intake of tea and soy during adolescence and adult life, years of physical activity, height
		≤ 10	319	1.00	
		> 10– ≤ 15	138	1.24 (0.90–1.72)	
		> 15– ≤ 20	95	1.10 (0.75–1.62)	
		> 20	95	1.66 (1.09–2.53)	
		[P_{trend}]		[0.036]	
		Weight gain (kg) since age 30 yr (recent weight − weight at age 30 yr)			
		≤ 10	518	1.00	
		> 10– ≤ 15	91	1.51 (1.02–2.22)	
		> 15– ≤ 20	44	1.17 (0.70–1.96)	
		> 20	27	2.23 (1.00–4.94)	
		[P_{trend}]		[0.023]	

Table 2.2.9m (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Slattery et al. (2007) USA 1999–2004	Hispanic women living in non-reservations and non-Hispanic White women 2325 2525 Non-Hispanic White: 1527 1601 Hispanic: 798 924 Population; matched by ethnicity, age in 5-yr classes, random selection	Total weight gain (kg) between age 15 yr and reference year			Age, height, physical activity, energy intake, parity, alcohol consumption, age at first pregnancy, age at menopause, centre
		No recent hormone exposure			
		Non-Hispanic White:			
		≤ 5.0	57	1.00	
		5.1–15.0	99	1.19 (0.67–2.09)	
		15.1–25.0	94	1.40 (0.79–2.48)	
		> 25.0	104	1.75 (1.00–3.05)	
		[P_{trend}]		[0.03]	
		Hispanic:			
		≤ 5.0	22	1.00	
		5.1–15.0	37	1.14 (0.49–2.67)	
		15.1–25.0	79	0.70 (0.32–1.52)	
		> 25.0	78	0.76 (0.35–1.65)	
		[P_{trend}]		[0.25]	
		Recent hormone exposure			
		Non-Hispanic White:			
		≤ 5.0	115	1.00	
		5.1–15.0	176	1.14 (0.80–1.61)	
		15.1–25.0	182	1.08 (0.77–1.53)	
		> 25.0	200	0.95 (0.66–1.35)	
		[P_{trend}]		[0.57]	
		Hispanic:			
		≤ 5.0	25	1.00	
		5.1–15.0	77	0.73 (0.37–1.43)	
		15.1–25.0	98	0.79 (0.41–1.51)	
		> 25.0	108	0.64 (0.34–1.23)	
		[P_{trend}]		[0.26]	
Shin et al. (2009) China 1996–1998 (phase 1), April 2002–February 2005 (phase 2)	3452 aged 20–64 yr (phase 1), 20–70 yr (phase 2) 3474 Population; controls frequency-matched to cases by age	Weight change (kg) since age 20 yr			
		≤ 0	141	1.0	
		0.1–9.4	383	1.3 (1.0–1.6)	
		9.5–14.9	307	1.5 (1.1–2.0)	
		≥ 15	471	1.8 (1.4–2.4)	
		[P_{trend}]		[< 0.001]	

Table 2.2.9m (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Berstad et al. (2010) USA July 1994–April 1998	4575 4682 Caucasian: 2953 3021 African American: 1622 1661 Population	Weight change (kg) since age 18 yr ≤ 5 5.1–15.0 15.1–25.0 ≥ 25.1 [P_{trend}]	1900 363 641 507 389	 1.00 1.10 (0.91–1.32) 1.01 (0.83–1.23) 1.03 (0.84–1.27) [0.92]	Also adjusted for BMI at age 18 yr
Cribb et al. (2011) Canada 1999–2002	207 621 Population; women presenting for routine mammography screening; matched by age, menopausal status, and family history of BC	Weight gain (kg) since age 25 yr > 10	 61%	 1.34 (0.85–2.12)	Parity, OC use, BMI, smoking
Sangaramoorthy et al. (2011) USA 1998–2002	Women aged 35–79 yr 931 of 1031 1050 of 1198 Hispanic: 650 766 African American: 134 137 Non-Hispanic White: 147 147 Population; frequency-matched by race and age in 5-yr groups, without history of BC	Relative weight vs peers at age 10 yr Women not currently using HRT Lighter Same Heavier [P_{trend}]	 205 114 61 23	 1.00 0.84 (0.55–1.29) 0.68 (0.37–1.25) [0.19]	Analysis of Hispanic women only Age, country of birth, education level, first-degree family history of BC, prior biopsy history of benign breast disease, number of FTPs, age at FFTP, lifetime breastfeeding, OC use, adult height, alcohol consumption, average energy intake, BMI Measures of relative weight vs peers at 15 yr and 20 yr gave similar results

Table 2.2.9m (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Bandera et al. (2013b) USA New York City: 2002–2008 New Jersey: 2006–2012	Postmenopausal women of African and European ancestry 1751 1673 African American: 979 958 European American: 772 715 Population	Weight gain (kg) since age 20 yr, quartiles			Age, ethnicity (Hispanic/non-Hispanic), country of origin, family history of BC, history of benign breast disease, age at menarche, age at menopause, parity, breastfeeding status, age at first birth, HRT use, OC use, current BMI
		African American:			
		Q1: ≤ 13.82	75	1.00	
		Q2: 13.83–23.72	115	1.35 (0.87–2.10)	
		Q3: 23.73–34.56	110	1.29 (0.80–2.09)	
		Q4: > 34.56	139	1.42 (0.80–2.53)	
		[P_{trend}]		[0.34]	
		European American:			
		Q1: ≤ 7.57	75	1.00	
		Q2: 7.58–14.57	77	0.97 (0.56–1.66)	
		Q3: 14.58–24.52	91	0.90 (0.52–1.57)	
		Q4: > 24.52	90	0.95 (0.46–1.95)	
		[P_{trend}]		[0.88]	
John et al. (2013) USA Hispanic cases: 1995–2002 African American cases: 1995–1999 Non-Hispanic White cases: 1995–1999	1389 of 2571 1644 of 2706 Hispanic: 1119 1462 African American: 543 598 Non-Hispanic White: 596 646 Population; controls randomly selected and frequency-matched by race/ethnicity and expected 5-yr age distribution of cases	Weight gain (kg) from 20s, all non-users of HRT			Subanalysis by race/ethnicity showed a positive association in White non-Hispanic women only
		Stable	78	1.00	
		3.0–9.9	180	1.15 (0.82–1.63)	
		10.0–19.9	217	1.06 (0.76–1.48)	
		20.0–29.9	142	1.03 (0.72–1.48)	
		≥ 30.0	111	1.19 (0.81–1.75)	
		[P_{trend}]		[0.75]	

Table 2.2.9m (continued)

Reference Study location Period	Study population[a] Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates
Troisi et al. (2013) USA 1974–2009	22 646 women aged < 85 yr, with primary in situ or invasive cancer 224 721 Population; frequency-matched to cases by parity, age, calendar year of delivery, and race/ethnicity	Weight gain (lb), since 1989			Age at delivery, race/ethnicity, parity at index birth, year of index birth
		Aged ≥ 50 yr at diagnosis:	299		
		< 25	62	1.00	
		25– < 31	99	1.33 (0.95–1.86)	
		31– < 40	72	1.23 (0.86–1.76)	
		≥ 40	66	1.06 (0.74–1.54)	
Robinson et al. (2014) USA 1993–2001	Women aged 20–74 yr 1783 1536 Black: 788 718 White: 995 818 Population; frequency-matched to cases by 5-yr age group	Adult weight gain (lb) since age 18 yr			Age, age squared, family history of BC, alcohol consumption, age at menarche, parity, age at FFTP composite, lactation, education level, smoking, reference BMI
		Black:			
		≤ 25	81	1.00	
		26–54	126	0.70 (0.44–1.12)	
		≥ 55	222	0.84 (0.50–1.40)	
		[P_{trend}]		[0.64]	
		White:			
		≤ 25	185	1.00	
		26–54	184	1.17 (0.82–1.65)	
		≥ 55	101	1.25 (0.70–2.23)	
		[P_{trend}]		[0.38]	
Sanderson et al. (2015) USA 2001–2011	2614 aged 25–75 yr, primary ductal carcinoma in situ or invasive breast cancer 2306 Population; matched by 5-yr age groups, race, and county of residence	Weight change (lb) since age 18 yr			Age, education level, first-degree family history of BC, OC use, age at menarche, weight at 18 yr
		Black:			
		≤ 0	23	1.0	
		1–31	79	0.8 (0.3–2.1)	
		32–60	138	0.9 (0.4–2.3)	
		> 61	200	0.9 (0.4–2.2)	
		[P_{trend}]		[0.90]	
		White:			
		≤ 0	71	1.0	$P_{interaction}$ = 0.62
		1–31	406	1.2 (0.8–1.6)	
		32–60	460	1.3 (0.9–1.9)	
		> 61	329	1.1 (0.8–1.6)	
		[P_{trend}]		[0.76]	

BC, breast cancer; BMI, body mass index (in kg/m^2); CI, confidence interval; FFTP, first full-term pregnancy; FTP, full-term pregnancy; HRT, hormone replacement therapy; MET, metabolic equivalent of task; OC, oral contraceptive; yr, year(s)

[a] In this table, the study population describes the population of the entire study, and the numbers of cases and controls refer to the number of women in the study, not necessarily the number of postmenopausal women.

Table 2.2.9o Mendelian randomization studies of body mass index and cancer of the breast

Reference Study	Study population	Sample size	Exposure assessment	Outcome	Relative risk (95% CI)
Gao et al. (2016) Genetic Associations and Mechanisms in Oncology (GAME-ON) Consortium	Women from 11 studies of individuals of European ancestry	33 832 (15 748 cases and 18 084 controls)	Adult BMI: Increase of 1 SD (equivalent to 4.5 kg/m^2) in genetically predicted adult BMI	Adult BMI: All breast cancer ER– breast cancer	0.91 (0.88–0.94) 0.89 (0.84–0.94)
			Increase of 1 SD (~0.073 kg/m^2) in genetically predicted childhood BMI	Childhood BMI: All breast cancer ER– breast cancer	0.71 (0.60–0.80) 0.69 (0.53–0.98)

BMI, body mass index (in kg/m^2); CI, confidence interval; ER, estrogen receptor; SD, standard deviation

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2.2.10 Cancer of the breast in men

Breast cancer in men is uncommon, with an incidence that is often cited as being less than 1% of that for breast cancer in women. Risk factors for breast cancer in men include Klinefelter syndrome, a rare hereditary condition characterized by a chromosomal abnormality of 46 XXY karyotype with associated hormonal alterations, and gynaecomastia, a condition linked with excess estrogen. Like for breast cancer in women, risk is likely to be mediated through hormonal mechanisms.

The single largest study of the association of BMI with breast cancer in men is the Male Breast Cancer Pooling Project, a consortium of 11 case–control studies and 10 cohort studies involving 2405 cases (1190 from case–control studies and 1215 from cohort studies) and 52 013 controls (Brinton et al., 2014).

(a) Adult body mass index

BMI at baseline was associated with a small but significant positive association between increased BMI and risk of male breast cancer. However, this association was observed only with case–control studies (OR per 5 kg/m^2, 1.24; 95% CI, 1.12–1.38), whereas the risk estimates based on cohort studies were not significant (OR per 5 kg/m^2, 1.11; 95% CI, 0.97–1.28).

(b) Body mass index at earlier ages

Recalled BMI at age 18–21 years (based on six cohort studies) showed no association with risk of male breast cancer (OR per 5 kg/m^2, 1.05; 95% CI, 0.80–1.38).

Reference

Brinton LA, Cook MB, McCormack V, Johnson KC, Olsson H, Casagrande JT, et al.; European Rare Cancer Study Group (2014). Anthropometric and hormonal risk factors for male breast cancer: Male Breast Cancer Pooling Project results. *J Natl Cancer Inst*, 106(3):djt465. doi:10.1093/jnci/djt465 PMID:24552677

2.2.11 Cancer of the endometrium

Cancer of the endometrium is the sixth most common cancer diagnosis in women (WCRF/AICR, 2013). Known risk factors for endometrial cancer include exogenous estrogens, as delivered in menopausal estrogen replacement therapies unopposed with progesterone, and diabetes. Tobacco smoking is associated with reduced risk, by mechanisms that are not well understood. There are two subtypes of endometrial cancer: type 1, which is most common (accounting for about 80–90% of endometrial cancer), and type 2, which is more lethal but much less common (about 10–20%).

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that there was *sufficient evidence* for a cancer-preventive effect of avoidance of weight gain for cancer of the endometrium. The 2007 WCRF review concluded that there was convincing evidence of a positive association between body fatness and risk of endometrial cancer (WCRF/AICR, 2007), and this was later reaffirmed (WCRF/AICR, 2013).

(a) Cohort studies

The scientific evidence since 2000 includes 20 publications from cohort studies (excluding analyses that were later updated and analyses based on fewer than 100 incident cases). Table 2.2.11a presents those findings by BMI at baseline, with comments on findings according to smoking status, use of HRT, weight change over the life-course, and waist circumference.

In general, findings are very consistent across studies, showing a strongly positive association between BMI and endometrial cancer risk. All of the 20 cohort studies showed a statistically significant positive association. There is an approximately linear pattern of increasing risk with increasing BMI. The relative risk per 5 kg/m^2 has been estimated to be 1.6–1.9 (Renehan et al., 2008; Yang et al., 2012; Bhaskaran et al., 2014).

Among those studies that distinguished endometrial cancers by type (Bjørge et al., 2007; McCullough et al., 2008; Yang et al., 2013), all studies showed positive associations with BMI for both type 1 and type 2, with a stronger association for type 1 cancers.

The association between BMI and endometrial cancer risk was much stronger in never-users of HRT than in ever-users (McCullough et al., 2008; Canchola et al., 2010); in a meta-analysis of 24 studies (Crosbie et al., 2010), the relative risk per 5 kg/m^2 was 1.18 in ever-users compared with 1.90 in never-users.

In the two studies that reported differences by smoking status, there was no difference in the association of BMI with endometrial cancer risk between smokers and never-smokers (Reeves et al., 2007; Bhaskaran et al., 2014).

In those studies that included measurements of waist circumference and hip circumference (Conroy et al., 2009; Canchola et al., 2010; Reeves et al., 2011; Kabat et al., 2015), waist circumference and waist-to-hip ratio were less strongly associated with risk than was BMI.

In those studies that examined the association between BMI at different ages and subsequent risk of endometrial cancer (Jonsson et al., 2003; Chang et al., 2007; McCullough et al., 2008; Canchola et al., 2010; Park et al., 2010; Yang et al., 2012), BMI at earlier times in life was generally more weakly related or was not related to risk of endometrial cancer, compared with BMI at baseline.

(b) Case–control studies

A total of 30 case–control studies have been published since 2000 on the association between BMI at diagnosis and endometrial cancer risk, including 21 population-based studies and 9 hospital-based studies (Table 2.2.11b). Studies were conducted in the USA (n = 10), Australia,

Canada, China, the Czech Republic, Israel, Italy, Japan, Mexico, Puerto Rico, the Republic of Korea, Switzerland, and the United Kingdom. In most of the studies, a statistically significant increased risk of endometrial cancer was observed in overweight and obese women compared with normal-weight women.

Among the case–control studies that evaluated BMI measured or recalled at different ages (Xu et al., 2006; Lucenteforte et al., 2007; Thomas et al., 2009; Dal Maso et al., 2011; Hosono et al., 2011; Lu et al., 2011; Nagle et al., 2013), an increased risk of endometrial cancer was also observed; the BMI measured or recalled closer to the date of diagnosis was usually related to the highest risk.

Six studies reported associations between waist circumference and endometrial cancer risk, showing a 2–5-fold increase in risk for women in the highest category of waist circumference versus the lowest.

(c) Pooled analyses and meta-analyses

Several recent pooled analyses and meta-analyses have been published on the association between BMI and endometrial cancer risk (Dobbins et al., 2013; Felix et al., 2013; Setiawan et al., 2013; Cote et al., 2015; Jenabi & Poorolajal, 2015; Table 2.2.11c).

A large meta-analysis of 20 case–control studies reported a relative risk of 1.43 (95% CI, 1.30–1.56) for overweight and of 3.33 (95% CI, 2.87–3.79) for obese women compared with normal-weight women (Jenabi & Poorolajal, 2015). In a pooled analysis of 7 cohort studies and 14 case–control studies, the risk of endometrial cancer was similar for obese Black and White women compared with their normal-weight counterparts (Cote et al., 2015).

A recent pooled analysis of 10 cohort studies and 14 case–control studies explored the heterogeneity of the association between BMI and endometrial cancer risk according to tumour types (Setiawan et al., 2013). They reported stronger associations among type 1 (RR per 2 kg/m^2, 1.20; 95% CI, 1.19–1.21) compared with type 2 tumours (RR, 1.12; 95% CI, 1.09–1.14) and among endometrioid grade 1 and 2 compared with endometrioid grade 3. The heterogeneity was present when cohort studies and case–control studies were considered separately, or when registry-based studies were compared with those where cases were further ascertained through pathology reports.

(d) Mendelian randomization studies

Nead et al. (2015) applied Mendelian randomization to assess the association of markers of metabolic disease, including BMI, with risk of endometrial cancer using 32 genetic variants as instrumental variables for BMI (Speliotes et al., 2010). Mendelian randomization analyses showed that each increase of 1 standard deviation in BMI was associated with a significant increase in risk of endometrial cancer (OR, 3.86; 95% CI, 2.24–6.64) (Table 2.2.11d).

Table 2.2.11a Cohort studies of measures of body fatness and cancer of the endometrium

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Subtype	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Calle et al. (2003) Population-based cohort USA 1982–1998	495 477 Mortality		BMI 18.5–24.9 25–29.9 30–34.9 35–39.9 ≥ 40 [P_{trend}]	 333 225 105 25 16	 1.00 1.50 (1.26–1.78) 2.53 (2.02–3.18) 2.77 (1.83–4.18) 6.25 (3.75–10.42) [< 0.001]	Age, education level, smoking, physical activity, alcohol consumption, marital status, aspirin use, fat intake, vegetable intake, HRT use	
Jonsson et al. (2003) Swedish Twin Registry Sweden 1969–1997	14 131 Incidence		BMI < 18.49 18.5–24.99 25–29.99 ≥ 30	 1 69 46 21	 0.4 (0.1–3.1) 1.0 1.3 (0.9–1.9) 3.2 (2.0–5.2)	Age	Recalled BMI at ages 25 yr and 40 yr gave RR for BMI ≥ 25.0 vs < 25.0 of 1.9 (1.2–3.0) and 2.0 (0.9–4.4), respectively
Rapp et al. (2005) Population-based cohort Austria 1985–2002	78 484 Incidence		BMI 18.5–24.9 25.0–29.9 30–34.9 ≥ 35 [P_{trend}]	 63 59 33 20	 1.0 1.29 (0.90–1.86) 2.13 (1.38–3.27) 3.93 (2.35–6.56) [< 0.001]	Age, smoking, occupation	
Lukanova et al. (2006) Population-based cohort Sweden 1994–2004	35 362 Incidence		BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 42 41 35	 1.0 1.45 (0.93–2.24) 2.93 (1.85–4.61) [0.0001]	Age, tobacco use	
Bjørge et al. (2007) Norwegian health surveys Norway 1963–2003	1 million Incidence	Type 1	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 82 2960 2361 1761	 0.90 (0.72–1.12) 1.00 1.39 (1.32–1.47) 2.72 (2.56–2.90) [< 0.001]	Age, birth cohort	Similar association for BMI at ages 20–49 yr and 50–74 yr
		Type 2	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 4 366 369 253	 0.42 (0.16–1.13) 1.00 1.26 (1.09–1.46) 1.94 (1.64–2.30) [< 0.001]	Age, birth cohort	Similar association for BMI at ages 20–49 yr and 50–74 yr

Table 2.2.11a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Subtype	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Chang et al. (2007) NIH-AARP cohort USA 1995–2000	103 882 Incidence		BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 200 181 296	 1.0 1.31 (1.07–1.61) 3.03 (2.50–3.68) [< 0.0001]	Age, physical activity, diabetes, HRT use, age at menarche, parity, age at menopause, OC use, smoking, race	BMI at ages 18 yr, 35 yr, and 50 yr not associated with risk
Friberg et al. (2007) Swedish mammography cohort Sweden 1987–2003	36 773 Incidence		BMI < 30 ≥ 30	 154 43	 1.0 2.49 (1.77–3.51)	Age, physical activity	Women without diabetes
Lundqvist et al. (2007) Twin cohort studies Sweden and Finland 1961–2004	14 017 older twins (mean baseline age, 56 yr) Incidence		BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 per 1 kg/m^2 [P_{trend}]	 1 92 57 30	 0.3 (0.1–2.5) 1.0 1.2 (0.8–1.6) 3.2 (2.1–4.8) 1.11 (1.06–1.15) [< 0.0001]	Smoking, physical activity, education level, diabetes	
Reeves et al. (2007) Population-based cohort United Kingdom 1996–2001	1.2 million Incidence		BMI < 22.5 22.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 per 10 kg/m^2	 340 524 516 366 911	 0.84 (0.75–0.93) 1.00 1.21 (1.11–1.32) 1.43 (1.29–1.58) 2.73 (2.55–2.92) 2.89 (2.62–3.18)	Age, region, SES, reproductive history, smoking, alcohol consumption, physical activity, HRT use	Association similar in never-smokers
Lindemann et al. (2008) HUNT cohort Norway 1984–2002	36 761 Incidence		BMI < 20 20–24 25–29 30–34 35–39 ≥ 40 [P_{trend}]	 4 64 90 32 23 9	 0.53 (0.19–1.47) 1.00 1.74 (1.25–2.43) 1.66 (1.06–2.59) 4.28 (2.58–7.09) 6.36 (3.08–13.16) [< 0.0001]	Age, physical activity, hypertension, alcohol consumption	Similar associations for women aged < 55 yr and aged ≥ 55 yr

Table 2.2.11a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Subtype	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
McCullough et al. (2008) Cancer Prevention Study II (CPS II) USA 1992–2003	33 436 Incidence		BMI < 22.5 22.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 54 53 91 76 44	 0.92 (0.63–1.34) 1.00 1.40 (0.99–1.96) 3.27 (2.29–4.67) 4.70 (3.12–7.07) [< 0.0001]	Age, age at menarche, age at menopause, parity, HRT use, smoking, exercise, OC use	Stronger association for never- vs ever-users of HRT. Stronger association for type 1 vs type 2 cancer; null association with BMI at age 18 yr
Song et al. (2008) Korean medical insurance cohort Republic of Korea 1994–2003	107 481 Incidence		BMI < 18.5 18.5–20.9 21–22.9 23.0–24.9 25.0–26.7 27.0–29.9 ≥ 30 per 1 kg/m²	 2 6 16 22 28 31 7	 1.26 (0.29–5.51) 0.74 (0.29–1.90) 1.00 1.20 (0.62–2.32) 1.61 (0.84–3.09) 2.70 (1.42–5.13) 2.95 (1.20–7.24) 1.13 (1.07–1.20)	Age, smoking, alcohol consumption, exercise	
Conroy et al. (2009) Women's Health Study USA 1992–2007	19 917 Incidence		BMI < 22.5 22.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 57 50 68 89	 1.00 0.97 (0.65–1.44) 1.09 (0.75–1.58) 2.49 (1.73–3.59) [< 0.0001]	Age, physical activity, smoking, alcohol consumption, diet, parity, HRT use	Weaker association with WC
Epstein et al. (2009) Lund cohort Sweden 1990–2007	17 822 Incidence		BMI < 25 25–29.9 ≥ 30	 45 41 36	 1.0 1.4 (0.9–2.2) 3.5 (2.2–5.4)	Age	
Canchola et al. (2010) California Teachers Study Cohort USA 1995–2006	28 418 never-users of HRT Incidence		BMI < 25 25–29.9 ≥ 30 [P_{trend}] per 1 kg/m²	 34 26 48	 1.0 1.2 (0.74–2.1) 3.5 (2.2–5.5) [< 0.001] 1.07 (1.04–1.09)	Age, parity, age at first pregnancy, physical activity, OC use	Much weaker association among HRT users. Similar risk for recalled BMI at age 18 yr; association also observed with WC

Table 2.2.11a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Subtype	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Dossus et al. (2010) EPIC cohort Europe 1992–2003	370 000 Incidence		BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 81 82 61	 1.0 1.23 (0.82–1.84) 2.02 (1.26–3.23) [0.005]	Age, centre	
Park et al. (2010) Multiethnic Cohort USA (California, Hawaii) 1993–2004	50 376 women aged 45–75 yr, from 5 racial/ ethnic populations		BMI at baseline < 25 25– < 30 ≥ 30 [P_{trend}]	 175 119 169	 1.00 1.36 (1.06–1.75) 3.54 (2.70–4.63) [< 0.001]	Age, ethnicity, education level, age at menarche, menopausal status, age at menopause, HRT use, OC use, parity, smoking history, diabetes, hypertension	Results available for BMI at age 21 yr, BMI change since age 21 yr, weight at baseline, and weight at age 21 yr
Reeves et al. (2011) Women's Health Initiative USA 1993–NR	86 937 Incidence		BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 264 207 334	 1.0 0.84 (0.67–1.05) 1.68 (1.33–2.13) [0.0001]	Age, race, education level, smoking, physical activity, intake of fruits and vegetables, diabetes, dietary fat, fibre intake	WHR more weakly associated, and association disappears with BMI adjustment
Ollberding et al. (2012) Multiethnic Cohort USA 1993–2007	46 027 Incidence		BMI < 25 25–29.9 ≥ 30 [P_{trend}]	489 total	 1.00 1.38 (1.09–1.74) 2.68 (2.10–3.42) [< 0.01]	Age, race, ethnicity, hypertension, diabetes, smoking, HRT use, OC use, parity	
Yang et al. (2012) Million Women Study United Kingdom 1996–2009	249 791 Incidence		BMI < 22.5 22.5–27.4 27.5–32.4 32.5–34.9 ≥ 35 per 5 kg/m^2	 139 465 390 158 258	 1.00 1.40 (1.27–1.53) 2.63 (2.39–2.91) 5.07 (4.33–5.93) 7.72 (6.79–8.77) 1.87 (1.77–1.96)	Age, region, height, age at menarche, age at menopause, parity, HRT use, alcohol consumption, smoking, exercise	(Update of study by Reeves et al., 2007) Body size and BMI at ages 10 yr and 20 yr less associated than BMI at baseline
Yang et al. (2013) NIH-AARP cohort USA 1995–2006	114 409 Incidence	Type 1	BMI < 30 ≥ 30	 708 570	 1.00 2.93 (2.62–3.28)	Age, OC use, HRT use, parity, age at menarche, menopausal status, race, smoking	Most women postmenopausal at time of study entry

Table 2.2.11a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Subtype	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Yang et al. (2013) (cont.)		Type 2	BMI < 30 ≥ 30	 86 47	 1.00 1.83 (1.27–2.63)	Age, OC use, HRT use, parity, menarche, menopause, race, smoking	
Bhaskaran et al. (2014) Health system clinical database United Kingdom 1987–2012	5.24 million Incidence		BMI per 5 kg/m²	2758	1.62 (1.56–1.69)	Age, sex, year, diabetes, alcohol consumption, smoking, SES	Similar association in never-smokers
Kabat et al. (2015) Women's Health Initiative cohort USA 1992–2013	143 901 Incidence		BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	1157 total	 1.0 0.93 (0.76–1.14) 1.08 (0.89–1.32) 1.29 (1.06–1.58) 2.32 (1.93–2.80) [< 0.0001]	Age, alcohol consumption, smoking, parity, HRT use, OC use, ethnicity, education	Similar association with WC

BMI, body mass index (in kg/m²); CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HRT, hormone replacement therapy; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; NR, not reported; OC, oral contraceptive; RR, relative risk; SES, socioeconomic status; WC, waist circumference; WHR, waist-to-hip ratio; yr, year or years

Table 2.2.11b Case–control studies of measures of body fatness and cancer of the endometrium

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
McCann et al. (2000) USA 1986–1991	232 639 Population	BMI < 27.5 ≥ 27.5	 112 120	 1.0 2.6 (1.9–3.6)	Age
Salazar-Martínez et al. (2000) Mexico 1995–1997	85 668 Population	BMI < 25 25–30 > 30	 21 28 35	 1.0 1.1 (0.61–2.1) 2.2 (1.2–4.2)	Age, an ovulatory index, smoking, physical activity, menopausal status, hypertension, diabetes
Benshushan et al. (2001, 2002) Israel 1989–1992	128 255 Population	BMI < 27 ≥ 27	 49 79	 1.00 2.47 [1.51–4.06]	
Newcomer et al. (2001) USA 1991–1994	740 2372 Population	BMI < 22.55 22.55–25.34 25.35–29.14 ≥ 29.15	 97 120 150 293	 1.0 1.2 (0.9–1.7) 1.6 (1.2–2.1) 3.0 (2.3–3.9)	Age
McElroy et al. (2002) USA 1991–1994	148 659 Population	BMI < 22.7 22.7–25.5 25.6–29.0 ≥ 29.1	 13 18 20 45	 1.00 1.52 (0.80–2.88) 1.60 (0.84–3.03) 3.72 (2.10–6.57)	Age
Augustin et al. (2003) Italy and Switzerland 1988 –1998	410 753 Hospital	BMI < 20 20–25 25– < 30 ≥ 30	 33 162 131 84	 1.0 1.2 (0.8–2.0) 1.3 (0.8–2.2) 2.2 (1.2–3.8)	Age, study centre, education level, history of diabetes and hypertension, HRT use, total energy intake
Dal Maso et al. (2004) Italy 1999–2002	87 132 Hospital	BMI < 25 25–29 ≥ 30	 20 34 33	 1.00 1.80 (0.90–3.59) 5.87 (2.58–13.38)	Age, education level

Table 2.2.11b (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Xu et al. (2005, 2006) China 1997–2001	832 846 Population	BMI, quartiles Recent BMI > 25.69 vs < 21.03 BMI at age 20 yr > 21.09 vs < 17.63 BMI at age 30 yr > 22.43 vs < 18.81 BMI at age 40 yr > 24.00 vs < 19.83 BMI at age 50 yr > 25.30 vs < 20.83 BMI at age 60 yr > 25.97 vs < 21.48	 302 205 226 269 217 122	 3.3 (2.4–4.5) 1.3 (1.0–1.8) 1.5 (1.1–2.0) 2.0 (1.5–2.8) 2.5 (1.7–3.6) 2.9 (1.7–4.9)	Age, education level, years of menstruation, OC use, number of pregnancies, menopausal status, family history of cancer; for recent BMI, additionally adjusted for BMI at age 20 yr
Xu et al. (2005) China 1997–2001	832 846 Population	WC (cm) ≤ 73 74–79 80–86 > 86	 102 157 215 357	 1.0 1.9 (1.4–2.7) 2.6 (1.9–3.6) 4.7 (3.4–6.4)	Age, education level, years of menstruation, number of pregnancies, BMI
Okamura et al. (2006) Japan 1998–2000	155 96 Hospital	BMI < 20.04 20.04–21.63 21.64–23.92 ≥ 23.93	 36 27 45 47	 1.00 0.47 (0.22–0.99) 1.24 (0.58–2.67) 1.92 (0.86–4.30)	Age
Trentham-Dietz et al. (2006) USA 1991–1994	740 2342 Population	BMI 14.5–22.6 22.6–25.4 25.5–29.2 29.1–82.4	 100 123 153 313	 1.00 1.19 (0.88–1.61) 1.62 (1.21–2.18) 3.20 (2.42–4.24)	Age, age at menarche, parity, menopausal status, age at menopause, smoking, HRT use, recent physical activity, diabetes
Weiss et al. (2006) USA 1985–1991, 1994–1995, 1997–1999	1304 1779 Population	BMI < 30.0 30.0–34.9 ≥ 35.0	Low tumour aggressiveness: 374 57 65	 1.0 1.6 (1.2–2.3) 5.1 (3.5–7.4)	HRT use, age, county of residence, reference year Tumours with moderate or high aggressiveness gave very similar results

Table 2.2.11b (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Lucenteforte et al. (2007) Italy and Switzerland 1988–2006	777 1550 Hospital	BMI at diagnosis < 30 ≥ 30 BMI at age 30–39 yr < 25 ≥ 25	 555 218 532 215	 1.0 2.4 (1.9–3.1) 1.0 1.6 (1.3–2.0)	Age, history of diabetes, physical activity, history of hypertension, year of interview, study centre, education level, parity, menopausal status, OC use, HRT use
Máchová et al. (2007) Czech Republic 1987–2002	87 20 776 Population	BMI < 25 ≥ 25– < 30 ≥ 30	NR	 1.00 1.84 (0.95–3.57) 3.25 (1.65–6.37)	Age, smoking, hypertension, height
Niwa et al. (2007) Japan 2001–2004	110 220 Hospital	BMI < 25.0 ≥ 25.0	 75 35	 1.00 2.35 (1.32–4.17)	
Wen et al. (2008) China 1997–2003	1046 1035 Population	BMI < 20.92 20.93–22.68 22.69–24.32 24.33–26.47 > 26.47 WC (cm) < 71 72–76 77–80 81–87 > 87	 104 128 190 214 408 71 141 168 282 382	 1.1 (0.9–1.5) 1.0 (0.9–1.1) 1.0 1.0 (0.9–1.2) 1.1 (0.8–1.5) 0.5 (0.3–0.6) 0.7 (0.6–0.8) 1.0 1.5 (1.3–1.7) 2.3 (1.7–3.1)	Age at menarche, menopausal status, total years of menstruation, OC use, cancer history in first-degree relatives, and BMI (for WC) or WC (for BMI)
Fortuny et al. (2009) USA 2001–2005	469 467 Population	BMI < 25 25– < 30 30– < 35 ≥ 35	 118 127 80 142	 1.0 1.6 (1.1–2.2) 2.0 (1.4–3.0) 7.6 (4.8–11.8)	Age
Thomas et al. (2009) USA 1980–1982	421 3159 Population	Adult BMI < 25.0 25.0–29.9 30.0–34.9 ≥ 35.0	LMP < 45 yr: 59 26 23 30	 1.0 2.9 (1.7–4.8) 6.0 (3.3–10.7) 21.7 (11.3–41.7)	Age, race, education level, OC use, parity, use of estrogen therapy, menopausal status, history of high blood pressure

Table 2.2.11b (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Thomas et al. (2009) (cont.)		Adult BMI	LMP ≥ 45 yr:		Weaker associations with BMI at age 18 yr vs adult BMI for both LMP < 45 yr and LMP ≥ 45 yr
		< 25.0	168	1.0	
		25.0–29.9	60	1.5 (1.0–2.1)	
		30.0–34.9	31	2.3 (1.4–3.6)	
		≥ 35.0	24	3.7 (2.0–6.6)	
Tong et al. (2009) Republic of Korea 1998–2006	125 302 Hospital	BMI			Age
		< 23	30	1.0	
		23–25	34	1.19 (0.62–2.29)	
		≥ 25	61	2.65 (1.44–4.89)	
Chandran et al. (2010) USA 2001–2005	424 398 Population	BMI			Age
		< 25	105	1.00	
		25–29.9	121	1.93 (1.36–2.75)	
		30–34.9	68	2.02 (1.32–3.08)	
		≥ 35	123	8.47 (5.16–13.89)	
Charneco et al. (2010) Puerto Rico 2004–2007	74 88 Hospital	BMI			Crude Age, education level, employment status, poultry consumption, OC use, diabetes, hypertension
		≤ 24.9	6	1.00	
		25.0–29.9	25	4.44 (1.60–12.26)	
		≥ 30	43	9.85 (3.61–26.87)	
		BMI			
		< 30	31	1.00	
		≥ 30	43	4.11 (1.76–9.93)	
John et al. (2010) USA 1996–1999	472 443 Population	BMI			Age, race/ethnicity
		< 25	176	1.00	
		25–29.9	135	0.92 (0.67–1.26)	
		≥ 30	184	1.93 (1.39–2.68)	
Zhang et al. (2010) China 2004–2008	942 1721 Population	BMI			
		18.5–24.9	571	1.00	
		25.0–29.9	284	1.51 (1.26–1.81)	
		≥ 30.0	80	6.15 (3.98–9.51)	
Dal Maso et al. (2011) Italy 1992–2006	454 908 Hospital	BMI ≥ 30:			Age, study centre, calendar period of interview, years of education, smoking habits, age at menarche, age at menopause, parity, OC use, HRT use
		BMI at baseline	168	4.08 (2.90–5.74)	
		BMI at age 30 yr	29	1.78 (1.01–3.14)	
		BMI at age 50 yr	96	3.37 (2.26–5.04)	
		BMI, 5 kg/m² increase		1.89 (1.65–2.17)	
		WC (cm)			
		≥ 96 vs < 84	127	2.68 (1.78–4.03)	

Table 2.2.11b (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Delahanty et al. (2011) China 1996–2005	832 2049 Population	BMI < 21.7 21.7–24.5 > 24.5	 14.0% 28.3% 57.7%	 1.00 1.68 (1.30–2.18) 3.13 (2.44–4.01)	Age, income, education level
Friedenreich et al. (2011) Canada 2002–2006	515 962 Population	WC (cm) ≥ 88	 343	 2.32 (1.82–2.96)	Reference WC not reported Age
Hosono et al. (2011) Japan 2001–2005	222 2162 Hospital	BMI at baseline < 25 ≥ 25 BMI at age 20 yr < 25 ≥ 25 BMI change from age 20 yr to enrolment ≤ 0 0–3 > 3	 152 65 196 17 57 73 82	 1.00 2.22 (1.59–3.09) 1.00 2.30 (1.29–4.11) 1.00 1.26 (0.86–1.84) 1.48 (0.95–2.29)	Age, smoking, alcohol consumption, regular exercise, age at menarche, duration of menstruation, parity, diabetes history, history of OC use, history of HRT use
Lu et al. (2011) USA 2004–2009	668 674 Population	BMI > 30 vs < 25: current 5 yr in the past at age 20s at age 30s at age 40s at age 50s at age 60s	 354 321 60 106 150 156 67	 4.76 (3.50–6.49) 4.22 (3.05–5.84) 1.96 (1.16–3.29) 2.19 (1.46–3.28) 3.84 (2.62–5.61) 5.44 (3.62–8.17) 4.09 (2.32–7.21)	Age, ethnic group, education level, pregnancy, family history of cancer, estrogen use, OC use, smoking, alcohol consumption
Rosato et al. (2011) Italy 1992–2006	454 798 Hospital	BMI ≤ 30 > 30 WC (cm) < 80 vs ≥ 80 ≤ 88 vs > 88	 312 142 266 195	 1.00 3.83 (2.74–5.36) 1.62 (1.00–2.62) 1.90 (1.34–2.71)	Age, study centre, year of interview, education level, age at menarche, parity, menopausal status, OC use, HRT use
Friedenreich et al. (2012) Canada 2002–2006	541 961 Population	BMI per 1 kg/m^2 increase	 	 1.10 (1.08–1.12)	Same study/data set as Friedenreich et al. (2011) Adjusted for age

Table 2.2.11b (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates Comments
Amankwah et al. (2013) Canada 2002–2006	524 1032 Population	BMI < 25 25– < 30 ≥ 30 [P_{trend}] WC (cm) > 96.0 vs ≤ 76.5	 87 124 256 220	 1.00 1.26 (0.91–1.73) 2.81 (2.06–3.84) [< 0.001] 4.21 (2.90–6.10)	Age, residence type (rural or urban), age at menarche, menopausal status/ hormone use, parity/age at first pregnancy, hypertension
Becker et al. (2013) United Kingdom 1995–2012	2554 15 324 Population	BMI < 25 25–29.9 30–59.9	 560 560 877	 1.00 1.49 (1.32–1.68) 3.18 (2.82–3.57)	Crude estimates
King et al. (2013) USA 2001–2005	424 398 Population	BMI < 25 25–29.9 30–34.9 ≥ 35	 105 121 68 123	 1.00 1.93 (1.36–2.75) 2.02 (1.32–3.08) 8.47 (5.16–13.89)	Age
Nagle et al. (2013) Australia 2005–2007	1398 1538 Population	Recent BMI ≥ 40 vs < 25 Maximum BMI ≥ 40 vs < 25 BMI at age 20 yr ≥ 30 vs < 25 BMI change from age 20 yr Always overweight vs always normal Change from maximum to recent BMI Always ≥ 30 vs always < 25	 192 257 72 203 637	 7.98 (5.41–11.77) 6.62 (4.72–9.29) 0.75 (0.43–1.33) 3.60 (2.62–4.95) 3.71 (2.96–4.67)	Age, age at menarche, parity, duration of OC use, HRT use ≥ 3 months, smoking status, diabetes

BMI, body mass index (in kg/m²); CI, confidence interval; HRT, hormone replacement therapy; LMP, last menstrual period; NR, not reported; OC, oral contraceptive; WC, waist circumference; yr, year or years

Table 2.2.11c Pooled analyses and meta-analyses of measures of body fatness and cancer of the endometrium

Reference	Number and type of studies	Population size and type	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustments Comments
Crosbie et al. (2010)	Meta-analysis of 24 studies published 1966–2009	17 710 cases	BMI 27 32 37 42 per 5 kg/m^2		 1.22 (1.19–1.24) 2.09 (1.94–2.26) 4.36 (3.75–5.10) 9.11 (7.26–11.51) 1.60 (1.52–1.68)	$P_{heterogeneity}$ = 0.215
Dobbins et al. (2013)	Meta-analysis of 16 cohort and case–control studies		Obese vs normal-weight		1.85 (1.30–2.65)	$P_{heterogeneity}$ = 0.00001
Felix et al. (2013)	Pooled analysis of 13 studies (E2C2)	8096 cases (primarily endometrioid endometrial carcinomas) and 28 829 controls	BMI < 25 25–30 ≥ 30 [P_{trend}]	 2675 2246 2479	 1.00 1.37 (1.28–1.46) 3.03 (2.82–3.26) [0.0001]	Age, race, age at menarche, parity, menopausal status, menopausal estrogen plus progestin, menopausal estrogen use, OC use, smoking status, history of diabetes, site
Setiawan et al. (2013)	Pooled analysis of 10 cohort studies and 14 case–control studies in China, Europe, and North America (E2C2)	14 069 cases and 35 312 controls	BMI 18– < 25 25– < 30 30– < 35 35– < 40 ≥ 40 [P_{trend}]	Type 1: 4602 3718 2294 1247 992	 1.00 1.45 (1.37–1.53) 2.52 (2.35–2.69) 4.45 (4.05–4.89) 7.14 (6.33–8.06) [< 0.0001]	Age, study, race/ethnicity, age at menarche, parity, OC use, menopausal status, menopausal HRT use, smoking status
			BMI 18– < 25 25– < 30 30– < 35 35– < 40 ≥ 40 [P_{trend}]	Type 2: 330 253 159 65 47	 1.00 1.16 (0.98–1.38) 1.73 (1.40–2.12) 2.15 (1.60–2.88) 3.11 (2.19–4.44) [< 0.0001]	
Cote et al. (2015)	Pooled analysis of 7 cohort studies and 4 case–control studies	2011 Black women (516 cases and 1495 controls)	BMI 18.5–24.9 25–29.9 ≥ 30	Black women: 76 129 300	 1.00 1.37 (0.97–1.94) 2.93 (2.11–4.07)	Age, smoking, OC use, diabetes, study site, age at menarche, parity as a continuous variable
		19 297 White women (5693 cases and 13 604 controls)	BMI 18.5–24.9 25–29.9 ≥ 30	White women: 1950 1541 2107	 1.00 1.43 (1.32–1.56) 2.99 (2.74–3.26)	

Table 2.2.11c (continued)

Reference	Number and type of studies	Population size and type	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustments Comments
Jenabi & Poorolajal (2015)	Meta-analysis of 20 cohort studies	32 281 242 participants total	BMI			
			Normal		1.00	$P_{heterogeneity}$:
			Overweight		1.34 (1.20–1.48)	Overweight: $P = 0.001$
			Obese		2.54 (2.27–2.81)	Obesity: $P = 0.001$
	Meta-analysis of 20 case–control studies		BMI			
			Normal		1.00	$P_{heterogeneity}$:
			Overweight		1.43 (1.30–1.56)	Overweight: $P = 0.017$
			Obese		3.33 (2.87–3.79)	Obesity: $P = 0.001$

BMI, body mass index (in kg/m^2); CI, confidence interval; E2C2, Epidemiology of Endometrial Cancer Consortium; OC, oral contraceptive; yr, year or years

Table 2.2.11d Mendelian randomization studies of measures of body fatness and cancer of the endometrium

Reference	Characteristics of study population	Sample size	Exposure	Outcome	Odds ratio (95% CI) with each SD increase in exposure
Nead et al. (2015)	Cases were from the Australian National Endometrial Cancer Study (ANECS) or the Studies of Epidemiology and Risk Factors in Cancer Heredity study (SEARCH), United Kingdom Control participants were from the Wellcome Trust Case Control Consortium (WTCCC), and Australian control participants were from parents of twins in the Brisbane Adolescent Twin Study and from the Hunter Community Study	9560 (1287 cases and 8273 controls)	BMI	Endometrial cancer	3.86 (2.24–6.64)

BMI, body mass index (in kg/m^2); CI, confidence interval; SD, standard deviation; yr, year or years

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2.2.12 Cancer of the cervix

Cancer of the cervix is the fourth most common cancer in women. Human papillomavirus (HPV) infection, which is present in almost all cases of cervical cancer, is not related to adiposity (Wee et al., 2008). In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and cervical cancer was *inadequate*.

(a) Cohort studies

Since 2001, at least eight cohort studies of cervical cancer and body weight (Wolk et al., 2001; Calle et al., 2003; Rapp et al., 2005; Reeves et al., 2007; Song et al., 2008; Ulmer et al., 2012; Lee et al., 2013; Bhaskaran et al., 2014) and one pooled analysis of 39 cohort studies (Parr et al., 2010) have been published (Table 2.2.12a; web only; available at: http://publications.iarc.fr/570). Although some studies reported statistically significant increases, the data overall remained inconsistent.

(b) Case–control studies

The five case–control studies assessing the association between body fatness and cervical cancer (Cusimano et al., 1989; Brinton et al., 1993; Ursin et al., 1996; Lacey et al., 2003; Máchová et al., 2007) had relatively small sample sizes (< 150 cases), and the results are inconsistent (Table 2.2.12b; web only; available at: http://publications.iarc.fr/570).

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2.2.13 Cancer of the ovary

Cancer of the ovary accounts for about 4% of all cancer diagnoses in women. Risk of ovarian cancer is known to be reduced with use of oral contraceptives, and increased with *BRCA* gene mutations and use of estrogen (unopposed) HRT. There are histologically distinct subtypes of ovarian cancer, including serous, mucinous, clear cell, endometrioid, and other/mixed types (Jayson et al., 2014).

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and ovarian cancer was *inadequate*. The 2007 WCRF review did not draw any conclusions regarding body fatness and ovarian cancer risk (WCRF/AICR, 2007). On the basis of many more studies, including pooled analyses, the WCRF Continuous Update Project in 2014 concluded that there was a small but convincing positive association between BMI and ovarian cancer risk, but limited and inconsistent evidence regarding waist circumference (WCRF/AICR, 2014).

Table 2.2.13a, Table 2.2.13b, and Table 2.2.13c present the findings from cohort studies, case–control studies, and meta-analyses, respectively, published since 2000. Findings are presented by BMI at baseline, with comments on findings according to weight change over the life-course and waist circumference.

(a) Cohort studies

The evidence published since 2000 includes 15 cohort studies (excluding analyses that were later updated and analyses based on fewer than 100 incident cases) (Table 2.2.13a) and several meta-analyses of cohort studies (Table 2.2.13c). In general, findings were consistent across studies, suggesting a modest positive association between baseline BMI and ovarian cancer risk. A meta-analysis including 13 cohort studies found significant increases in risk of 7% in overweight women and of 23% in obese women compared with women of normal BMI (Liu et al., 2015). Aune et al. (2015), in a meta-analysis including 25 prospective studies, found a summary relative risk per 5 kg/m^2 increase in BMI of 1.07 (95% CI, 1.03–1.11) [moderate heterogeneity (54%) across studies was reported] (Aune et al., 2015).

The association is stronger in never-users of HRT (Leitzmann et al., 2009). The Collaborative Group on Epidemiological Studies of Ovarian Cancer found the relative risk per 5 kg/m^2 increase in BMI to be 1.10 (95% CI, 1.07–1.13; P_{trend} = 0.02) in never-users of HRT, but 0.95 (95% CI, 0.92–0.99; P_{trend} = 0.02) in ever-users of HRT (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012).

The Collaborative Group on Epidemiological Studies of Ovarian Cancer (2012) also examined the relationship between BMI and ovarian cancer risk separately by histological type. The association was broadly similar across the common histological subtypes of ovarian cancer, except for serous tumours of borderline malignancy, for which the association was considerably greater than for the other tumour subtypes.

There was no consistency in the evidence for whether BMI earlier in life is more or less predictive of ovarian cancer than is BMI at a later age. The systematic review by Aune et al. (2015) and a twin cohort study by Lundqvist and collaborators (Lundqvist et al., 2007) found marginally stronger associations with BMI in early adulthood than with BMI later in life. However, a pooled analysis including 13 548 cases found the opposite (Olsen et al., 2013). Two cohort studies examining weight gain from age 18–20 years reported positive associations (Ma et al., 2013 based on 152 cases; P_{trend} = 0.05; Canchola et al., 2010), whereas the meta-analyses by Aune et al. (2015) based on 6 cohort studies and 1338 cases did not find evidence of this association [significant heterogeneity was reported in this study; $P_{heterogeneity}$ = 0.01].

In three of the four cohorts that included measurements of waist circumference, this was found to be less associated with ovarian cancer risk than was BMI (Chionh et al., 2010; Lahmann et al., 2010; Ma et al., 2013); one study showed significant positive associations stronger than those reported with BMI (Canchola et al., 2010).

(b) *Case–control studies*

A total of 35 case–control studies (including 7 hospital-based studies) from Asia, Australia, Canada, Europe, and the USA and several meta-analyses including case–control studies have been published since 2000 on the association between BMI at diagnosis and ovarian cancer risk (Table 2.2.13b and Table 2.2.13c). An increase in risk was generally observed, although estimates were not statistically significant in most individual studies. However, a meta-analysis including 13 case–control studies and presenting low heterogeneity (I^2 = 11.3%) found significant increased risk of ovarian cancer in overweight women (RR, 1.09; 95% CI, 1.00–1.19) and in obese women (RR, 1.31; 95% CI, 1.12–1.54) compared with women of normal BMI (Liu et al., 2015). Another meta-analysis of 47 epidemiological studies, which included 30 case–control studies, showed a significant 5% increase in risk in those studies with population-based controls (n = 17) and a significant 8% decrease in risk in those studies with hospital-based controls (n = 13) [the decreased risk in hospital-based studies is probably due to selection bias related to BMI] (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012).

When stratifying by menopausal status or HRT use, the Collaborative Group on Epidemiological Studies of Ovarian Cancer (2012) reported a significant interaction with HRT use, with evidence of a 10% increased risk only among never-users of HRT (n = 11 456 cases). A pooled analysis from 15 case–control studies (Olsen et al., 2013) also reported that the associations were stronger among premenopausal women who had never used HRT.

In the few studies that examined the relationship between BMI and ovarian cancer risk separately by histological type, the associations seemed to be confined to non-serous and low-grade serous tumours (Olsen et al., 2013). An earlier pooled analysis of 10 case–control studies found no association for serous cancers, but there was an association for all other ovarian cancer types (Kurian et al., 2005). The risk was significantly increased in both invasive and borderline ovarian cancer subtypes, with a somewhat stronger association with borderline tumours (Olsen et al., 2013).

Among the 10 studies that reported on the association between BMI in young adulthood and ovarian cancer risk, 7 observed a non-significant increase in risk, two observed a significant increase in risk (Lubin et al., 2003; Olsen et al., 2013), and one observed a significant decrease in risk (Kuper et al., 2002). Four studies evaluated BMI change between early adulthood and diagnosis and showed no significant association with ovarian cancer risk (Lubin et al., 2003; Zhang et al., 2005; Greer et al., 2006; Peterson et al., 2006).

(c) *Mendelian randomization studies*

One large-scale Mendelian randomization study has been conducted to assess the association of childhood and adult BMI with ovarian cancer risk, separated into histological subtypes including clear cell, endometrioid, and serous cancer (Gao et al., 2016; Table 2.2.13d). With each 1 kg/m^2 increase in adult BMI (assuming that a standard deviation was equivalent to 4.5 kg/m^2), there was evidence for an increased risk of all ovarian cancer (OR, 1.07; 95% CI, 1.01–1.13; P = 0.02) and weak, not statistically significant, evidence for an increased risk of clear cell ovarian cancer (OR, 1.12; 95% CI, 0.96–1.31; P = 0.14) and serous ovarian cancer (OR, 1.06; 95% CI, 0.99–1.13; P = 0.09). There was no evidence for

statistically significant associations between childhood BMI and risk of any ovarian cancer types.

In sensitivity analyses exploring the validity of the genetic variants used, there was evidence for negative pleiotropy in the association between adult BMI and endometrioid ovarian cancer [thus suggesting that the positive association may have been underestimated in the main analyses].

Table 2.2.13a Cohort studies of measures of body fatness and cancer of the ovary

Reference Cohort Location Follow-up period	Total number of women Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Calle et al. (2003) Population-based cohort USA 1982–1998	495 477 Mortality	BMI 18.5–24.9 25–29.9 30–34.9 35–39.9 [P_{trend}]	 873 437 126 49	 1.00 1.15 (1.02–1.29) 1.16 (0.96–1.40) 1.51 (1.12–2.02) [0.001]	Age, education level, smoking, physical activity, alcohol consumption, marital status, aspirin use, fat intake, vegetable intake, HRT use	Women who had either a hysterectomy or ovarian surgery were excluded
Rapp et al. (2005) Population-based cohort Austria 1985–2002	78 484 Incidence	BMI 18.5–24.9 25.0–29.9 ≥ 30 [P_{trend}]	 61 39 21	 1.0 1.03 (0.68–1.56) 1.25 (0.75–2.08) [0.44]	Age, smoking, occupation	
Lacey et al. (2006) Breast Cancer Detection Demonstration Project Follow-Up Study USA 1973–1997	46 026 Incidence	BMI < 18.5 18.5–24.9 25.0–29.9 30–34.9 ≥ 35 per 1 kg/m^2	 7 219 83 20 11	 0.95 (0.45–2.01) 1.00 1.00 (0.78–1.29) 0.94 (0.59–1.48) 1.55 (0.84–2.84) 1.01 (0.98–1.03)	Age, race, menopausal status, parity, OC use, HRT use	
Lundqvist et al. (2007) Twin cohort studies Sweden and Finland 1961–2004	14 058 twins (mean age, 56 yr) Incidence	BMI at baseline < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 1 86 57 7	 0.4 (0.1–2.6) 1.0 1.2 (0.8–1.6) 0.7 (0.3–1.5) [0.95]	Age, country, smoking, physical activity, education level, diabetes, parity	
	22 432 twins (mean age, 30 yr) Incidence	BMI at baseline < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 8 120 31 3	 0.7 (0.3–1.4) 1.0 1.5 (1.0–2.3) 0.8 (0.2–2.6) [0.01]	Age, smoking, physical activity, education level, diabetes, parity	

Table 2.2.13a (continued)

Reference Cohort Location Follow-up period	Total number of women Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Reeves et al. (2007) Million Women Study United Kingdom 1996–2001	1.2 million Incidence	BMI < 22.5 22.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 per 10 kg/m²	 478 631 510 349 438	 0.98 (0.89–1.07) 1.00 0.99 (0.91–1.08) 1.13 (1.02–1.25) 1.12 (1.02–1.23) 1.14 (1.03–1.27)	Age, region, SES, reproductive history, smoking, alcohol consumption, physical activity, HRT use	
Schouten et al. (2008) Pooling Project of Prospective Studies of Diet and Cancer (12 cohorts pooled) North America and western Europe Follow-up varied by cohort	531 583 Incidence	BMI < 23 23–24.9 25.0–26.9 27–29.9 ≥ 30 [P_{trend}] BMI < 23 23–24.9 25.0–26.9 27–29.9 ≥ 30 [P_{trend}]	Postmenopausal: 426 291 222 206 191 Premenopausal: 64 34 14 14 22	 1.0 0.91 (0.78–1.06) 0.95 (0.80–1.13) 0.96 (0.80–1.14) 1.07 (0.87–1.33) [0.53] 1.0 1.29 (0.83–2.00) 0.95 (0.50–1.81) 1.28 (0.59–2.79) 1.72 (1.02–2.29) [0.13]		
Song et al. (2008) Korean medical insurance cohort Republic of Korea 1994–2003	107 481, postmenopausal Incidence	BMI < 18.5 18.5–20.9 21–22.9 23.0–24.9 25.0–26.7 27.0–29.9 ≥ 30 per 1 kg/m²	 3 13 30 53 42 30 5	 0.98 (0.29–3.24) 0.85 (0.43–1.68) 1.00 1.63 (1.01–2.63) 1.62 (0.98–2.67) 1.57 (0.91–2.73) 0.93 (0.32–2.67) 1.04 (0.99–1.09)	Age, smoking, alcohol consumption, physical exercise, income level at study entry	Ovary and other unspecified female genital organs
Leitzmann et al. (2009) NIH-AARP cohort USA 1996–2003	94 525 Incidence	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	Never-users of HRT: 39 43 43	 1.00 1.39 (0.89–2.14) 1.83 (1.18–2.84) [0.007]	Age, race/ethnicity, family history, OC use, physical activity	

Table 2.2.13a (continued)

Reference Cohort Location Follow-up period	Total number of women Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Leitzmann et al. (2009) (cont.)		BMI	Ever-users of HRT:			
		< 25	102	1.00		
		25–29.9	43	0.68 (0.48–0.98)		
		≥ 30	33	0.96 (0.65–1.43)		
		[P_{trend}]		[0.53]		
Canchola et al. (2010) California Teachers Study Cohort USA 1995–2007	56 091 Never-users of HRT Incidence	BMI			Race, OC use, parity, wine intake, physical activity, smoking, tubal ligation	Weight gain from age 18 yr to baseline positively associated
		< 25	57	1.0		
		25–29.9	29	1.1 (0.71–1.8)		
		≥ 30	21	1.2 (0.72–2.0)		
		WC (in)				
		< 35	32	1.0		
		≥ 35	29	1.8 (1.1–3.0)		
Chionh et al. (2010) Melbourne Collaborative Cohort Study Australia 1990–2008	18 700 Incidence	BMI			Country of birth, education level, age at menarche, parity, OC use, hysterectomy, tobacco use, physical activity, energy intake from diet	
		< 25	39	1.00		
		25–29.9	40	1.05 (0.66–1.65)		
		≥ 30	34	1.58 (0.96–2.62)		
		per 5 kg/m^2		1.22 (1.00–1.48)		
		[P_{trend}]		[0.06]		
		WC, quartiles				
		Q1	24	1.00		
		Q2	27	0.97 (0.56–1.69)		
		Q3	30	1.03 (0.59–1.78)		
		Q4	32	0.96 (0.54–1.69)		
		[P_{trend}]		[0.71]		
Kotsopoulos et al. (2010) Nurses' Health Study 1 and 2 USA 1976–2006	182 700 Incidence	BMI			Age, age at menarche, parity, OC use, tubal ligation, height, family history of breast or ovarian cancer, caffeine intake, hysterectomy; for WC, additionally adjusted for BMI	
		< 21	125	1.00		
		21–22.9	155	0.97 (0.77–1.23)		
		23–24.9	168	1.02 (0.81–1.29)		
		25.0–29.9	242	0.96 (0.77–1.19)		
		≥ 30	177	1.12 (0.89–1.42)		
		[P_{trend}]		[0.29]		

Table 2.2.13a (continued)

Reference Cohort Location Follow-up period	Total number of women Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Kotsopoulos et al. (2010) (cont.)		WC (in)				
		< 28	67	1.0		
		28–29.9	65	0.91 (0.64–1.29)		
		30–31.9	56	0.89 (0.61–1.30)		
		32–34.9	68	0.90 (0.61–1.33)		
		≥ 35	79	1.00 (0.62–1.88)		
		[P_{trend}]		[0.65]		
Lahmann et al. (2010) EPIC cohort Europe 1992–2007	226 798 Incidence	BMI			Age, parity, age at menarche, smoking, OC use	Stronger association in postmenopausal women than in premenopausal women
		< 25	287	1.00		
		25–29.9	211	1.14 (0.94–1.37)		
		≥ 30	113	1.33 (1.05–1.68)		
		[P_{trend}]		[0.02]		
		WC, quartiles				Similar association in premenopausal and postmenopausal women
		Q1	122	1.00		
		Q2	155	1.03 (0.81–1.31)		
		Q3	175	1.10 (0.87–1.41)		
		Q4	159	1.12 (0.86–1.45)		
		[P_{trend}]		[0.32]		
Yang et al. (2012) NIH-AARP cohort USA 1995–2006	169 391 Incidence	BMI			Age, OC use, HRT use, parity	Stronger association with endometrioid histological subtype
		< 30	617	1.00		
		≥ 30	197	1.15 (0.98–1.35)		
Ma et al. (2013) Shanghai Women's Health Study (SWHS) (population-based cohort) Shanghai, China 1996–2009	70 258 Incidence	BMI			Age, education level	Weight gain from age 20 yr also positively associated with risk
		< 18.5	7	1.73 (0.80–3.75)		
		18.5–24.9	75	1.00		
		25.0–29.9	55	1.49 (1.05–2.13)		
		≥ 30	15	2.42 (1.37–4.28)		
		[P_{trend}]		[0.008]		
		WC, quartiles			Age, education level	
		Q1	27	1.00		
		Q2	34	1.36 (0.82–2.26)		
		Q3	41	1.50 (0.92–2.46)		
		Q4	50	1.61 (0.98–2.64)		
		[P_{trend}]		[0.06]		

Table 2.2.13a (continued)

Reference Cohort Location Follow-up period	Total number of women Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Bhaskaran et al. (2014) Health system clinical database United Kingdom 1987–2012	2 864 658 Incidence	BMI per 5 kg/m^2	3684	1.09 (1.04–1.14)	Age, sex, year, diabetes, alcohol consumption, smoking, SES	Similar association in never-smokers
Gay et al. (2015) Singapore Breast Cancer Screening Project (SBCSP) Singapore 1994–2012	28 234 Incidence	BMI < 18.5 18.5–22.9 23–27.4 ≥ 27.5 [P_{trend}]	 6 28 56 17	 1.96 (0.64–5.97) 1.00 1.34 (0.69–2.58) 0.55 (0.19–1.55) [0.22]	Age, housing, family history of breast cancer	

BMI, body mass index (in kg/m^2); CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HRT, hormone replacement therapy; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; OC, oral contraceptive; SES, socioeconomic status; WC, waist circumference; yr, year or years

Table 2.2.13b Case–control studies of measures of body fatness and cancer of the ovary

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Greggi et al. (2000) Italy 1998	440 Hospital	BMI < 22.5 22.5–26 > 26	 118 129 140	 1.0 (0.8–1.5) (0.8–1.6)	Age, education level, parity, OC use, family history of ovarian cancer	
Purdie et al. (2001) Australia 1990–1993	775 Population	BMI, percentiles < 15th 15th–35th 35th–65th 65th–85th ≥ 85th [P_{trend}]	518 total	 1.0 (0.7–1.6) 1.5 (1.0–2.2) 1.0 1.3 (0.9–1.9) 1.7 (1.1–2.6) [0.12]	Age, age squared, geographical location, education level, parity, duration of OC use, smoking history, ever-use of talc in the perineal region, tubal sterilization, hysterectomy, history of breast or ovarian cancer in a first-degree relative	Stronger risks were observed in premenopausal women above the 65th percentile
Dal Maso et al. (2002) Italy 1992–1999	1031 Hospital	BMI < 21 21– < 25 25– < 30 ≥ 30 [P_{trend}]	 143 406 299 173	 1.00 0.99 (0.77–1.27) 0.76 (0.58–0.99) 1.07 (0.79–1.44) [0.53]	Age, education level, parity, OC use	A significant association was observed with waist-to-hip ratio. No association was observed with increased body weight
Kuper et al. (2002) USA 1992–1997	563 Population	BMI < 20 ≥ 20– < 25 ≥ 25– < 30 ≥ 30	 67 255 138 104	 1.00 0.97 (0.64–1.45) 1.02 (0.65–1.60) 1.24 (0.77–2.01)	Age, site, parity, OC use, family history of breast, ovarian, or prostate cancer in a first-degree relative, tubal ligation, education level, marital status	In stratified analyses, a higher risk with BMI and weight was observed in premenopausal women
Lubin et al. (2003) Israel 1994–1999	1269 Population	BMI at age 18 yr < 19.1 19.1–20.9 21.0–22.8 22.9–35.2 [P_{trend}]		 1.00 1.16 (0.89–1.51) 1.13 (0.87–1.48) 1.42 (1.08–1.85) [0.009]		

Table 2.2.13b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Lubin et al. (2003) (cont.)		BMI change from age 18 yr				
		< 0.73		1.00		
		0.73–2.70		0.82 (0.63–1.06)		
		2.71–5.71		0.79 (0.60–1.03)		
		≥ 5.72		0.91 (0.69–1.20)		
		[P_{trend}]		[0.50]		
Yen et al. (2003) Taiwan, China 1993–1998	86 Hospital	BMI			Age, income during marriage, education level	
		< 25	63	1.00		
		≥ 25	23	0.77 (0.45–1.33)		
Pan et al. (2004) Canada 1994–1997	442 Population	BMI	442 total		5-year age group, province of residence, education level, pack-years of smoking, alcohol consumption, total energy intake, vegetable intake, dietary fibre intake, recreational physical activity, menopausal status, number of live births, age at menarche, age at end of first pregnancy	
		< 25		1.00		
		25– < 30		1.16 (0.90–1.50)		
		≥ 30		1.95 (1.44–2.64)		
Pike et al. (2004) USA 1992–1998	477 Population	BMI			Ethnicity, age, education level, SES, family history of ovarian cancer, tubal legation, use of talc in the genital area, nulliparity, age at last birth, number of births, number of incomplete pregnancies, OC use, menopausal status, age at natural menopause, age at surgical menopause, HRT use	
		< 25	261	1.00		
		25–29	120	0.97 (0.71–1.33)		
		30–34	56	1.29 (0.83–1.99)		
		≥ 35	40	1.46 (0.87–2.44)		

Table 2.2.13b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Riman et al. (2004) Sweden 1993–1995	655 Population	BMI 1 yr ago < 22 22– < 25 25– < 27 27– < 30 ≥ 30	 122 197 127 115 93	 1.00 0.99 (0.77–1.28) 1.06 (0.80–1.40) 1.10 (0.83–1.46) 1.37 (1.01–1.85)	Age, parity, and age at menopause as categorized variables, duration of OC use, ever-use of HRT	Stronger associations were observed for the mucinous histological subgroup, and no associations for the serous and endometrioid types
Hoyo et al. (2005) USA 1999–2003	593 Population	BMI < 25 25–29.99 ≥ 30	 230 158 192	 1.0 1.0 (0.7–1.3) 1.4 (1.0–1.8)	Race, age, parity, history of ovarian cancer, history of breast cancer, hysterectomy, OC use, menstrual status	Positive non-significant associations with weight gain from age 18 yr (3rd tertile, 204 cases) and with WC (3rd tertile, 213 cases). In stratified analyses, associations with recent BMI were only significant among Whites (vs African Americans)
Kurian et al. (2005) Pooled analysis of 10 case–control studies of ovarian cancer in the USA	1834 cases with invasive epithelial ovarian cancer Serous: 1067 Mucinous: 254 Endometrioid: 373 Clear cell: 140 Controls: 7 population, 3 hospital	BMI < 24 ≥ 24 BMI < 24 ≥ 24 BMI < 24 ≥ 24 BMI < 24 ≥ 24	Serous: 241 Mucinous: 57 Endometrioid: 82 Clear cell: 28 	 1.00 0.72 (0.59–0.88) 1.0 1.3 (0.88–2.0) 1.0 1.3 (0.95–1.9) 1.0 0.9 (0.55–1.6)	Parity, OC use	
Zhang et al. (2005) China 1999–2000	254 Hospital	BMI at diagnosis < 18.5 18.5–21.9 22.0–24.9 ≥ 25.0 [P_{trend}]	 93 28 86 47	 1.60 (0.91–2.83) 1.00 0.98 (0.69–1.41) 0.88 (0.57–1.34) [0.19]	Age at diagnosis, locality, tobacco smoking, alcohol consumption, parity, menopausal status, HRT, OC use, ovarian cancer in first-degree relatives, total energy intake	No significant associations were observed with body weight at diagnosis or with BMI/weight change. Statistically significant associations with BMI and weight were observed 5 yr before diagnosis

Table 2.2.13b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Zhang et al. (2005) (cont.)		BMI at age 21 yr				
		< 18.5	134	0.94 (0.62–1.45)		
		18.5–21.9	41	1.00		
		22.0–24.9	66	1.04 (0.73–1.50)		
		≥ 25.0	11	1.20 (0.56–2.56)		
		[P_{trend}]		[0.37]		
Beehler et al. (2006) USA 1982–1998	427 Hospital	BMI			Age, geographical area, year of study participation	
		≤ 24.9	229	1.00		
		25.0–29.9	116	1.02 (0.77–1.36)		
		≥ 30.0	82	1.17 (0.84–1.65)		
Greer et al. (2006) USA 1994–1998	762 Population	BMI, quartiles			Age, race, number of live births, family history of ovarian cancer, tubal ligation, OC use	Highest BMI (4th quartile, 69 cases) and adult weight gain were associated with increased ovarian cancer risk among nulliparous women only
		Q1	173	1.00		
		Q2	196	1.10 (0.85–1.44)		
		Q3	192	1.14 (0.87–1.49)		
		Q4	201	1.24 (0.95–1.63)		
		[P_{trend}]		[0.12]		
Huusom et al. (2006) Denmark 1995–1999	202 Population	BMI			Age, childbirth, number of additional births, age at first birth, breastfeeding, duration of OC use, smoking, intake of milk	Significant associations with BMI among the serous histological subgroup only
		< 22	67	1.00		
		22–24	52	0.76 (0.51–1.14)		
		25–26	29	1.06 (0.64–1.74)		
		27–29	29	1.33 (0.80–2.19)		
		≥ 30	24	1.09 (0.64–1.84)		
Peterson et al. (2006) USA 1993–2001	700 Population	Recent BMI			Age, state, enrolment period, education level, family history of breast or ovarian cancer, OC use, parity, history of bilateral tubal ligation	Positive, non-significant association with recent weight was reported
		< 18.5	13	1.12 (0.62–2.03)		
		18.5–24.9	304	1.00		
		25.0–29.9	232	1.23 (0.67–2.23)		
		30.0	151	1.29 (0.70–2.37)		
		[P_{trend}]		[0.15]		
		Weight change (kg)				
		Loss	45	1.00 (0.68–1.48)		
		0–9.06 gain	93	1.00		
		9.07–15.87 gain	121	0.89 (0.66–1.20)		
		15.88–23.58 gain	90	0.90 (0.65–1.24)		
		23.59 gain	85	0.77 (0.56–1.06)		
		[P_{trend}]		[0.14]		

Table 2.2.13b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Rossing et al. (2006) USA 1994–1998	355 Population	BMI 5 yr before diagnosis or reference date < 25 25– < 30 ≥ 30	 130 96 127	 1.0 1.2 (0.9–1.7) 1.5 (0.9–2.4)	Age, race, study site, number of full-term births, duration of OC use, weight/BMI	Similar associations were observed for BMI and for weight at ages 18 yr and 30 yr
Máchová et al. (2007) Czech Republic 1987–2002	174 Population	BMI 18.5– < 25 ≥ 25– < 30 ≥ 30	174 total	 1.00 1.05 (0.68–1.61) 1.38 (0.87–2.20)	Age, smoking, hypertension, height	
Olsen et al. (2007) Meta-analysis (Australia, North America, western Europe)	Meta-analysis Population	BMI at age 17–20 yr ≥ 25 vs < 25 ≥ 25 vs < 25		Overall: 1.22 (1.02–1.45) Case–control: 1.21 (0.97–1.52)		
Soegaard et al. (2007) Denmark 1995–1999	554 Population	BMI at age 30–39 yr, quartiles Q1 Q2 Q3 Q4	 124 153 114 138	 1.00 1.31 (0.98–1.73) 1.00 (0.74–1.36) 1.23 (0.92–1.65)	Age, pregnancy, additional pregnancies, duration of OC use	Associations seemed somewhat stronger in mucinous and endometrioid tumours; no association with BMI ≥ 25 in adulthood
Lurie et al. (2008) USA 1993–2006	274 Population	BMI ≤ 18.5 18.5– < 25 25– < 30 ≥ 30	 6 141 64 64	 1.00 1.72 (0.64–4.75) 1.44 (0.50–4.09) 1.63 (0.57–4.71)		
Nagle et al. (2008) Australia NR	Endometrioid: 142 Clear cell: 90 Controls: 1508 Population	BMI 1 yr before diagnosis < 18 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	Endometrioid: 2 52 46 30	 0.9 (0.2–4.0) 1.0 1.3 (0.8–2.0) 1.2 (0.7–1.9) [0.41]	Age, education level, parity, OC use	

Table 2.2.13b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Nagle et al. (2008) (cont.)			Clear cell:			
		< 18	3	2.9 (0.8–11.1)		
		18.5–24.9	23	1.0		
		25–29.9	27	1.7 (0.9–3.0)		
		≥ 30	25	2.2 (1.2–4.1)		
		[P_{trend}]		[0.01]		
Boyce et al. (2009) USA 1988–2008	72 Population	BMI			Age, race	This study investigated granulosa cell tumours
		20–24.9	14	1.00		
		25–29.9	15	1.72 (0.82–3.59)		
		30–39.9	22	5.02 (2.52–10.0)		
		> 40	5	6.60 (2.19–19.8)		
Delort et al. (2009) Auvergne, France 1996–1999, 2005–2006	55 (with no *BRCA* mutation) Mammographic screening centre	BMI			Age	BMI at age 20 yr not significantly associated with increased risk. WC significantly associated with increased risk
		< 20	10	1.00		
		20–25	29	0.88 (0.62–1.26)		
		25.1–30	9	0.78 (0.38–1.60)		
		> 30	6	0.69 (0.24–2.02)		
Moorman et al. (2009) USA 1999–2008	African American: 143/189 White: 943/868 Population	BMI	White:		Age	
		< 25	312	1.00		
		25– < 30	212	0.96 (0.76–1.22)		
		30– < 35	114	1.08 (0.80–1.45)		
		≥ 35	83	1.04 (0.75–1.45)		
		BMI	African American:			
		< 25	17	1.00		
		25– < 30	26	0.84 (0.39–1.78)		
		30– < 35	22	0.94 (0.43–2.07)		
		≥ 35	42	1.62 (0.79–3.35)		
Reis & Kizilkayabeji (2010) Turkey 2002–2003	217 Hospital	BMI			Not specified	
		18.5–24.99	86	1.00		
		≥ 25	131	1.96 (1.41–2.72)		
		[P_{trend}]		[< 0.001]		
Bandera et al. (2011) USA 2004–2008	205 Population	BMI			Age	
		18.5–25	90	1.00		
		25–29.9	54	1.07 (0.69–1.65)		
		30–34.9	36	1.39 (0.83–2.32)		
		≥ 35	24	1.54 (0.81–2.89)		

Table 2.2.13b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Bodmer et al. (2011) United Kingdom 1995–2009	1611 Hospital	BMI < 25 25–29.9 ≥ 30	 562 453 293	 1.00 1.08 (0.94–1.23) 1.11 (0.95–1.29)		
Su et al. (2012) China 2006–2008	500 Hospital	BMI 5 yr ago ≤ 18.49 18.5–22.9 ≥ 23 BMI 5 yr ago ≤ 18.49 18.5–22.9 ≥ 23 BMI 5 yr ago ≤ 18.49 18.5–22.9 ≥ 23	All: 36 348 116 Serous: 15 175 60 Mucinous: 8 58 14	 1.00 1.15 (0.72–1.85) 1.77 (1.04–3.02) 1.00 1.43 (0.77–2.69) 2.26 (1.13–4.52) 1.00 0.87 (0.38–1.98) 1.00 (0.38–2.61)	Age, OC use, parity, menopausal status, ovarian and/or breast cancer in a first-degree relative, age at menarche, smoking status, alcohol consumption; for weight, additional adjustment for height	Asian population cut-offs used for BMI Significant associations were observed for weight (kg), especially in the serous ovarian cancer subtype
Su et al. (2012) China 2006–2008	500 Hospital	BMI 5 yr ago, tertiles vs T1: ≤ 20.00 T2: 20.01–21.88 T3: ≥ 21.89 T2: 20.01–21.88 T3: ≥ 21.89 T2: 20.01–21.88 T3: ≥ 21.89 Weight (kg), tertiles vs T1: ≤ 50 T3: ≥ 55.1 T3: ≥ 55.1 T3: ≥ 55.1	All: 158 221 Serous: 83 112 Mucinous: 26 35 All: 187 Serous: 100 Mucinous: 27	 1.24 (0.89–1.72) 1.75 (1.28–2.40) 1.47 (0.97–2.22) 1.98 (1.33–2.95) 1.31 (0.69–2.49) 1.84 (1.00–3.38) 1.84 (1.34–2.54) 2.23 (1.50–3.33) 1.67 (0.91–3.06)	Age, OC use, parity, menopausal status, ovarian or breast cancer in a first-degree relative, age at menarche, smoking status, alcohol consumption	

Table 2.2.13b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
King et al. (2013) USA 2001–2008	205 Population	BMI < 25 25–29.9 30–34.9 ≥ 35	 91 54 36 24	 1.00 1.07 (0.69–1.65) 1.39 (0.83–2.32) 1.54 (0.82–2.89)	Age	
Olsen et al. (2013) Pooled analyses of 15 case–control studies	13 548 cases Invasive: 8763 Borderline: 2465 1 study hospital -based, 14 studies population-based	BMI < 18.5 18.5–24.9 25.0–29.9 30–34.5 35–39.9 ≥ 40 per 5 kg/m² BMI < 18.5 18.5–24.9 25.0–29.9 30–34.5 35–39.9 ≥ 40 per 5 kg/m²	Invasive: 183 4020 2500 1166 511 383 Borderline: 57 1080 662 379 150 137	 1.08 (0.84–1.39) 1.00 1.00 (0.92–1.09) 1.06 (0.97–1.16) 1.21 (1.07–1.38) 1.22 (1.05–1.41) 1.04 (1.00–1.08) 1.13 (0.82–1.55) 1.00 1.23 (1.09–1.39) 1.61 (1.40–1.85) 1.68 (1.37–2.06) 1.96 (1.57–2.46) 1.18 (1.14–1.23)	Age, parity, OC use, family history of breast or ovarian cancer in a first-degree relative, race/ethnicity where appropriate	BMI in early adulthood was significantly associated with 8% and 15% increased risk of invasive and borderline ovarian cancer subtypes, respectively
Le et al. (2014) Canada 2001–2007	608 Population	BMI < 25 25–30 30–35 ≥ 35	 330 180 57 41	 1.00 0.80 (0.59–1.09) 0.87 (0.54–1.41) 0.91 (0.53–1.58)	Age	
Schildkraut et al. (2014) USA 2010–2014	403 Population	BMI < 24.9 25–29.9 30–34.9 ≥ 35	 54 95 107 113	 1.00 1.31 (0.86–1.99) 1.50 (0.99–2.27) 1.27 (0.85–1.91)	Age, months of OC use, parity	Study in African American women

Table 2.2.13b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Burghaus et al. (2015) Germany 2002–2013	289 Hospital	BMI, tertiles (median) Low (21.7) Medium (25.0) High (30.1)	NR	Low vs medium: 0.99 (0.83–1.17) High vs medium: 1.26 (1.09–1.46) High vs low: 1.28 (0.95–1.72)	Age, OC use, pregnancies, self-reported endometriosis	

BMI, body mass index (in kg/m²); CI, confidence interval; HRT, hormone replacement therapy; NR, not reported; OC, oral contraceptive; WC, waist circumference; yr, year or years

Table 2.2.13c Meta-analyses of measures of body fatness and cancer of the ovary

Reference	Total number of studies Total number of cases	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
Olsen et al. (2007)	16 studies for adult BMI (8 case–control and 8 cohort) and 9 for BMI in early adulthood (5 case–control and 4 cohort) NR	Adult BMI 18.5–24.9 25.0–29.9 ≥ 30 BMI at age 17–20 yr 18.5–24.9 ≥ 25	 1.00 1.16 (1.01–1.32) 1.30 (1.12–1.50) 1.00 1.22 (1.02–1.45)		In adult BMI, no difference was observed when stratifying by study design type
Guh et al. (2009)	9 cohort studies NR	BMI 18.5–24.9 25.0–29.9 ≥ 30	 1.00 1.18 (1.12–1.23) 1.28 (1.20–1.36)	Unadjusted RRs	
Collaborative Group on Epidemiological Studies of Ovarian Cancer (2012)	47 studies (17 prospective and 30 case–control) 25 157 cases	BMI < 22.5 22.5–24.9 25–27.4 27.5–29.9 ≥ 30 [P_{trend}]	 1.00 (0.95–1.05) 1.05 (1.00–1.11) 1.08 (1.02–1.13) 1.07 (0.99–1.17) 1.13 (1.06–1.20) [0.01]	Study, age at diagnosis, parity, menopausal status/hysterectomy, OC use, HRT use, height	In stratified analyses, associations were only significant among never-users of HRT (RR, ~1.1 for overweight; ~1.2 for obesity)
Poorolajal et al. (2014)	10 cohort studies and 9 case–control studies NR	BMI 18.5–24.9 25.0–29.9 ≥ 30 BMI 18.5–24.9 25.0–29.9 ≥ 30	Case–control: 1.00 1.08 (0.90–1.31) 1.27 (1.19–1.35) Cohort: 1.00 1.26 (0.97–1.63) 1.26 (1.06–1.50)	NR	In stratified analysis by menopausal status, stronger associations were found in all cases in the premenopausal period
Aune et al. (2015)	25 studies 19 825 cases	BMI per 5 kg/m^2 increase	1.07 (1.03–1.11)	Maximally adjusted HR, RR, or OR were used (covariates NR)	Non-linearity, with risk increasing significantly from BMI above 28 kg/m^2; relatively stronger risk with BMI increase in early adulthood, based on 6 studies (RR, 1.12); no association with weight gain

Table 2.2.13c (continued)

Reference	Total number of studies Total number of cases	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
Liu et al. (2015)	26 studies (13 case–control and 13 cohort) 12 963 cases	BMI 18.5–24.9 25.0–29.9 ≥ 30	Case–control: 1.00 1.09 (1.00–1.18) 1.31 (1.21–1.54)		No associations with BMI were found in postmenopausal women
		BMI 18.5–24.9 25.0–29.9 ≥ 30	Cohort: 1.00 1.07 (1.01–1.13) 1.23 (1.10–1.39)		
		BMI 18.5–24.9 25.0–29.9 ≥ 30	Overall: 1.00 1.07 (1.02–1.12) 1.28 (1.16–1.41)		

BMI, body mass index (in kg/m^2); CI, confidence interval; HR, hazard ratio; HRT, hormone replacement therapy; NR, not reported; OC, oral contraceptive; OR, odds ratio; RR, relative risk; yr, year or years

Table 2.2.13d Mendelian randomization studies of measures of body fatness and cancer of the ovary

Reference Study	Characteristics of study population	Sample size	Exposure (unit)	Odds ratio (95% CI) P_{trend}	Comments
Gao et al. (2016) Genetic Associations and Mechanisms in Oncology (GAME-ON) Consortium	Women from 3 studies of individuals of European ancestry	13 492 (4369 cases and 9123 controls)	Increase of 1 SD in genetically predicted childhood BMI or adult BMI	Childhood BMI: 1.07 (0.82–1.39) P_{trend} = 0.62 Adult BMI: 1.07 (1.01–1.13) P_{trend} = 0.02	Similar associations were found for adult BMI with serous ovarian cancer, and moderate but not statistically significant with clear cell and endometrioid histological subtypes. No associations were observed between childhood BMI and subtypes of ovarian cancer

BMI, body mass index (in kg/m^2); CI, confidence interval; SD, standard deviation

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2.2.14 Cancer of the prostate

Cancer of the prostate is the fourth most commonly diagnosed cancer worldwide, and one of the most frequent causes of cancer-related mortality in developed countries.

The relationship between body weight and prostate cancer risk is complex, for several reasons. First, prostate cancer-specific mortality (death attributed to the underlying cancer) is a proxy for incidence in some studies, whereas it is a primary end-point in other studies, along with different types of prostate cancer incidence defined by tumour characteristics. However, prostate cancer-specific mortality may be over-represented in patients who die *with* but not *of* the disease. This is a particular concern if, for example, obese patients with prostate cancer have other comorbid disease and more regular contact with the health-care system; the cancer may be more prominent in their management and may be recorded on the death certificate, even if heart disease is the underlying cause of death. Second, detection bias could also be a concern in studies of prostate cancer incidence; because obese men have lower levels of prostate-specific antigen (PSA), their tumours are more difficult to detect, and they are less likely to undergo a biopsy (Allot et al., 2013). However, potential biological mechanisms have also been proposed to explain a lower risk of early-stage prostate cancer in men who are overweight or obese (see Section 4.3.1d).

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and prostate cancer was *inadequate*. Since then, numerous prospective studies with at least 100 cases (Table 2.2.14a) and case–control studies (Table 2.2.14b) have been published, as well as several meta-analyses of observational studies addressing different measures of body fatness (Table 2.2.14c).

(a) Cohort studies

The *IARC Handbook* on weight control and physical activity (IARC, 2002), in the evaluation of prostate cancer risk and measures of body fatness, included 13 prospective cohort studies with at least 100 cases (not shown in Table 2.2.14a). Of those, four found a positive association and nine found no association. Notably, across all prospective studies, the highest category of BMI was overweight (25–29.9 kg/m^2) but not obese (≥ 30 kg/m^2).

Since 2000, associations of body fatness assessed at baseline with total prostate cancer incidence have been examined in numerous individual prospective studies with at least 100 cases and in at least two meta-analyses. In most studies, neither BMI nor weight was associated with risk (Habel et al., 2000; Schuurman et al., 2000; Lee et al., 2001; Jonsson et al., 2003; Rapp et al., 2005; Gong et al., 2006; Lukanova et al., 2006; Tande et al., 2006; Fujino et al., 2007; Giovannucci et al., 2007; Littman et al., 2007; Máchová et al., 2007; Rodriguez et al., 2007; Pischon et al., 2008; Wallström et al., 2009; Andreotti et al., 2010; Stocks et al., 2010; Bassett et al., 2012). However, in some studies statistically significant positive associations (or trends) between BMI at baseline and prostate cancer incidence were found (Engeland et al., 2003; Samanic et al., 2004, 2006; Jee et al., 2008; Barrington et al., 2015), and four prospective studies found lower risk of prostate cancer with increasing BMI (Wright et al., 2007; Bhaskaran et al., 2014; Møller et al., 2015). In a meta-analysis of 27 prospective studies, there was a statistically significant positive association with prostate cancer incidence (RR per 5 kg/m^2 increase in BMI, 1.03; 95% CI, 1.00–1.07) (Renehan et al., 2008).

Associations of body fatness at baseline with stage of the disease were examined in several studies. Regarding the incidence of localized, low-grade, or non-aggressive disease, although five studies found no association (Schuurman et

al., 2000; Giovannucci et al., 2007; Pischon et al., 2008; Wallström et al., 2009; Bassett et al., 2012), at least seven other studies found an inverse association of BMI and/or weight with the incidence of non-aggressive (Littman et al., 2007; Stocks et al., 2010), non-metastatic low- to moderate-grade (Gong et al., 2006; Rodriguez et al., 2007; Møller et al., 2016 for BMI at age 21 years), or localized (Wright et al., 2007; Discacciati et al., 2011; Hernandez et al., 2009 for BMI at age 21 years) prostate cancer. In the Selenium and Vitamin E Cancer Prevention Trial (SELECT), there was evidence of a significant inverse trend between BMI and the incidence of low-grade prostate cancer in non-Hispanic White men, and a statistically significant positive association in African American men (Barrington et al., 2015).

Nine prospective studies found no associations of BMI and/or weight with the incidence of regional or distant prostate cancer (Habel et al., 2000), advanced, high-grade, or moderately to poorly differentiated prostate cancer (Schuurman et al., 2000; Pischon et al., 2008; Discacciati et al., 2011; Møller et al., 2015), aggressive prostate cancer (Littman et al., 2007; Wallström et al., 2009; Stocks et al., 2010), or extraprostatic prostate cancer (Wright et al., 2007). However, five other studies found positive associations or trends of BMI and/or weight with the incidence of high-grade or advanced prostate cancer (Gong et al., 2006; Giovannucci et al., 2007; Rodriguez et al., 2007; Hernandez et al., 2009 for BMI at age 21 years; Bassett et al., 2012; Barrington et al., 2015). A meta-analysis combining data from 24 prospective studies found a statistically significant positive association between BMI and risk of advanced, high-grade, or fatal prostate cancer (RR per 5 kg/m^2 increase in BMI, 1.08; 95% CI, 1.04–1.12) (WCRF/AICR, 2014).

There is considerable evidence of a positive association of BMI with prostate cancer mortality, based on findings from both individual prospective studies (Rodriguez et al., 2001; Calle et al., 2003; Giovannucci et al., 2007; Wright et al., 2007; Stocks et al., 2010 Bassett et al., 2012) and a large pooled analysis of 57 prospective studies from Europe, Japan, and the USA, reporting a relative risk of mortality per 5 kg/m^2 increase in BMI of 1.13 (95% CI, 1.02–1.24) across the BMI range of 15–50 kg/m^2 (Whitlock et al., 2009). However, at least six other individual prospective studies found no association between BMI at baseline and death from prostate cancer (Batty et al., 2005; Fujino et al., 2007; Burton et al., 2010 for BMI at age < 30 years; Discacciati et al., 2011; Meyer et al., 2015; Møller et al., 2015). Similarly, BMI was not associated with prostate cancer mortality in a pooled analysis from the Asia Cohort Consortium (Fowke et al., 2015). [The Working Group noted that in this analysis, the reference group was men with a BMI of 22.5–24.9 kg/m^2, compared with men with a BMI of 25–50 kg/m^2. A possible effect of obesity (BMI > 30 kg/m^2) on prostate cancer mortality might have been missed in this study.]

At least six prospective studies found no associations between BMI or weight at younger ages of adulthood and risk of prostate cancer (total, localized, advanced, or fatal) (Giovannucci et al., 1997; Jonsson et al., 2003; Fujino et al., 2007; Hernandez et al., 2009; Burton et al., 2010; Discacciati et al., 2011; Bassett et al., 2012), whereas in two other studies higher BMI (Schuurman et al., 2000) or weight (Littman et al., 2007) in young adulthood was significantly associated with increased total prostate cancer incidence. In the NIH-AARP cohort, both BMI and weight at age 18 years were not associated with the incidence of total prostate cancer or extraprostatic prostate cancer, whereas inverse associations with localized prostate cancer were reported (P_{trend} = 0.04) (Wright et al., 2007). Similarly, in the Multiethnic Cohort Study and the Health Professionals Follow-up Study, BMI at age 21 years was inversely associated with the incidence of total, localized, and low- and moderate-grade prostate cancer and was not associated with the incidence of high-grade or fatal prostate cancer (Hernandez et al.,

2009; Møller et al., 2016). Similarly, in the study by Littman et al. (2007), the positive association with weight in young adulthood (ages 18, 30, or 45 years) was restricted to the aggressive type. In a meta-analysis of nine prospective studies, Robinson et al. (2008) found a positive association between BMI in early life (i.e. < 29 years) and prostate cancer incidence or mortality (RR per 5 kg/m^2 increase in BMI, 1.08).

In at least four individual prospective studies, change in neither BMI nor weight during adulthood was associated with prostate cancer incidence (Jonsson et al., 2003; Samanic et al., 2006; Rodriguez et al., 2007; Rapp et al., 2008). Similarly, a meta-analysis of four prospective studies also found no associations of adult weight gain [after adjustment for age and baseline BMI or weight in all studies] with total, localized, or advanced prostate cancer incidence (Keum et al., 2015). However, in the Netherlands Cohort Study, there was suggestive evidence of an inverse trend between increase in BMI from age 20 years to baseline (≥ 6 kg/m^2) and total prostate cancer incidence (P_{trend} = 0.07), and this association was statistically significant for poorly differentiated or undifferentiated prostate tumours (Schuurman et al., 2000). In the Vitamins and Lifestyle (VITAL) cohort, both weight loss and weight gain were associated with a lower risk of non-aggressive prostate cancer, but there was no association with aggressive prostate cancer (Littman et al., 2007). In the NIH-AARP cohort, weight gain from age 18 years to baseline was not associated with prostate cancer incidence (total, localized, or extraprostatic), but was associated with prostate cancer mortality (P_{trend} = 0.009) (Wright et al., 2007).

The association between waist circumference and total prostate cancer incidence was examined in at least eight individual prospective studies, and no study found evidence of statistically significant associations with total prostate cancer incidence (Giovannucci et al., 1997; Lee et al., 2001; MacInnis et al., 2003; Gong et al., 2006; Tande et al., 2006; Pischon et al., 2008; Wallström et al., 2009; Møller et al., 2015). On the basis of four prospective studies, the WCRF Continuous Update Project summary (WCRF/AICR, 2014) found no dose–response association between waist circumference and risk of total or non-advanced prostate cancer, but a statistically significant positive association with risk of advanced or fatal prostate cancer (RR per 10 cm increase, 1.12; 95% CI, 1.04–1.21).

(b) Case–control studies

Case–control studies of BMI and other adiposity indices in relation to prostate cancer risk are presented in Table 2.2.14b. In the *IARC Handbook* on weight control and physical activity (IARC, 2002), 15 case–control studies of BMI and prostate cancer were reviewed (not shown here). Since then, at least 35 case–control studies and 5 meta-analyses including case–control study designs, focused on the association between weight, BMI, or waist circumference and prostate cancer, have been conducted in Asia (China, India, Japan, and Pakistan), the Caribbean (Barbados and Jamaica), Europe, the Islamic Republic of Iran, Nigeria, North America, and Oceania (Australia and New Zealand). In all of these studies, BMI was assessed on the basis of self-reported height and body weight, or body weight and height verified at the time of a hospital consultation.

Positive associations between high BMI and total prostate cancer incidence were reported in six of the case–control studies. Bashir et al. (2014), in a hospital-based case–control study in Pakistan with 140 cases and 280 controls, found a significant increase in the risk of prostate cancer for men with BMI > 25 kg/m^2 (OR, 5.78; 95% CI, 2.67–12.6). In a multicentre hospital-based case–control study in Italy, Dal Maso et al. (2004) identified a dose–response relationship between BMI at age 30 years and prostate cancer risk, based on 1257 cases (P_{trend} = 0.004). Ganesh et al. (2011) reported a 2-fold greater risk of prostate cancer

in Indian men with BMI ≥ 25 kg/m² (OR, 2.1; 95% CI, 1.1–4.4). A hospital-based case–control study in France found a positive association between BMI > 29 kg/m² and risk of prostate cancer (OR, 2.47; 95% CI, 1.41–4.34) (Irani et al., 2003). Similarly, a study in Canada reported a significant 27% increase in risk of prostate cancer in men with BMI ≥ 30 kg/m² compared with those with BMI < 25 kg/m² (Pan et al., 2004).

An inverse association between BMI and prostate cancer has also been reported in several studies. Beebe-Dimmer et al. (2009), in a hospital-based case–control study in the USA, found an inverse relationship between high BMI (≥ 30 kg/m²) and prostate cancer risk in Caucasian men, based on 494 cases (OR, 0.51; 95% CI, 0.33–0.80), but not in African American men. Similarly, a study in Canada found a statistically significant inverse relationship between BMI ≥ 30 kg/m² and prostate cancer risk (OR, 0.72; 95% CI, 0.60–0.87), but no associations with waist circumference or waist-to-hip ratio were found (Boehm et al., 2015). A population-based case–control study in the Islamic Republic of Iran (Hosseini et al., 2010), with 137 cases and 137 controls, also found a significant inverse relationship between high BMI (≥ 25 kg/m²) and prostate cancer risk (OR, 0.4; 95% CI, 0.2–0.8). Finally, Agalliu et al. (2015) conducted a small hospital-based case–control study in Nigeria, with 50 cases and 50 controls. Inverse associations were reported for weight (OR per kg increase, 0.97; 95% CI, 0.94–1.00) and waist circumference (OR per cm increase, 0.91; 95% CI, 0.87–0.96).

One additional case–control study found an increased risk of total prostate cancer in men with an increased waist circumference (Beebe-Dimmer et al., 2007).

Three meta-analyses that included case–control studies suggested a small increase in risk of prostate cancer associated with higher BMI (Bergström et al., 2001; MacInnis & English, 2006; Robinson et al., 2008). In one additional meta-analysis, a significant positive association with adult weight was observed for high-risk (RR, 1.13; 95% CI, 1.00–1.28) and fatal (RR, 1.58; 95% CI, 1.01–2.47) prostate cancer subtypes (Chen et al., 2016).

Six case–control studies differentiated prostate cancer by grade, stage, or aggressiveness, and generally reported positive associations of BMI, waist circumference, or waist-to-hip ratio with prostate cancers with higher Gleason scores. Fowke et al. (2012) analysed 809 hospital-based cases and 1057 controls in the USA by Gleason score. On the basis of 135 cases, BMI and waist circumference were marginally associated with increased risk of high-grade prostate cancer (OR per 1 kg/m² increase in BMI, 1.04; 95% CI, 1.00–1.08 and OR per 1 cm increase in waist circumference, 1.01; 95% CI, 0.99–1.03). Jackson et al. (2010) separated patients with high-grade prostate cancer in their hospital-based case–control study (243 cases and 275 controls) in Jamaica. Waist circumference and waist-to-hip ratio were positively associated with high-grade prostate cancer after adjustment for BMI. A dose–response relationship was also observed for waist circumference, and no association was found with BMI. A case–control study in Italy observed significant positive associations of BMI and prostate cancer of Gleason score 7–10 only (P_{trend} < 0.01) (Dal Maso et al., 2004). Liu et al. (2005) conducted a population-based sibling case–control study in the USA with 439 cases and 479 controls and found no association of aggressive prostate cancer (defined as Gleason score ≥ 7 or tumour stage T2C or greater) with increased BMI, whereas an inverse association was observed for lean body mass (P_{trend} = 0.02). Nemesure et al. (2012) conducted a population-based case–control study in Barbados with 963 cases and 941 controls and reported a positive association of waist circumference with all prostate cancers (OR for highest versus lowest quartiles, 1.84; 95% CI, 1.19–2.85), which did not hold when stratifying by disease grade. Robinson et al. (2005) in the USA reported an inverse association between

BMI > 30 kg/m^2 at age 20–29 years and advanced prostate cancer [based on 12 cases].

Several studies assessed BMI and body weight at different ages, and BMI/weight change. In a population-based case–control study in Sweden, Gerdtsson et al. (2015) investigated several anthropometric measures, including BMI and weight, at multiple time points in life. Weight increase in adolescence (age 16–22 years) was associated with increased risk of prostate cancer (OR per 5 kg increase in weight, 1.05; 95% CI, 1.01–1.09), and increase in BMI and weight in middle age (age 44–50 years) was associated with increased mortality from prostate cancer, and with increased metastasis. Weight gain of 10.0–14.9 kg in adulthood was significantly associated with a 3–4-fold greater risk of prostate cancer in a population-based case–control study in Japan (Mori et al., 2011). In the same study, BMI of 23.0–24.9 kg/m^2 at age 20 years was associated with a reduced risk of prostate cancer (OR, 0.47; 95% CI, 0.22–0.98) (Mori et al., 2011) [based on 11 cases only]. In contrast, a total of 16 case–control studies conducted in Australia, Canada, the Czech Republic, Italy, Japan, New Zealand, Spain, Sweden, Switzerland, the United Kingdom, and the USA reported no associations between risk of total prostate cancer and BMI or other adiposity indices at different ages (Putnam et al., 2000; Sharpe & Siemiatycki, 2001; Giles et al., 2003; Friedenreich et al., 2004; Porter & Stanford, 2005; Robinson et al., 2005; Wuermli et al., 2005; Cox et al., 2006; Gallus et al., 2007; Máchová et al., 2007; Nagata et al., 2007; Magura et al., 2008; Dimitropoulou et al., 2011; Pelucchi et al., 2011; Möller et al., 2013; Alvarez-Cubero et al., 2015; Zhang et al., 2015) or BMI change or weight gain from early adulthood (Putnam et al., 2000; Giles et al., 2003; Friedenreich et al., 2004).

(c) Mendelian randomization studies

Three Mendelian randomization studies have been conducted in this context (Table 2.2.14d).

Lewis et al. (2010) showed that each additional A allele of the *FTO* rs9939609 SNP was associated with an increase of 0.56 kg/m^2 (P = 0.007) in BMI across all groups (cases and controls). Estimates obtained from Mendelian randomization analyses provided odds ratios of 0.77 (95% CI, 0.52–1.15; P = 0.20) for prostate cancer and 1.35 (95% CI, 0.90–2.03; P = 0.14) for high-grade versus low-grade cancer with each 1 kg/m^2 increase in BMI.

Davies et al. (2015) extended this work by using a genetic risk score based on 32 SNPs associated with BMI (Speliotes et al., 2010) as an instrument for BMI within a much larger sample size. Each increase of 1 standard deviation in genetically predicted BMI was associated on average with a nonsignificant 2% reduction in risk (95% CI, 0.96–1.00; P = 0.07) in any prostate cancer diagnosis.

In Mendelian randomization analyses that used genetic risk scores based on 77 SNPs for adult BMI (Locke et al., 2015) and 15 SNPs for childhood BMI (Felix et al., 2016), Gao et al. (2016) found no strong evidence for associations of childhood or adult BMI with either total or aggressive prostate cancer risk.

[Although results from Lewis et al. (2010) and Davies et al. (2015) point towards an inverse association between BMI and prostate cancer risk, this association was not significant and was not consistently found in all three studies.]

Table 2.2.14a Cohort studies of measures of body fatness and cancer of the prostate

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Giovannucci et al. (1997) Health Professionals Follow-up Study USA 1986–1994	47 781 Incidence	Prostate, advanced	BMI at age 21 yr			Age, height	
			< 20	81	1.00		
			20–21.9	117	0.91 (0.69–1.22)		
			22–22.9	59	0.88 (0.62–1.24)		
			23–23.9	56	0.77 (0.54–1.10)		
			24–25.9	60	0.71 (0.50–1.02)		
			≥ 26	26	0.53 (0.33–0.86)		
			[P_{trend}]		[< 0.006]		
		Prostate, all	BMI at age 21 yr				WC also not associated with increased risk
			< 20	229	1.00		
			20–21.9	353	0.98 (0.83–1.16)		
			22–22.9	188	1.00 (0.82–1.22)		
			23–23.9	200	1.03 (0.84–1.26)		
			24–25.9	223	1.00 (0.82–1.22)		
			≥ 26	104	0.87 (0.67–1.12)		
			[P_{trend}]		[0.60]		
Habel et al. (2000) Kaiser Permanente USA 1964–1973 to 1996	70 712 Incidence	Prostate	BMI	2079 total		Age, race, year of birth	Weight also not associated with increased risk No associations were observed in results stratified by race
			< 22.7		1.00		
			22.7–24.3		1.09 (0.93–1.27)		
			24.4–25.9		1.04 (0.89–1.21)		
			26–27.9		1.04 (0.90–1.21)		
			> 27.9		0.99 (0.85–1.15)		
		Prostate, regional/distant	BMI	578 total			
			< 22.7		1.00		
			22.7–24.3		0.84 (0.62–1.13)		
			24.4–25.9		1.05 (0.80–1.39)		
			26–27.9		1.04 (0.79–1.37)		
			> 27.9		0.91 (0.69–1.20)		
Schuurman et al. (2000) Netherlands Cohort Study The Netherlands 1986–1982	58 279 Incidence	Prostate	BMI at baseline			Age, family history of prostate cancer, SES; BMI change results also adjusted for BMI at age 20 yr	
			< 22	63	1.00		
			22–23	164	1.20 (0.84–1.73)		
			24–25	236	1.35 (0.95–1.90)		
			26–27	150	1.26 (0.87–1.83)		
			≥ 28	62	0.89 (0.58–1.37)		
			[P_{trend}]		[0.73]		
			per 2 kg/m^2		1.00 (0.92–1.07)		

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Schuurman et al. (2000) (cont.)	58 279 Incidence		BMI at age 20 yr				
			< 19	57	1.00		
			19–20.9	122	1.06 (0.72–1.56)		
			21–22.9	176	1.09 (0.76–1.58)		
			23–24.9	119	1.39 (0.93–2.06)		
			≥ 25	44	1.33 (0.81–2.19)		
			[P_{trend}]		[0.02]		
			per 2 kg/m^2		1.08 (0.99–1.18)		
			BMI change				
			−9.2 to < 0	47	1.19 (0.74–1.90)		
			0–1.9	120	1.00		
			2–3.9	176	1.32 (0.98–1.79)		
			4–5.9	113	1.04 (0.74–1.47)		
			6–7.9	43	0.83 (0.52–1.31)		
			≥ 8	19	0.67 (0.36–1.23)		
			[P_{trend}]		[0.07]		
			per 2 kg/m^2		0.93 (0.84–1.03)		
		Prostate, localized TNM: T0–2, M0	BMI, per 2 kg/m^2	239 total			
			BMI at baseline		0.96 (0.86–1.06)		
			BMI at age 20 yr		1.18 (1.04–1.35)		
			BMI change		0.87 (0.74–1.02)		
		Prostate, advanced TNM: T3–4, M0; T0–4, M1	BMI, per 2 kg/m^2	226 total			
			BMI at baseline		1.01 (0.90–1.13)		
			BMI at age 20 yr		1.03 (0.91–1.18)		
			BMI change		0.93 (0.80–1.08)		

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Schuurman et al. (2000) (cont.)		Prostate, well-differentiated	BMI, per 2 kg/m^2	194 total			
			BMI at baseline		0.92 (0.82–1.04)		
			BMI at age 20 yr		1.09 (0.94–1.26)		
			BMI change		0.77 (0.65–0.92)		
		Prostate, moderately differentiated	BMI, per 2 kg/m^2	247 total			
			BMI at baseline		1.02 (0.93–1.13)		
			BMI at age 20 yr		1.15 (1.01–1.31)		
			BMI change		0.97 (0.83–1.13)		
		Prostate, poorly differentiated or undifferentiated	BMI, per 2 kg/m^2	174 total			
			BMI at baseline		1.01 (0.89–1.14)		
			BMI at age 20 yr		0.97 (0.83–1.13)		
			BMI change		0.68 (0.58–0.81)		
Lee et al. (2001) Harvard Alumni Health Study USA 1988–1993	8922 Incidence	Prostate	BMI at baseline			Age, smoking, alcohol consumption, paternal history of prostate cancer	WC also not associated with increased risk BMI at age 18 yr (available for 92% of the men) also not associated with increased risk
			< 22.5	87	1.00		
			22.5–24.9	172	1.27 (0.94–1.71)		
			25.0–27.4	134	1.26 (0.92–1.72)		
			27.5	46	1.02 (0.68–1.53)		
			[P_{trend}]		[0.71]		
Rodriguez et al. (2001) Cancer Prevention Study I (CPS I) USA 1959–1972	381 638 Mortality	Prostate ICD-7: 177	BMI			Age, race, height, education level, exercise, smoking status, family history of prostate cancer	
			< 25	782	1.00		
			25–29.99	698	1.02 (0.92–1.14)		
			≥ 30	110	1.27 (1.04–1.56)		
			[P_{trend}]		[0.06]		
Calle et al. (2003) Cancer Prevention Study II (CPS II) USA 1982–1998	404 576 Mortality	Prostate	BMI			Age, education level, smoking, physical activity, alcohol consumption, marital status, race, aspirin use, fat consumption, vegetable consumption	
			18.5–24.9	1681	1.00		
			25–29.9	1971	1.08 (1.01–1.15)		
			30–34.9	311	1.20 (1.06–1.36)		
			≥ 35	41	1.34 (0.98–1.83)		
			[P_{trend}]		[< 0.001]		

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Engeland et al. (2003) Norwegian clinical population Norway 1963–1999 to 2001	951 466 Incidence	Prostate ICD-7: 177	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 147 16 720 14 524 1923	 0.92 (0.78–1.08) 1.00 1.07 (1.05–1.09) 1.09 (1.04–1.15) [0.001]	Age at BMI measurement, birth cohort	In stratified analyses by age at BMI measurement, no differences in risk by age strata were observed
Jonsson et al. (2003) Swedish Twin Registry Sweden 1969–2003	8998 Incidence	Prostate ICD-7: 177	BMI at baseline < 18.5 18.5–24.9 25.0–29.9 ≥ 30 BMI at age 25 yr < 18.5 18.5–24.9 ≥ 25 BMI at age 40 yr < 18.5 18.5–24.9 25.0–29.9 ≥ 30 Adult weight change (kg) < 0 0–5 6–10 11–20 ≥ 21	 6 355 248 22 4 436 64 6 368 155 13 96 178 114 95 21	 1.4 (0.6–3.1) 1.0 1.0 (0.8–1.2) 1.0 (0.6–1.5) 0.5 (0.2–1.5) 1.0 1.0 (0.7–1.3) 2.5 (1.1–5.5) 1.0 0.9 (0.7–1.1) 0.9 (0.5–1.6) 0.9 (0.7–1.2) 1.0 1.0 (0.8–1.3) 0.9 (0.7–1.2) 1.1 (0.8–1.8)	Age; BMI at age 25 yr and 40 yr also controlled for BMI at baseline	No associations were observed in stratified analyses by age at diagnosis (≥ 70 yr vs < 70 yr)
Samanic et al. (2004) United States Veterans cohort USA 1969–1996	4 500 700 Incidence	Prostate ICD-9: 185	Obesity Non-obese Obese Non-obese Obese	 Black men: 15 272 815 White men: 45 901 3206	 1.00 1.12 (1.04–1.20) 1.00 1.19 (1.15–1.24)	Age, calendar year	Obesity defined as discharge diagnosis of obesity: ICD-8: 277; ICD-9: 278.0

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Batty et al. (2005) Whitehall Study United Kingdom 1967–2002	18 403 Mortality	Prostate	BMI 18.5–24.9 25.0–29.9 ≥ 30 [P_{trend}]	 243 175 13	 1.00 0.92 (0.75–1.13) 0.91 (0.51–1.63) [0.45]	Age, employment grade, physical activity, smoking, marital status, prevalent disease, past-year weight loss, BP medication, height, skinfold thickness, systolic BP, plasma cholesterol, glucose intolerance, diabetes	
Rapp et al. (2005) Vorarlberg VHM&PP Austria 1985–2001	67 447 Incidence	Prostate ICD-9: 185	BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 446 583 99 10	 1.00 1.03 (0.91–1.17) 0.82 (0.66–1.03) 0.73 (0.39–1.37) [0.16]	Age, smoking status, occupation	
Gong et al. (2006) Prostate Cancer Prevention Trial (PCPT) USA N/A–2003	10 258 Incidence	Prostate	BMI < 25 25–26.9 27–29.9 ≥ 30 [P_{trend}]	1936 total	 1.00 0.91 (0.79–1.05) 0.96 (0.83–1.10) 0.96 (0.83–1.10) [0.67]	Age, race, treatment, diabetes, family history of prostate cancer	Analyses of the association of WC with total prostate, and low-grade and high-grade subtypes also reported
		Prostate, low-grade	BMI < 25 25–26.9 27–29.9 ≥ 30 [P_{trend}]	1300 total	 1.00 0.88 (0.74–1.04) 0.88 (0.75–1.04) 0.82 (0.69–0.98) [0.03]		
		Prostate, high-grade	BMI < 25 25–26.9 27–29.9 ≥ 30 [P_{trend}]	521 total	 1.00 0.97 (0.75–1.27) 1.09 (0.85–1.40) 1.29 (1.01–1.67) [0.04]		

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Lukanova et al. (2006) Northern Sweden Health and Disease Cohort (NSHDC) 1985–2003	33 424 Incidence/ mortality	Prostate	BMI 18.5–23.4 23.5–25.3 25.4–27.6 ≥ 27.1 [P_{trend}]	 93 114 129 125	 1.00 1.00 (0.76–1.32) 0.96 (0.74–1.26) 0.89 (0.68–1.16) [0.31]	Age, calendar year, smoking	
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1958–1999	362 552 Incidence 107 815 (in BMI change analysis) Incidence	Prostate ICD-7: 177	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}] 6-yr BMI change −4% to 4.9% 5–9.9% 10–14.9% ≥ 15% [P_{trend}]	 3003 3160 528 1281 417 97 22	 1.00 1.06 (1.01–1.12) 1.09 (0.99–1.19) [< 0.05] 1.00 1.09 (0.98–1.22) 0.93 (0.75–1.14) 0.75 (0.49–1.15) [> 0.5]	Attained age, calendar year, smoking	
Tande et al. (2006) Atherosclerosis Risk in Communities (ARIC) Study USA 1987–2000	6332 Incidence	Prostate	BMI < 24.7 24.7–26.9 27.0–29.7 ≥ 29.8	 94 99 91 101	 1.00 1.17 (0.88–1.55) 0.97 (0.72–1.29) 1.14 (0.86–1.50)	Age, race	WC also not associated with increased risk Men with metabolic syndrome were 27% less likely to develop prostate cancer
Fujino et al. (2007) Japan Collaborative Cohort Study for Evaluation of Cancer (JACC) Japan NR	NR Mortality	Prostate	BMI < 18.5 18.5–24 25–29 ≥ 30	 17 107 31 1	 1.39 (0.83–2.34) 1.00 1.56 (1.04–2.34) 0.87 (0.12–6.29)	Age, area of study	[No information reported on follow-up period or total number of participants included in the study] Weight at baseline and at age 20 yr also not associated with increased mortality

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Giovannucci et al. (2007) Health Professionals Follow-up Study USA 1986–2002 Updated follow-up from Giovannucci et al. (1997)	47 750 Incidence	Prostate	BMI < 21 21–22.9 23–24.9 25–27.4 27.5–29.9 ≥ 30 [P_{trend}]	3544 total	 1.00 1.21 1.36 1.24 1.24 1.13 (0.91–1.41) [0.84]	Age, time period, BMI at age 21 yr, height, pack-years of smoking, physical activity, family history of prostate cancer, diabetes, race, energy intake, intake of processed meat, fish, α-linolenic acid, tomato sauce, vitamin E supplements	[CI provided only for the last BMI category] No association was observed with BMI for low-grade or high-grade prostate cancer (based on Gleason score)
		Prostate, advanced TNM: T3b or T4 or N1 or M1	BMI < 21 ≥ 30 [P_{trend}]	523 total	 1.00 1.34 (0.79–2.26) [≤ 0.05]		
	47 750 Mortality	Prostate	BMI 21–22.9 23–24.9 25–27.4 27.5–29.9 ≥ 30	323 total	 1.00 1.44 1.30 1.43 1.80 (1.10–2.93)		
Littman et al. (2007) Vitamins and Lifestyle (VITAL) cohort USA 2000–2004	34 754 Incidence	Prostate	BMI at baseline < 25 25–29.9 ≥ 30 [P_{trend}]	 218 435 155	 1.0 1.1 (0.97–1.4) 0.87 (0.71–1.1) [0.13]	Age, family history of prostate cancer, race, baseline BMI, recent PSA screening	BMI at ages 18 yr, 30 yr, and 45 yr also not associated with increased risk
		Prostate, non-aggressive Gleason score < 7	BMI at baseline < 25 25–29.9 ≥ 30 [P_{trend}]	 129 222 73	 1.0 0.99 (0.79–1.2) 0.69 (0.52–0.93) [0.01]		BMI at ages 18 yr, 30 yr, and 45 yr also not associated with increased risk
		Prostate, aggressive Gleason score 7–10	BMI at baseline < 25 25–29.9 ≥ 30 [P_{trend}]	 85 209 179	 1.0 1.4 (1.1–1.8) 1.1 (0.83–1.6) [0.69]		BMI at ages 18 yr, 30 yr, and 45 yr also not associated with increased risk

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Littman et al. (2007) (cont.)	34 754 Incidence	Prostate	Weight (lb) at age 18 yr			Age, family history of prostate cancer, race, baseline BMI, recent PSA screening	For non-aggressive prostate cancer, weight at age 18 yr and 30 yr was not associated with an increased risk
			< 139	166	1.0		
			139–154	203	1.2 (0.96–1.5)		
			155–170	198	1.1 (0.93–1.4)		
			≥ 171	231	1.2 (1.0–1.5)		
			[P_{trend}]		[0.08]		
			Weight (lb) at age 30 yr				
			< 154	174	1.0		
			154–169	192	1.2 (0.95–1.4)		
			170–184	188	1.1 (0.93–1.4)		
			≥ 185	241	1.3 (1.0–1.6)		
			[P_{trend}]		[0.03]		
			Weight (lb) at age 45 yr				
			< 165	194	1.0		
			165–179	182	1.0 (0.82–1.2)		
			180–199	224	1.1 (0.91–1.3)		
			≥ 200	200	1.1 (0.87–1.3)		
			[P_{trend}]		[0.46]		
			Weight (lb) at baseline				
			< 173	211	1.0		
			174–189	181	1.0 (0.83–1.2)		
			190–214	233	0.99 (0.82–1.2)		
			≥ 215	192	0.92 (0.75–1.1)		
			[P_{trend}]		[0.35]		
		Prostate, non-aggressive Gleason score < 7	Weight (lb) at baseline				Weight gain of ≥ 30 lb since age 18 yr associated with 33% lower risk of incidence
			< 173	130	1.00		
			174–189	90	0.82 (0.62–1.1)		
			190–214	116	0.81 (0.63–1.1)		
			≥ 215	92	0.71 (0.54–0.93)		
			[P_{trend}]		[0.02]		
		Prostate, aggressive Gleason score 7–10	Weight (lb) at age 18 yr			Age, family history of prostate cancer, race, baseline BMI, recent PSA screening	
			< 139	71	1.00		
			139–154	94	1.3 (0.92–1.7)		
			155–170	89	1.2 (0.86–1.6)		
			≥ 171	117	1.4 (1.0–1.9)		
			[P_{trend}]		[0.04]		

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Littman et al. (2007) (cont.)	34 754 Incidence		Weight (lb) at age 30 yr				
			< 154	72	1.0		
			154–169	84	1.2 (0.90–1.7)		
			170–184	93	1.4 (0.99–1.9)		
			≥ 185	119	1.5 (1.1–2.0)		
			[P_{trend}]		[0.01]		
			Weight (lb) at age 45 yr				
			< 165	72	1.0		
			165–179	86	1.3 (0.93–1.8)		
			180–199	111	1.5 (1.1–2.0)		
			≥ 200	102	1.4 (1.1–2.0)		
			[P_{trend}]		[0.032]		
			Weight (lb) at baseline				Weight gain since age 18 yr not associated with risk of incidence
			< 173	78	1.0		
			174–189	87	1.3 (0.96–1.8)		
			190–214	115	1.3 (0.97–1.7)		
			≥ 215	98	1.3 (0.93–1.7)		
			[P_{trend}]		[0.23]		
Máchová et al. (2007) National Cancer Registry Nested case–control study in the population of the Šumperk District Czech Republic 1987–2002	17 334 Incidence	Prostate ICD-10: C61	BMI	338 total		Age, smoking, hypertension, height	
			18.5–24.9		1.00		
			25–29.9		1.05 (0.72–1.39)		
			≥ 30		0.97 (0.66–1.41)		

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Rodriguez et al. (2007) Cancer Prevention Study II (CPS II) Nutrition Cohort USA 1992–2003	69 991 Incidence	Prostate	BMI			Age, race, education level, family history of prostate cancer, energy intake, smoking status, PSA testing, diabetes, physical activity; Weight change also adjusted for BMI in 1982 and height	When stratifying by subtype, weight change also not associated with increased risk for any subtype
			< 25	1935	1.00		
			25–27.4	1742	1.02 (0.96–1.09)		
			27.5–29.9	920	0.98 (0.90–1.06)		
			30–34.9	556	0.94 (0.85–1.04)		
			≥ 35	99	0.91 (0.75–1.12)		
			[P_{trend}]		[0.14]		
			Weight change (lb), 1982–1992				
			≥ 21 loss	113	0.84 (0.69–1.02)		
			11–20 loss	349	0.84 (0.75–0.95)		
			6–19 loss	541	0.98 (0.89–1.08)		
			5 loss to 5 gain	2450	1.00		
			6–10 gain	751	0.98 (0.90–1.06)		
			11–20 gain	687	0.97 (0.89–1.05)		
			≥ 21 gain	322	0.89 (0.79–1.00)		
		Prostate, non-metastatic, low-grade TNM: T1–3, N0, M0 Gleason score ≤ 8	BMI				
			< 25	1544	1.00		
			25–27.4	1409	1.03 (0.96–1.10)		
			27.5–29.9	700	0.92 (0.84–1.01)		
			30–34.9	412	0.86 (0.77–0.97)		
			≥ 35	73	0.84 (0.66–1.06)		
			[P_{trend}]		[0.002]		
		Prostate, non-metastatic high-grade TNM: T1–3, N0, M0 Gleason score > 8	BMI				
			< 25	239	1.00		
			25–27.4	180	0.87 (0.72–1.06)		
			27.5–29.9	140	1.23 (1.00–1.53)		
			≥ 30	103	1.22 (0.96–1.55)		
			[P_{trend}]		[0.03]		
	69 991 Incidence or mortality	Prostate, metastatic or fatal TNM: T4, Nx, Mx or Tx, N1–2, Mx or Tx, Nx, M1	BMI				
			< 25	92	1.00		
			25–27.4	104	1.41 (1.06–1.87)		
			27.5–29.9	46	1.14 (0.79–1.63)		
			≥ 30	46	1.54 (1.06–2.23)		
			[P_{trend}]		[0.05]		

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Wright et al. (2007) NIH-AARP cohort USA 1995–2000	172 961 Incidence	Prostate ICD-9: 185 ICD-10: C61	BMI			Age, race, smoking status, education level, diabetes, family history of prostate cancer For BMI at age 18 yr, also BMI at baseline, height	
			< 25	3076	1.00		
			25–29.9	5054	1.00 (0.95–1.04)		
			30–34.9	1532	0.97 (0.91–1.03)		
			35–39.9	269	0.84 (0.74–0.95)		
			≥ 40	55	0.65 (0.50–0.85)		
			[P_{trend}]		[0.0008]		
			BMI at age 18 yr				
			< 18.5	723	0.95 (0.87–1.04)		
			18.5–20.9	1787	1.00		
			21–22.9	1510	1.01 (0.95–1.09)		
			23–24.9	775	0.90 (0.83–0.98)		
			≥ 25	641	0.93 (0.84–1.02)		
			[P_{trend}]		[0.17]		
			Weight (kg) at age 18 yr, quintiles			Age, race, smoking status, education level, diabetes, family history of prostate cancer, BMI, height	
			< 58.6	1004	1.0		
			58.7–64.5	1338	1.01 (0.93–1.10)		
			64.6–69.9	1043	0.99 (0.91–1.09)		
			70–76.7	1138	0.99 (0.91–1.09)		
			> 76.7	1071	0.92 (0.84–1.02)		
			[P_{trend}]		[0.08]		
			Weight (kg) at baseline, quintiles				Weight at baseline also not associated with increased risk for localized and with metastatic prostate cancer subtypes
			< 74.5	1126	1.0		
			74.6–81.3	1224	1.02 (0.93–1.11)		
			81.4–87.2	1204	1.01 (0.92–1.10)		
			87.3–97.2	1157	1.00 (0.91–1.09)		
			> 97.2	1014	0.91 (0.82–1.00)		
			[P_{trend}]		[0.99]		

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Wright et al. (2007) (cont.)	172 961 Incidence		Weight change (kg), age 18 yr to baseline				Weight change also not associated with increased risk for localized and for extraprostatic prostate cancer subtypes
			< −4	161	1.00 (0.83–1.19)		
			−4 to 3.9	430	1.0		
			4–9.9	936	1.04 (0.93–1.17)		
			10–19.9	1896	1.12 (1.00–1.24)		
			20–29.9	1425	1.12 (1.00–1.26)		
			30–39.9	469	0.99 (0.87–1.14)		
			≥ 40	277	1.03 (0.88–1.20)		
			[P_{trend}]		[0.81]		
		Prostate, localized TNM: T1a to T2b, N0, M0	BMI			Age, race, smoking status, education level, diabetes, family history of prostate cancer For BMI at age 18 yr, also BMI at baseline, height	
			< 25	2652	1.00		
			25–29.9	4328	0.99 (0.94–1.04)		
			30–34.9	1277	0.94 (0.88–1.01)		
			35–39.9	236	0.86 (0.75–0.98)		
			≥ 40	48	0.67 (0.50–0.89)		
			[P_{trend}]		[0.0006]		
			BMI at age 18 yr				
			< 18.5	633	0.95 (0.86–1.04)		
			18.5–20.9	1570	1.0		
			21–22.9	1317	1.01 (0.94–1.09)		
			23–24.9	653	0.87 (0.80–0.96)		
			≥ 25	535	0.89 (0.80–0.99)		
			[P_{trend}]		[0.04]		
			Weight (kg) at age 18 yr, quintiles			Age, race, smoking status, education level, diabetes, family history of prostate cancer, BMI, height	
			< 58.6	881	0.95 (0.86–1.04)		
			58.7–64.5	1185	1.00		
			64.6–69.9	903	1.01 (0.94–1.09)		
			70–76.7	988	0.87 (0.80–0.96)		
			> 76.7	891	0.89 (0.80–0.99)		
			[P_{trend}]		[0.04]		
		Prostate, extraprostatic TNM: T3 or T4, N1, or M1	BMI			Age, race, smoking status, education level, diabetes, family history of prostate cancer For BMI at age 18 yr, also BMI, height	
			< 25	424	1.0		
			25–29.9	726	1.03 (0.91–1.16)		
			30–34.9	255	1.14 (0.97–1.33)		
			≥ 35	40	0.68 (0.49–0.94)		
			[P_{trend}]		[0.64]		

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Wright et al. (2007) (cont.)	172 961 Incidence		BMI at age 18 yr				
			< 18.5	90	0.98 (0.77–1.26)		
			18.5–20.9	217	1.00		
			21–22.9	193	1.04 (0.86–1.27)		
			23–24.9	122	1.11 (0.88–1.39)		
			≥ 25	106	1.15 (0.90–1.47)		
			[P_{trend}]		[0.18]		
			Weight (kg) at age 18 yr, quintiles			Age, race, smoking status, education level, diabetes, family history of prostate cancer, BMI, height	
			< 58.6	123	1.0		
			58.7–64.5	153	0.95 (0.74–1.20)		
			64.6–69.9	140	1.08 (0.84–1.38)		
			70–76.7	150	1.03 (0.80–1.33)		
			> 76.7	180	1.18 (0.91–1.54)		
			[P_{trend}]		[0.13]		
Wright et al. (2007) NIH-AARP cohort USA 1995–2000	Mortality	Prostate ICD-9: 185 ICD-10: C61	BMI			Age, race, smoking status, education level, diabetes, family history of prostate cancer For BMI at age 18 yr, also BMI at baseline, height	Weight at baseline also associated with increased risk Weight (kg) at age 18 yr also not associated with increased mortality
			< 25	44	1.0		
			25–29.9	87	1.25 (0.87–1.80)		
			30–34.9	31	1.46 (0.92–2.33)		
			≥ 35	11	2.12 (1.08–4.15)		
			[P_{trend}]		[0.02]		
			BMI at age 18 yr				
			< 18.5	13	1.67 (0.82–3.42)		
			18.5–20.9	18	1.0		
			21–22.9	25	1.65 (0.90–3.02)		
			23–24.9	16	1.71 (0.86–3.39)		
			≥ 25	11	1.35 (0.62–2.95)		
			[P_{trend}]		[0.73]		
			Weight change (kg), age 18 yr to baseline			Age, race, smoking status, education level, diabetes, family history of prostate cancer, BMI, height	
			< –4	3	1.18 (0.29–4.74)		
			–4 to 3.9	6	1.0		
			4–9.9	12	1.06 (0.40–2.83)		
			10–19.9	23	1.17 (0.47–2.92)		
			20–29.9	24	1.74 (0.69–4.40)		
			30–39.9	10	2.05 (0.72–5.90)		
			40	8	2.98 (0.99–9.04)		
			[P_{trend}]		[0.009]		

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Jee et al. (2008) National Health Insurance Corporation (NHIC) medical evaluation Republic of Korea 1992–2006	770 556 Incidence	Prostate	BMI < 20.0 20.0–22.9 23.0–24.9 25.0–29.9 ≥ 30.0 [P_{trend}]	 265 896 747 638 23	 0.67 (0.56–0.80) 0.87 (0.77–0.98) 1.00 0.95 (0.83–1.08) 1.39 (0.90–2.17) [< 0.0001]	Age, smoking	
Pischon et al. (2008) EPIC cohort 8 European countries, 1992–2000 (8.5 yr follow-up on average)	129 502 Incidence	Prostate ICD-10: C61	BMI, quintiles < 23.6 23.6–25.3 25.4–27 27.1–29.3 ≥ 29.4 [P_{trend}] per 5 kg/m^2	2446 total	 1.00 1.06 (0.93–1.20) 1.08 (0.95–1.23) 0.95 (0.83–1.09) 0.99 (0.86–1.13) [0.37] 0.96 (0.90–1.02)	Study centre, age, smoking status, education level, alcohol consumption, physical activity, height	Also examined hip circumference and waist-to-hip ratio WC also not associated with increased risk
		Prostate, localized TNM: T0–T2 and N0/Nx, M0	BMI, quintiles < 23.6 23.6–25.3 25.4–27 27.1–29.3 ≥ 29.4 [P_{trend}] continuous	991 total	 1.00 1.09 (0.89–1.34) 1.02 (0.83–1.25) 0.88 (0.71–1.10) 0.95 (0.77–1.18) [0.22] 0.92 (0.84–1.01)	Study centre, age, smoking status, education level, alcohol consumption, physical activity, height	WC also not associated with increased risk
		Prostate, advanced TNM: T3–T4 and/or N1–N3 and/or M1	BMI < 23.6 23.6–25.3 25.4–27 27.1–29.3 ≥ 29.4 [P_{trend}] continuous	499 total	 1.00 1.05 (0.78–1.40) 1.25 (0.94–1.66) 1.08 (0.81–1.46) 1.17 (0.86–1.58) [0.34] 1.09 (0.96–1.24)	Study centre, age, smoking status, education level, alcohol consumption, physical activity, height	WC also not associated with increased risk

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Pischon et al. (2008) (cont.)	129 502 Incidence	Prostate, low-grade Gleason score < 7	BMI < 23.6 23.6–25.3 25.4–27 27.1–29.3 ≥ 29.4 [P_{trend}] continuous	841 total	 1.00 0.97 (0.78–1.21) 0.95 (0.77–1.19) 0.83 (0.66–1.04) 0.84 (0.66–1.06) [0.06] 0.88 (0.79–0.98)	Study centre, age, smoking status, education level, alcohol consumption, physical activity, height	WC also not associated with increased risk
		Prostate, high-grade Gleason score ≥ 7	BMI < 23.6 23.6–25.3 25.4–27 27.1–29.3 ≥ 29.4 [P_{trend}] continuous	580 total	 1.00 1.26 (0.96–1.65) 1.34 (1.02–1.76) 1.16 (0.87–1.54) 1.23 (0.92–1.65) [0.37] 1.04 (0.92–1.18)	Study centre, age, smoking status, education level, alcohol consumption, physical activity, height	WC also not associated with increased risk
Rapp et al. (2008) VHM&PP Austria 1985–2002	28 711 Incidence	Prostate ICD-10: C61	BMI change, annual < −0.1 −0.1– < 0.1 0.1– < 0.3 0.3– < 0.5 ≥ 0.5 [P_{trend}]	 164 317 231 72 12	 0.96 (0.79–1.16) 1.00 1.00 (0.85–1.19) 1.01 (0.78–1.31) 0.43 (0.24–0.76) [0.06]	Age, smoking status, blood glucose, occupational group, BMI at baseline	
Hernandez et al. (2009) Multiethnic Cohort USA 1993/1996–2002/2005	83 879 Incidence	Prostate, advanced	BMI at age 21 yr < 18.5 18.5–24.9 ≥ 25.0 [P_{trend}]	 41 475 86	 0.96 (0.69–1.35) 1.00 1.09 (0.85–1.40) [0.46]		No associations were observed with high grade either Inverse associations were observed with localized and with low-grade subtypes

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Wallström et al. (2009) Malmö Diet and Cancer Study Sweden 1991–2005	11 063 Incidence	Prostate ICD-9: 185	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 8 287 417 105	 2.29 (1.13–4.63) 1.00 1.02 (0.88–1.19) 1.06 (0.84–1.33) [0.15]	Age, height, cohabitation status, SES, alcohol consumption, smoking, prevalent diabetes, physical activity, country of birth, total intake of eicosapentaenoic acid, docosahexaenoic acid, red meat, calcium	WC also not associated with increased risk
		Prostate, aggressive TNM: T3–T4, or N1 or M1, or Gleason score ≥ 8, or PSA > 50 ng/mL	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 4 102 140 35	 3.15 (1.15–8.62) 1.00 0.99 (0.76–1.29) 1.02 (0.69–1.52) [0.16]		WC also not associated with increased risk
		Prostate, non-aggressive Not stage T3–T4, or N1 or M1, or Gleason score ≥ 8, or PSA > 50 ng/mL	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 4 183 274 69	 0.84 (0.63–1.11) 1.00 1.16 (0.89–1.50) 1.11 (0.85–1.44) [0.65]		WC also not associated with increased risk
Whitlock et al. (2009) Prospective Studies Collaboration (pooled analysis of 57 cohorts from Europe, Japan, and the USA) Follow-up varied by cohort	894 576 Mortality	Prostate ICD-9: 185	BMI, per 5 kg/m^2 For BMI 15–25 For BMI 25–50 For BMI 15–50	 578 665	 1.00 (0.75–1.32) 1.09 (0.91–1.31) 1.13 (1.02–1.24)	Study, sex, age, smoking	

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Andreotti et al. (2010) Agricultural Health Study USA 1993–2005	39 628 Incidence	Prostate	BMI			Race, smoking status, exercise, family history of prostate cancer	
			< 18.5	0	–		
			18.5–24.9	308	1.00		
			25–29.9	696	1.06 (0.89–1.27)		
			30–34.9	226	0.89 (0.71–1.13)		
			≥ 35	44	0.94 (0.61–1.44)		
			[P_{trend}]		[0.56]		
Burton et al. (2010) Glasgow Alumni Cohort United Kingdom 1948–1968 to 2009	9549 Incidence	Prostate ICD-9: 185 ICD-10: C61	BMI, young adult (age < 30 yr)			Smoking, SES, height	
			< 19	25	1.30 (0.84–1.99)		
			19–22.9	125	1.00		
			23–24.9	33	1.14 (0.78–1.68)		
			≥ 25	14	1.18 (0.68–2.06)		
			per 1 kg/m^2		1.00 (0.93–1.06)		
			[P_{trend}]		[0.89]		
	9549 Mortality	Prostate ICD-9: 185 ICD-10: C61	BMI, young adult (age < 30 yr)				
			< 19	14	1.58 (0.88–2.83)		
			19–22.9	59	1.00		
			23–24.9	21	1.52 (0.92–2.50)		
			≥ 25	8	1.43 (0.68–3.00)		
			per 1 kg/m^2		1.02 (0.93–1.11)		
			[P_{trend}]		[0.74]		
Stocks et al. (2010) Swedish Construction Worker Cohort Sweden 1971–2004	336 159 Mortality	Prostate ICD-7: 177	BMI			Birth cohort, smoking	No association of BMI with incidence of prostate (total), or aggressive prostate cancer subtypes. Significant negative association observed between BMI and incidence for non-aggressive prostate cancer subtype
			< 21.9	230	1.00		
			21.9– < 23.5	383	1.17 (1.00–1.39)		
			23.5– < 25	476	1.09 (0.93–1.27)		
			25– < 27	702	1.26 (1.08–1.46)		
			≥ 27	810	1.28 (1.11–1.49)		
			[P_{trend}]		[0.0004]		

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Discacciati et al. (2011) Sweden 1998–2008	36 959 Incidence	Prostate, localized TNM: T1–2 and NX–0 and MX–0 or PSA < 20 ng/mL or Gleason score < 7	BMI at baseline			BMI at age 30 yr, age, energy intake, physical activity, education level, smoking, family history of prostate cancer, diabetes	
			< 21	62	0.78 (0.54–1.13)		
			21–22.9	245	1.00		
			23–24.9	401	1.00 (0.94–1.06)		
			25–27.4	467	0.95 (0.86–1.05)		
			27.5–29.9	204	0.88 (0.76–1.02)		
			≥ 30	124	0.71 (0.53–0.94)		
			BMI at age 30 yr				
			< 21	287	1.01 (0.91–1.12)		
			21–22.9	539	1.00		
			23–24.9	467	0.99 (0.94–1.05)		
			25–27.4	154	0.99 (0.89–1.10)		
			27.5–29.9	41	0.98 (0.82–1.16)		
			≥ 30	15	0.96 (0.69–1.34)		
			per 5 kg/m^2		0.98 (0.87–1.12)		
		Prostate, advanced TNM: T3–4 and NX–1 and MX–1 or PSA > 100 ng/mL or Gleason score > 7	BMI at baseline			BMI at age 30 yr, age, energy intake, physical activity, education level, smoking, family history of prostate cancer, diabetes	
			< 21	27	0.97 (0.85–1.10)		
			21–22.9	72	1.00		
			23–24.9	163	1.02 (0.95–1.08)		
			25–27.4	150	1.03 (0.90–1.18)		
			27.5–29.9	79	1.05 (0.85–1.31)		
			≥ 30	47	1.11 (0.73–1.68)		
			per 5 kg/m^2		1.04 (0.88–1.22)		
			BMI at age 30 yr				
			< 21	108	1.09 (0.92–1.29)		
			21–22.9	185	1.00		
			23–24.9	164	0.96 (0.88–1.04)		
			25–27.4	69	0.91 (0.77–1.09)		
			27.5–29.9	8	0.87 (0.65–1.15)		
			≥ 30	4	0.76 (0.44–1.30)		
			per 5 kg/m^2		0.90 (0.73–1.11)		

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Discacciati et al. (2011) (cont.)	36 959 Mortality	Prostate	BMI at baseline < 21 21–22.9 23–24.9 25–27.4 27.5–29.9 ≥ 30 per 5 kg/m²	 11 35 62 59 29 23	 0.91 (0.75–1.11) 1.00 1.05 (0.95–1.16) 1.11 (0.89–1.36) 1.16 (0.83–1.63) 1.34 (0.70–2.55) 1.12 (0.87–1.43)	BMI at age 30 yr, age, energy intake, physical activity, education level, smoking, family history of prostate cancer, diabetes	BMI at age 30 yr also not associated with increased risk
Bassett et al. (2012) Melbourne Collaborative Cohort Study (MCCS) Australia 1990–2004 Same cohort as MacInnis et al. (2003)	16 525 Incidence	Prostate ICD-9: 185 ICD-10: C61	BMI at baseline < 18.5 18.5–22.9 23–24.9 ≥ 25 per 5 kg/m² [P_{trend}]	 111 259 757 247	 0.73 (0.59–0.91) 1.00 0.98 (0.85–1.12) 0.96 (0.80–1.15) 1.06 (0.97–1.17) [0.19]	Country of birth, education level	No associations were observed between weight at baseline, BMI or weight (kg) at age 18 yr, or WC, and prostate cancer risk (incidence)
		Prostate, non-aggressive Not Gleason score > 7, stage 4, or death from prostate cancer	BMI at baseline < 18.5 18.5–22.9 23–24.9 ≥ 25 per 5 kg/m² [P_{trend}]	 83 194 527 160	 0.73 (0.56–0.94) 1.00 0.91 (0.77–1.08) 0.83 (0.67–1.03) 0.99 (0.89–1.10) [0.83]	Country of birth, education level	No associations were observed between weight at baseline, BMI or weight (kg) at age 18 yr, or WC, and non-aggressive prostate cancer risk (incidence)
		Prostate, aggressive Gleason score > 7, stage 4, or death from prostate cancer	BMI at baseline < 18.5 18.5–22.9 23–24.9 ≥ 25 per 5 kg/m² [P_{trend}]	 28 65 230 87	 0.74 (0.47–1.15) 1.00 1.17 (0.89–1.54) 1.33 (0.96–1.84) 1.27 (1.08–1.49) [0.004]	Country of birth, education level	No associations were observed between weight at baseline, BMI or weight (kg) at age 18 yr, or WC, and aggressive prostate cancer risk (incidence)
	16 525 Mortality	Prostate ICD-9: 185 ICD-10: C61	BMI at baseline < 18.5 18.5–22.9 23–24.9 ≥ 25 per 5 kg/m² [P_{trend}]	 7 23 71 38	 0.53 (0.23–1.24) 1.00 0.95 (0.59–1.53) 1.52 (0.89–2.58) 1.49 (1.11–2.00) [0.01]	Country of birth, education level	Weight at baseline also associated with increased mortality No association was observed with BMI or weight at age 18 yr and mortality

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Bhaskaran et al. (2014) Clinical Practice Research Datalink United Kingdom 1987–2012	2 379 320 Incidence	Prostate ICD-10: C61	BMI per 5 kg/m^2 [P_{trend}]	24 901 total	0.98 (0.95–1.00) [0.0042]	Age, diabetes, smoking, alcohol consumption, SES, calendar year, sex	No differences were found in non-smokers only
Barrington et al. (2015) Participants in the Selenium and Vitamin E cancer Prevention Trial (SELECT) USA 2001–2008	26 035 Incidence	Prostate	BMI < 25.0 25.0–27.5 27.5–29.9 30–34.9 35–50 [P_{trend}] BMI < 25.0 25.0–27.5 27.5–29.9 30–34.9 35–50 [P_{trend}]	Non-Hispanic White: 289 438 333 299 94 African American: 39 63 57 74 37 	 1.00 1.12 (0.97–1.30) 1.04 (0.89–1.22) 0.96 (0.82–1.13) 0.94 (0.74–1.19) [0.63] 1.28 (0.91–1.80) 1.67 (1.27–2.21) 1.64 (1.23–2.19) 1.68 (1.29–2.18) 1.90 (1.34–2.70) [0.03]	Age, education level, diabetes, smoking, family history of prostate cancer, study arm	For African Americans, BMI < 25.0 in Non-Hispanic Whites was taken as reference
	26 035 Incidence	Prostate, low-grade Gleason score 2–6	BMI < 25.0 25.0–27.5 27.5–29.9 30–34.9 35–50 [P_{trend}] BMI < 25.0 25.0–27.5 27.5–29.9 30–34.9 35–50 [P_{trend}]	Non-Hispanic White: 182 293 202 170 51 African American: 16 37 35 37 23 	 1.00 1.18 (0.98–1.42) 1.00 (0.82–1.22) 0.86 (0.70–1.06) 0.80 (0.58–1.09) [0.02] 0.80 (0.48–1.43) 1.47 (1.03–2.10) 1.52 (1.05–2.20) 1.27 (0.83–1.82) 1.77 (1.14–2.76) [0.05]	Age, education level, diabetes, smoking, family history of prostate cancer, study arm	

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Barrington et al. (2015) (cont.)	26 035 Incidence	Prostate, high-grade Gleason score 7–10	BMI < 25.0 25.0–27.5 27.5–29.9 30–34.9 35–50 [P_{trend}] BMI < 25.0 25.0–27.5 27.5–29.9 30–34.9 35–50 [P_{trend}]	Non-Hispanic White: 84 115 101 104 37 African American: 11 19 17 29 12	 1.00 1.03 (0.78–1.37) 1.11 (0.83–1.49) 1.18 (0.88–1.58) 1.33 (0.90–1.97) [0.01] 1.32 (0.70–2.51) 1.94 (1.17–3.22) 1.87 (1.10–3.16) 2.53 (1.64–3.90) 2.39 (1.29–4.43) [0.02]	Age, education level, diabetes, smoking, family history of prostate cancer, study arm	
Fowke et al. (2015) Pooled analysis in Asia Cohort Consortium (ACC) Different Asian countries (1963–2001) to 2006	522 736 Mortality	Prostate	BMI 12–19.9 20–22.4 22.5–24.9 25–50 [P_{trend}]	 142 188 184 120	 0.98 (0.78–1.23) 0.92 (0.75–1.13) 1.00 1.08 (0.85–1.36) [0.58]	Age, education level, population density, marital status, history of severe cancer, heart disease, or stroke at baseline	Similar results were observed in stratified analyses by region
Meyer et al. (2015) Population-based Swiss cohort study Switzerland 1977–2008	35 703 in cohort, number of men NR Mortality	Prostate ICD-8: 185 ICD-10: C61	BMI < 25 25–29.9 ≥ 30	170 total	 1.00 1.45 (1.03–2.04) 1.54 (0.93–2.55)	Age, survey, alcohol consumption, physical activity, civil status, years of education, nationality, diet	Those who were overweight and who also smoked (ever smoking) had a higher risk

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Møller et al. (2015) Diet, Cancer and Health Study Denmark 1993–2011	26 044 Incidence	Prostate	BMI 15.4–24.9 25–29.9 30–52.7 [P_{trend}]	 649 920 244	 1.00 0.94 (0.85–1.04) 0.86 (0.74–0.99) [0.03]	NR	WC showed no association with total prostate cancer incidence Inverse associations were observed with the upper quartile of body fat percentage (15% decreased risk)
		Prostate Stage 3–4	BMI 15.4–24.9 25–29.9 30–52.7 [P_{trend}]	 208 314 104	 1.00 1.00 (0.84–1.19) 1.14 (0.90–1.44) [0.37]	NR	WC also no associated with advanced prostate cancer incidence Positive associations were observed with the upper quartile of body fat percentage (31% increased risk)
	26 044 Mortality	Prostate	BMI 15.4–24.9 25–29.9 30–52.7 [P_{trend}]	 92 147 51	 1.00 1.10 (0.85–1.43) 1.27 (0.90–1.80) [0.19]	Stage at diagnosis	WC also not associated with increased mortality A positive association was observed with increasing body fat percentage
Møller et al. (2016) Health Professionals Follow-up Study USA 1986–2010	47 491 Incidence and mortality	Prostate	BMI at age 21 yr < 20 20–21.9 22–23.9 24–25.9 ≥ 26 [P_{trend}] per 5 kg/m^2	 825 1546 1852 1132 588	 0.99 (0.90–1.08) 1.00 0.98 (0.91–1.05) 0.92 (0.85–1.00) 0.89 (0.80–0.98) [0.01] 0.94 (0.89–0.98)	Age, calendar time, ethnicity, physical activity, energy intake, smoking, diabetes, family history of prostate cancer, PSA testing	When analysing cumulative BMI average, the significant decrease in risk persisted only in those younger than 65 yr

Table 2.2.14a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Incidence/ mortality	Organ site or cancer subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Møller et al. (2016) (cont.)	47 491 Incidence and mortality	Prostate, fatal	BMI at age 21 yr				BMI at age 21 yr also not associated with lethal subtypes (incident cases and deaths due to prostate cancer or distant metastases at diagnosis or during follow-up)
			< 20	94	0.83 (0.64–1.07)		
			20–21.9	181	1.00		
			22–23.9	177	0.92 (0.74–1.14)		
			24–25.9	88	0.74 (0.57–0.97)		
			≥ 26	51	0.77 (0.56–1.07)		
			[P_{trend}]		[0.20]		
			per 5 kg/m²		0.88 (0.75–1.02)		
		Prostate, high-grade Gleason score 8–10	BMI at age 21 yr				
			< 20	85	0.82 (0.63–1.07)		
			20–21.9	181	1.00		
			22–23.9	204	0.93 (0.75–1.15)		
			24–25.9	130	0.91 (0.72–1.16)		
			≥ 26	79	1.10 (0.83–1.45)		
			[P_{trend}]		[0.27]		
			per 5 kg/m²		1.03 (0.90–1.19)		
		Prostate, moderate-grade Gleason score 7	BMI at age 21 yr			Age, calendar time, ethnicity, physical activity, energy intake, smoking, diabetes, family history of prostate cancer, PSA testing	
			< 20	233	0.98 (0.83–1.15)		
			20–21.9	446	1.00		
			22–23.9	548	0.98 (0.86–1.11)		
			24–25.9	333	0.90 (0.78–1.04)		
			≥ 26	159	0.77 (0.64–0.93)		
			[P_{trend}]		[0.01]		
			per 5 kg/m²		0.87 (0.80–0.95)		
		Prostate, low-grade Gleason score 2–6	BMI at age 21 yr				
			< 20	333	1.01 (0.88–1.16)		
			20–21.9	620	1.00		
			22–23.9	735	0.94 (0.84–1.05)		
			24–25.9	465	0.90 (0.79–1.02)		
			≥ 26	236	0.88 (0.75–1.03)		
			[P_{trend}]		[0.03]		
			per 5 kg/m²		0.93 (0.87–1.01)		

BMI, body mass index (in kg/m²); BP, blood pressure; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; ICD, International Classification of Diseases; N/A, not applicable; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; NR, not reported; PSA, prostate-specific antigen; SD, standard deviation; SES, socioeconomic status; TNM, tumour–node–metastasis; VHM&PP, Vorarlberg Health Monitoring and Prevention Program; WC, waist circumference; yr, year or years

Table 2.2.14b Case–control studies of measures of body fatness and cancer of the prostate

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Putnam et al. (2000) USA 1986–1989	101 Population	BMI < 24.1 24.1–26.6 > 26.6 BMI change (%) from age 20 yr > 5% loss 5% loss to 5% gain 5.1–10.0% gain 10.1–15.0% gain > 15.0% gain Weight (kg) < 74.8 74.8–83.9 > 83.9	 27 31 38 1 12 15 14 51 22 41 33	 1.0 1.0 (0.6–1.7) 1.3 (0.8- 2.2) 0.2 (0.02–1.5) 1.0 1.3 (0.6–2.7) 1.0 (0.5–1.9) 1.3 (0.8–2.2) 1.0 1.4 (0.8–2.3) 1.2 (0.7–2.1)	Age	
Sharpe & Siemiatycki (2001) Canada 1979–1985	399 Population	BMI < 24.05 24.05–26.66 > 26.66	 127 128 141	 0.87 (0.6–1.22) 1.00 1.14 (0.81–1.61)	Age, ethnicity, respondent status, family income, alcohol consumption	
Giles et al. (2003) Australia 1994–1998	1476 Population	BMI at age 21 yr < 20.5 20.5–22.1 22.2–23.9 > 23.9	 353 372 337 332	 1.00 0.99 (0.79–1.23) 0.96 (0.76–1.20) 1.10 (0.88–1.39)	Age, country of birth, family history of prostate cancer, study centre, calendar year	No associations were observed for weight or WC at age 21 yr
Irani et al. (2003) France 1993–1999	194 Hospital	BMI < 29 > 29	NR	 1.00 2.47 (1.41–4.34)	Age	

Table 2.2.14b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Dal Maso et al. (2004) Italy 1991–2002	1294 Hospital	BMI at baseline			Age, study centre, education level, physical activity, family history of prostate cancer	No associations were observed between weight (kg), waist-to-hip ratio, or lean body mass and prostate cancer. When stratified by grade, associations of BMI at diagnosis were only significant with prostate cancer of Gleason score 7–10 (384 cases, $P_{trend} < 0.01$)
		< 24.22	301	1.00		
		24.22–26.18	346	1.18 (0.95–1.47)		
		26.18–28.41	324	1.12 (0.89–1.40)		
		≥ 28.41	319	1.18 (0.94–1.47)		
		[P_{trend}]		[0.23]		
		BMI at age 30 yr				
		< 22.65	406	1.00		
		22.65–24.69	437	1.33 (1.09–1.62)		
		≥ 24.69	414	1.22 (1.01–1.48)		
		[P_{trend}]		[0.004]		
Friedenreich et al. (2004) Canada 1997–2000	988 Population	BMI, quartiles			Age, region, education level, average lifetime total alcohol intake, first-degree family history of prostate cancer, number of times had PSA test done, number of digital rectal exams, total lifetime physical activity	
		Q1	252	1.00		
		Q2	236	0.95 (0.74–1.23)		
		Q3	245	0.98 (0.76–1.26)		
		Q4	254	1.07 (0.83–1.38)		
		[P_{trend}]		[0.57]		
		Weight, quartiles				
		Q1	268	1.00		
		Q2	233	0.93 (0.72–1.21)		
		Q3	262	1.00 (0.78–1.28)		
		Q4	224	0.91 (0.70–1.18)		
		[P_{trend}]		[0.18]		
		Weight gain (kg) since age 20 yr				
		< 4.54	241	1.00		
		4.54–13.6	286	1.14 (0.89–1.47)		
		13.6–20.4	238	1.05 (0.82–1.36)		
		≥ 20.4	215	0.91 (0.70–1.19)		
		[P_{trend}]		[0.26]		

Table 2.2.14b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Pan et al. (2004) Canada 1994–1997	1801 Population	BMI < 25 25–30 ≥ 30 [P_{trend}]		 1.00 1.16 (0.94–1.43) 1.27 (1.09–1.47) [0.026]	Age group, province of residence, education level, pack-years of smoking, alcohol consumption, total energy intake, vegetable intake, dietary fibre intake, recreational physical activity	
Liu et al. (2005) USA NR	439 Population (sibling-based)	BMI, quartiles Q1 Q2 Q3 Q4 [P_{trend}] LBM, quartiles Q1 Q2 Q3 Q4 [P_{trend}]	 106 112 110 106 LBM > 66.3: 113 104 114 103	 1.00 1.57 (0.85–2.89) 1.43 (0.78–2.61) 0.91 (0.49–1.70) [0.73] 1.00 0.58 (0.31–1.08) 0.43 (0.22–0.81) 0.41 (0.20–0.84) [0.02]	Age, education, calorie intake	Results are presented for high-aggressiveness prostate cancer (Gleason score ≥ 7, or tumour stage T2C or greater)
Porter & Stanford (2005) USA 1993–1996	753 Population	BMI 18–24.4 24.4–26.5 26.5–29.1 29.1–55 [P_{trend}] Weight (kg) < 77.2 77.2–85.8 85.9–95.3 > 95.3 [P_{trend}]	 195 202 178 178 175 222 193 163	 1.00 1.04 (0.78–1.39) 0.85 (0.64–1.14) 0.91 (0.66–1.21) [0.04] 1.00 0.96 (0.70–1.30) 0.77 (0.56–1.06) 0.74 (0.53–1.03) [0.03]	Age, race, education level, smoking, family history of prostate cancer, prostate cancer screening, dietary fat, energy intake	
Robinson et al. (2005) USA 1997–2000	568 Population	BMI at age 20–29 yr < 25.0 25.0–29.9 ≥ 30.0	 361 191 12	 1.00 1.13 (0.87–1.47) 0.40 (0.20–0.81)	Age, race, family history of prostate cancer, saturated fat intake	This study evaluated the association with advanced prostate cancer

Table 2.2.14b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Wuermli et al. (2005) Switzerland 1997–2002	504 Hospital	BMI < 30 > 30	NR	 1.00 0.97 (0.93–1.01)	Age, BMI, diabetes, lipid-lowering drugs	
Cox et al. (2006) New Zealand 1996–1998	550 Population	BMI 5 yr before interview, quintiles Q1 Q2 Q3 Q4 Q5	 50 40 105 122 233	 1.0 0.9 (0.5–1.6) 0.8 (0.6–1.2) 0.9 (0.6–1.3) 0.9 (0.6–1.3)	Age	No associations were observed between BMI or weight at age 20 yr and prostate cancer
Beebe-Dimmer et al. (2007) USA 1996–2002	139 Population (community-based)	WC (cm) ≤ 102 > 102	59	 1.00 1.84 (1.17–2.91)	Age, smoking history	
Gallus et al. (2007) Italy 1991–2002	219 Hospital	BMI < 24.84 24.84–27.76 ≥ 27.77 [P_{trend}]	 69 80 70	 1.0 1.3 (0.8–2.0) 1.2 (0.8–1.9) [0.38]	Age, education level, study centre, occupational physical activity, family history of prostate cancer	
Máchová et al. (2007) Czech Republic 1987–2002	338 Population	BMI 18.5–< 25 25–30 ≥ 30	NR	 1.00 1.05 (0.72–1.39) 0.97 (0.66–1.41)	Age, smoking, hypertension, height	
Nagata et al. (2007) Japan 1996–2003	200 Hospital	BMI 1 yr before diagnosis < 23.0 23.0–24.9 > 25.0 [P_{trend}]	 81 60 59	 1.00 1.28 (0.87–1.87) 1.06 (0.72–1.55) [0.65]	Smoking	BMI at age 40–45 yr not associated with increased risk of prostate cancer
Magura et al. (2008) USA 2004–2006	312 Hospital	BMI < 25 ≥ 25	30 282	 1.00 1.04 (0.58–1.85)	Age, family history of prostate cancer, type 2 diabetes, smoking, use of multivitamins, use of statins	

Table 2.2.14b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Beebe-Dimmer et al. (2009) USA 2001–2004	637 Hospital	BMI < 30 ≥ 30	 – 208	 1.00 0.51 (0.33–0.80)	Age, PSA screening history, hypertension, diabetes, low HDL, high triglycerides	Inverse association was observed only in Caucasians (n = 494). No association observed in African Americans (n = 381)
Hosseini et al. (2010) Islamic Republic of Iran 2005–2008	137 Population	BMI ≤ 25 > 25	 105 35	 1.0 0.4 (0.2–0.8)	Age, family history of prostate cancer, history of other cancers, history of prostatitis, alcohol consumption, smoking, physical activity	[Discrepancy in the number of reported cases]
Jackson et al. (2010) Jamaica 2005–2007	243 Hospital	BMI, quartiles Q4 vs Q1 (ref) [P_{trend}] WC, tertiles T3 vs T1 (ref) [P_{trend}] Waist-to-hip ratio < 0.95 ≥ 0.95	NR	 0.90 (0.42–1.91) [0.28] 5.57 (1.43–18.63) [0.008] 1.00 2.94 (1.34–6.38)	BMI: age, education level, medical history, first-degree family history of prostate cancer, smoking, physical activity WC and waist-to-hip ratio: age, height and BMI as continuous; education level, current smoker, physical activity	Results are presented for high-grade cancer (Gleason score ≥ 7) 12% of the cases were obese
Dimitropoulou et al. (2011) United Kingdom 2001–2008	960 Population	BMI < 25.0 25.0–29.9 > 30.0 [P_{trend}] WC, tertiles T1 T2 T3 [P_{trend}]	 264 481 174 385 286 289	 1.00 0.98 (0.82–1.16) 0.83 (0.67–1.03) [0.097] 1.00 1.01 (0.85–1.20) 0.94 (0.80–1.12) [0.517]	Age, family history of prostate cancer	
Ganesh et al. (2011) India 1999–2001	123 Hospital	BMI < 25 ≥ 25	 41 76	 1.0 2.1 (1.1–4.4)	Age, religion, education level, hypertension	

Table 2.2.14b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Mori et al. (2011) Japan 2007–2008	117 Population	BMI < 21.0 21.0–22.9 23.0–24.9 ≥ 25.0 [P_{trend}] Weight (kg) < 55 55.0–64.9 65.0–74.9 ≥ 75.0 Weight gain (kg) in adult life < 5 5.0–9.9 10.0–14.9 ≥ 15	 14 29 41 33 7 52 45 13 18 24 43 32	 1.00 1.05 (0.50–2.21) 1.63 (0.77–3.45) 1.39 (0.66–2.96) [0.07] 1.00 1.49 (0.57–3.85) 1.74 (0.65–4.64) 1.64 (0.55–4.91) 1.00 1.22 (0.58–2.55) 3.55 (1.71–7.39) 1.73 (0.83–3.59)	Dietary intake, physical activity, smoking, alcohol consumption	BMI of 23–25 at age 20 yr associated with a 53% reduced risk (based on 11 cases) No associations between body weight at age 20 yr and prostate cancer risk
Pelucchi et al. (2011) Italy 1991–2002	1294 Hospital	BMI < 28 ≥ 28 WC (cm) < 94 ≥ 94 Abdominal obesity (combined WC, BMI) No Yes	 909 381 242 730 470 820	 1.00 0.98 (0.83–1.17) 1.00 1.13 (0.91–1.40) 1.00 1.02 (0.86–1.21)	Age, study centre, education level, smoking, alcohol consumption, physical activity, family history of prostate cancer, non-alcohol energy intake	
Fowke et al. (2012) USA NR	809 Hospital	BMI per 1 kg/m² increase WC per 1 cm increase	 135 135	 1.04 (1.00–1.08) 1.01 (0.99–1.03)	Age, PSA, prostate volume, race, family history of prostate cancer, current treatment for diabetes, benign prostatic hyperplasia, CVD, or hyperlipidaemia	Results are presented for high-grade (Gleason score 8–10) prostate cancer

Table 2.2.14b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Nemesure et al. (2012) Barbados 2002–2011	963 Population	WC (cm), quartiles Q1: < 84 Q2: 84–92 Q3: 92–99 Q4: ≥ 99	NR	 1.00 1.36 (1.01–1.85) 1.67 (1.14–2.44) 1.84 (1.19–2.85)	Age, marital status, religion, occupation, smoking, family history of prostate cancer, BMI	Study in African Barbadian population. When stratifying by high-grade (n = 434) vs low-grade (n = 480) prostate cancer, the associations were not significant in either group
Möller et al. (2013) Sweden 2001–2002	1499 Population	BMI < 22.5 22.5– < 25 25– < 27.5 ≥ 27.5 per 5 kg/m^2 [P_{trend}]	 382 655 295 120	 1.00 0.94 (0.76–1.15) 0.90 (0.71–1.15) 0.96 (0.69–1.33) 0.98 (0.83–1.16) [0.54]	Age, region of residence, time span between first and last recalled weight	No associations with BMI when stratifying by low- and intermediate-grade vs high-grade prostate cancer No significant associations with BMI at age 20 yr
Bashir et al. (2014) Pakistan 2012–2013	140 Hospital	BMI ≤ 25 > 25	 66 74	 1.00 5.78 (2.67–12.6)	Age, lifestyle (physical activity), family history of prostate cancer, smoking, diet	
Agalliu et al. (2015) Nigeria 2011–2012	50 Hospital	BMI < 25 25–29.9 ≥ 30 Weight (kg) per kg increase WC (cm) per cm increase	 21 21 8	 1 1.39 (0.59–3.28) 1.35 (0.42–4.36) 0.97 (0.94–1.00) 0.91 (0.87–0.96)	Age	
Alvarez-Cubero et al. (2015) Spain 2011–2014	100 Hospital	BMI ≥ 30 vs < 30	31	1.65 (0.36–7.57)	Age, residential area, family history of prostate cancer	

Table 2.2.14b (continued)

Reference Study location Period	Total number of cases Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding	Comments
Boehm et al. (2015) Canada 2005–2012	1933 Population	BMI < 25 25–29.9 ≥ 30 WC (cm) < 102 ≥ 102	 649 922 351 1073 711	 1.00 0.87 (0.74–1.01) 0.72 (0.60–0.87) 1.00 1.03 (0.89–1.19)	Age, ancestry, first-degree family history of prostate cancer, annual physician visits, number of PSA tests within 5 yr before index date	No associations were observed with waist-to-hip ratio
Gerdtsson et al. (2015) Sweden 1974–1996	1355 Population	Weight at age 16–22 yr per 5 kg increase BMI at age 44–50 yr per 5 kg increase Weight at age 44–50 yr per 5 kg increase		Incidence: 1.05 (1.01–1.09) Mortality: 1.08 (1.03–1.13) Mortality: 1.11 (1.03–1.19)		No associations were observed with BMI or weight at age 44–50 yr and prostate cancer risk BMI and weight at age 44–50 yr also associated with metastasis
Zhang et al. (2015) China 2013–2014	101 Hospital	BMI < 24 ≥ 24	 35 66	 1.00 2.51 (0.18–9.52)	WC, BP, triglyceride levels, free blood glucose	

BMI, body mass index (in kg/m^2); BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; HDL, high-density lipoprotein; LBM, lean body mass; NR, not reported; PSA, prostate-specific antigen; SD, standard deviation; WC, waist circumference; yr, years or years

Table 2.2.14c Meta-analyses of measures of body fatness and cancer of the prostate

Reference	Total number of studies Total number of cases	Organ site or cancer subtype	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
Bergström et al. (2001)	6 observational studies (4 cohort and 2 case–control) 4592	Prostate	BMI per 1 kg/m^2 increase	1.01 (1.00–1.02)	Different adjustment by study, some non-adjusted	
MacInnis & English (2006)	43 observational studies (22 cohort and 21 case–control) (9 studies for WC) 68 753	Prostate	BMI per 5 kg/m^2 increase	1.05 (1.01–1.08)	Different adjustment by study	No associations were found with WC
Renehan et al. (2008)	27 prospective studies 70 421	Prostate	BMI per 5 kg/m^2 increase	1.03 (1.00–1.07)		Between-study heterogeneity of I^2 = 73% No differences in the results were observed by region (Asia-Pacific, Australia, Europe, North America)
Robinson et al. (2008)	9 cohort studies and 7 case–control studies NR	Prostate	BMI before age 29 yr, per 5 kg/m^2 increase	Cohort: 1.08 (0.97–1.19) Case–control: 1.07 (0.98–1.17)	Age for all; other factors depending on the study	
Guh et al. (2009)	7 cohort studies NR	Prostate	BMI Normal Overweight Obesity	 1.00 1.14 (1.00–1.31) 1.05 (0.85–1.30)	NR	
Esposito et al. (2013)	13 observational studies (cohort and case–control) 4634	Prostate	BMI High vs low	 1.05 (0.97–1.15)	NR	[Cut-off values differ by study]
WCRF/AICR (2014) Continuous Update Project	24 prospective studies for BMI, 4 for WC 11 149	Prostate, advanced	BMI per 5 kg/m^2 increase WC per 10 cm increase	1.08 (1.04–1.12) 1.12 (1.04–1.21)	NR	Advanced prostate cancer includes advanced, high-grade, and fatal prostate cancers

Table 2.2.14c (continued)

Reference	Total number of studies Total number of cases	Organ site or cancer subtype	Exposure categories	Relative risk (95% CI)	Adjustment for confounding	Comments
Keum et al. (2015)	4 prospective studies 6882	Prostate	Weight gain per 5 kg increase	0.98 (0.94–1.02)	Age and baseline BMI or weight in all, and different additional covariates depending on the study	
		Prostate, localized	Weight gain per 5 kg increase	0.96 (0.92–1.00)		
		Prostate, advanced	Weight gain per 5 kg increase	1.04 (0.99–1.09)		
			WC per 10 cm increase	1.03 (0.99–1.07)		
Chen et al. (2016)	9 observational studies (5 cohort, 1 nested case–control, and 3 case–control) 22 338	All Low- and intermediate-grade High-grade Fatal	Adult weight per 5 kg increase	1.01 (0.94–1.08) 0.97 (0.87–1.07) 1.13 (1.00–1.28) 1.58 (1.01–2.47)	Age (in all studies except one) and different covariates depending on the study	

BMI, body mass index (in kg/m^2); CI, confidence interval; NR, not reported; WC, waist circumference; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research; yr, years or years

Table 2.2.14d Mendelian randomization studies of measures of body fatness and cancer of the prostate

Reference Study	Characteristics of study population	Sample size	Exposure (unit)	Odds ratio (95% CI) and *P* value (with each unit increase in exposure) of the association between the exposure and outcome(s)	Adjustment for confounding
Lewis et al. (2010) Prostate Testing for Cancer and Treatment Study (ProtecT)	Men aged 50–69 yr from 300 general practices across 9 regions in the United Kingdom	4540 (1550 cases and 2990 controls)	BMI per 1 kg/m² increase per 1 kg/m² increase	All: 0.77 (0.52–1.15) *P* = 0.20 High-grade vs low-grade: 1.35 (0.90–2.03) *P* = 0.15	Age, centre
Davies et al. (2015) Prostate Cancer Association Group to Investigate Cancer-Associated Alterations in the Genome (PRACTICAL) Consortium	19 independent studies of individuals of European descent	41 062 (20 848 cases and 20 214 controls)	Increase of 1 SD in genetically predicted BMI	0.98 (0.96–1.00) *P* = 0.07	8 principal components of population stratification
Gao et al. (2016) Genetic Associations and Mechanisms in Oncology (GAME-ON) Consortium	6 studies of individuals of European ancestry	26 884 (14 160 cases and 12 724 controls)	Increase of 1 SD in genetically predicted BMI (~0.073 kg/m²) Childhood BMI: Adult BMI:	 All: 1.01 (0.83–1.22) *P* = 0.91 Aggressive: 1.10 (0.83–1.45) *P* = 0.49 All: 1.00 (0.96–1.04) *P* = 0.97 Aggressive: 1.02 (0.96–1.08) *P* = 0.44	N/A

BMI, body mass index (in kg/m²); CI, confidence interval; N/A, not applicable; SD, standard deviation; vs, versus; yr, years or years

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2.2.15 Cancer of the testis

Cancer of the testis is a rare malignancy, accounting for 1% of incident cases of cancer in men, but the testis is the most common cancer site for men aged 15–44 years in developed countries. To date, the most important identified risk factor for testicular cancer is an undescended testicle. Increased risk has also been associated with family history of testicular cancer, various genetic factors, and several perinatal risk factors.

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and testicular cancer was *inadequate*.

(a) Cohort studies

Since 2000, only one cohort study of excess body weight in relation to risk of testicular cancer has been published: a Norwegian cohort of approximately 600 000 men aged 14–44 years (Bjørge et al., 2006). For overweight and obesity compared with normal BMI, the relative risks were 0.89 (95% CI, 0.77–1.03) and 0.83 (95% CI, 0.58–1.17), respectively, and the relative risk per 1 kg/m^2 increase in BMI was 0.97 (95% CI, 0.95–1.00). There was no statistically significant heterogeneity of results between histological subtypes of testicular cancer.

(b) Case–control studies

A total of seven population- or hospital-based case–control studies published after 2000 focused on the association between BMI and weight and testicular cancer (Table 2.2.15; web only; available at: http://publications.iarc.fr/570). In four studies, there was no overall significant association with BMI for all testicular cancer cases (Dieckmann & Pichlmeier, 2002; Richiardi et al., 2003; Pan et al., 2004; McGlynn et al., 2007). Giannandrea et al. (2012) found an inverse association with all testicular cancer cases for men with BMI > 27.4 kg/m^2 (n = 26) compared with men with BMI ≤ 23.15 kg/m^2 (OR, 0.42; 95% CI, 0.24–0.75). One study showed that high BMI in men aged 18–29 years was significantly more frequent in testicular cancer cases than in controls (Dieckmann et al., 2009). In one study, analysis by subtype yielded an odds ratio of 3.66 (95% CI, 1.87–7.15) for obese men (BMI > 31 kg/m^2) with non-seminoma testicular cancer (n = 11) (Garner et al., 2003).

A meta-analysis of the earlier cohort study and 10 case–control studies showed an inverse association between overweight and testicular cancer (OR, 0.92; 95% CI, 0.86–0.98), which was not significant for obesity (OR, 0.93; 95% CI, 0.75–1.15) (Lerro et al., 2010).

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2.2.16 *Cancer of the kidney (renal cell carcinoma)*

Cancer of the kidney accounts for about 2% of all cancers diagnosed. Established epidemiological risk factors for kidney cancer include tobacco smoking, which can double the risk of the disease in smokers compared with non-smokers. Other established risk factors, which are closely associated with obesity, are high blood pressure and pre-existing diabetes mellitus.

The two most common types of kidney cancer are renal cell carcinoma (RCC) and transitional cell carcinoma (also known as urothelial cell carcinoma) of the renal pelvis. About 90% of kidney cancers are RCCs. Histological subtypes of RCC include clear cell tumours (about 70% of RCCs), papillary tumours (also called chromophilic RCC; about 10% of RCCs), and chromophobe RCC (about 5% of RCCs). Various rarer types of RCC exist, each representing less than 1% of RCCs.

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that there was *sufficient evidence* for a cancer-preventive effect of avoidance of weight gain for RCC. The 2007 WCRF review concluded that there was convincing evidence of a positive association between body fatness and kidney cancer risk (WCRF/AICR, 2007). In 2015, the WCRF Continuous Update Project reaffirmed the 2007 conclusions (WCRF/AICR, 2015).

(a) Cohort studies

Since 2000, 19 cohort studies of anthropomorphic measures and risk of kidney cancer have been published (excluding analyses that were later updated and analyses based on fewer than 100 incident cases). Table 2.2.16a shows those findings by BMI at baseline, with comments on findings according to other anthropometric measures of body fatness and weight changes over the life-course.

The findings are remarkably consistent across studies, showing increasing risk of kidney cancer with increasing BMI. The association is approximately linear with increasing BMI. A meta-analysis of 21 cohort studies concluded that there was consistency of the association across sexes and world regions, with a relative risk for obesity compared with normal weight of 1.63 (95% CI, 1.50–1.77) in men and 1.95 (95% CI, 1.81–2.10) in women (Wang & Xu, 2014).

Some investigators have assessed the association between BMI at different ages and subsequent risk of kidney cancer (Nicodemus et al., 2004; van Dijk et al., 2004; Adams et al., 2008). In general, the strong positive association between baseline BMI and kidney cancer risk was also seen for BMI in middle adulthood, but much less so for BMI in early adulthood (ages 18–20 years).

Five cohort studies reported on the association between measures of waist circumference and kidney cancer risk (Nicodemus et al., 2004; Pischon et al., 2006; Adams et al., 2008; Sanfilippo et al., 2014; Kabat et al., 2015). In all of the studies, measures of waist circumference were associated with kidney cancer risk similarly to BMI.

(b) Case–control studies

Since 2000, a total of nine case–control studies in China, Europe, and North America have reported on the association of BMI with risk of RCC (Table 2.2.16b). In all of the studies except one (Wang et al., 2012), BMI was assessed through self-reports by patients with RCC and control subjects, with reference to a variable time frame before cancer diagnosis and an equivalent time frame for the controls. Of the nine studies, seven adjusted for smoking and two did not. Other possible confounding factors considered and adjusted for in some studies included use of artificial sweeteners, pre-existing diabetes mellitus, use of anti-hypertensive drugs, and

exposures to pesticides, herbicides, or certain industrial exposures.

Most of the studies showed an increased risk of RCC with higher BMI, in men, women, or both sexes, although this positive association was not statistically significant in all studies. In all the larger studies, including the earlier studies, there was a statistically significant trend of increasing RCC risk with increasing BMI, up to an approximately 2–3-fold increased risk for the highest versus the lowest BMI categories, both in men and in women. In several studies, RCC risk was also found to be positively associated with BMI at younger ages (20–40 years) (Brock et al., 2007; Dal Maso et al., 2007; Beebe-Dimmer et al., 2012).

Purdue et al. (2013) combined the data from a large case–control study in the USA (Beebe-Dimmer et al., 2012) and a multicentre study in central and eastern Europe (Brennan et al., 2008) to examine the association of BMI with different histological subtypes of RCC and found a positive association of BMI with risk of clear cell RCC (n = 1524; OR per 5 kg/m^2, 1.2; 95% CI, 1.1–1.3) and chromophobe RCC (n = 80; OR per 5 kg/m^2, 1.2; 95% CI, 1.1–1.4), but not papillary RCC (n = 237; OR per 5 kg/m^2, 1.1; 95% CI, 1.0–1.2) or RCC not otherwise specified (n = 367; OR per 5 kg/m^2, 1.0; 95% CI, 0.7–1.4).

(c) Meta-analyses

Several meta-analyses of cohort and/or case–control studies assessed the association between BMI and kidney cancer risk (Table 2.2.16c). Bergström et al. (2001) combined data from 14 studies in men and 14 studies in women, and reported a summary relative risk of RCC of 1.07 per 1 kg/m^2 increase in BMI in both men and women. Two more recent meta-analyses reported summary relative risks for cohort studies and case–control studies separately, for women (Mathew et al., 2009) and for men (Ildaphonse et al., 2009) respectively, all in the range of 1.05 to 1.07.

(d) Mendelian randomization study

There has been one Mendelian randomization study, which used the *FTO* rs9939609 SNP, robustly associated with BMI (Frayling et al., 2007; Scuteri et al., 2007; Peeters et al., 2008), to estimate the causal association between BMI and kidney cancer, among other cancer types (Brennan et al., 2009; Table 2.2.16d). Those with the *FTO* AA genotype had a higher BMI than controls with the TT genotype (difference, 1.14 kg/m^2; 95% CI, 0.66–1.61; P < 0.00001). Mendelian randomization analyses showed that each 1 kg/m^2 increase in BMI was weakly associated with an increased risk of kidney cancer (OR, 1.11; 95% CI: 0.91–1.37; P = 0.31), which was more pronounced in those younger than 50 years (OR, 1.90; 95% CI, 1.16–2.27; P = 0.0002).

Table 2.2.16a Cohort studies of measures of body fatness and cancer of the kidney

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Calle et al. (2003) Population-based cohort USA 1982–1998	404 576 Men Mortality	BMI 18.5–24.9 25–29.9 30–34.9 35–39.9 [P_{trend}]	 305 437 81 14 	 1.00 1.18 (1.02–1.37) 1.36 (1.06–1.74) 1.70 (0.99–2.92) [0.002]	Age, education level, smoking, physical activity, alcohol consumption, marital status, aspirin, fat intake, vegetable intake	
	495 477 Women Mortality	BMI 18.5–24.9 25–29.9 30–34.9 35–39.9 ≥ 40 [P_{trend}]	 243 153 55 12 10 	 1.00 1.33 (1.08–1.63) 1.66 (1.23–2.24) 1.70 (0.94–3.05) 4.75 (2.50–9.04) [< 0.001]	Age, education level, smoking, physical activity, alcohol consumption, marital status, aspirin, fat intake, vegetable intake, HRT	
Bjørge et al. (2004) Population-based cohort Norway 1963–2001	1 037 788 Women Incidence	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 1061 977 568 	 1.00 1.32 (1.21–1.45) 1.85 (1.66–2.06) [< 0.001]	Age	Association weaker in current and former smokers than in never-smokers
	963 442 Men Incidence	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 1908 1638 267 	 1.00 1.18 (1.11–1.26) 1.55 (1.36–1.76) [< 0.001]	Age	Association weaker in current and former smokers than in never-smokers
Nicodemus et al. (2004) Iowa Women's Health Study USA 1986–2000	34 637 Women Incidence	BMI < 22.9 22.9–25.0 25.0–27.4 27.4–30.6 > 30.6 [P_{trend}]	 16 13 24 31 40 	 1.00 0.80 (0.38–1.65) 1.46 (0.77–2.74) 1.87 (1.02–3.41) 2.49 (1.39–4.44) [< 0.0001]	Age	Postmenopausal women. Weight at ages 30 yr, 40 yr, and 50 yr (but not at 18 yr) associated similarly. WC also associated

Table 2.2.16a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
van Dijk et al. (2004) Netherlands Cohort Study The Netherlands 1986–1995	120 852 Women and men Incidence	BMI 23–24.9 25–26.9 27–29.9 ≥ 30 [P_{trend}] per 1 kg/m²	 83 54 62 16 	 1.00 0.92 (0.61–1.38) 1.46 (0.97–2.21) 1.04 (0.54–1.99) [0.04] 1.07 (1.02–1.12)	Age, sex	No association with BMI at age 20 yr
Flaherty et al. (2005) Nurses' Health Study USA 1976–2000	118 191 Women Incidence	BMI < 22.0 22.0–24.9 25.0–27.9 28.0–29.9 ≥ 30 [P_{trend}]	 40 47 27 14 26 	 1.0 1.3 (0.9–2.0) 1.6 (0.9–2.5) 2.2 (1.2–4.1) 2.7 (1.6–4.4) [< 0.001]	Age, hypertension, smoking	RR for BMI ≥ 30 adjusted for age only
Flaherty et al. (2005) Health Professionals Follow-Up Study USA 1986–1998	48 953 Men Incidence	BMI < 22.0 22.0–24.9 25.0–27.9 28.0–29.9 ≥ 30 [P_{trend}]	 4 37 45 12 10 	 1.0 2.1 (0.7–5.9) 2.4 (0.9–6.8) 2.1 (0.7–6.6) 2.1 (0.7–6.8) [0.19]	Age, hypertension, smoking	
Rapp et al. (2005) Population-based cohort Austria 1985–2002	67 447 Men Incidence	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 46 70 21 	 1.00 1.19 (0.82–1.74) 1.46 (0.87–2.46) [0.14]	Age, smoking, occupation	
	78 484 Women Incidence	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 32 44 12 	 1.00 1.81 (1.13–2.89) 1.14 (0.58–2.24) [0.3]	Age, smoking, occupation	

Table 2.2.16a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Pischon et al. (2006) EPIC cohort Europe 1992–2004	218 889 Women Incidence	BMI, quintiles < 21.8 21.8–23.7 23.8–25.9 26.0–28.9 > 29.0 [P_{trend}]	 12 22 24 37 37	 1.00 1.48 (0.73–3.01) 1.39 (0.69–2.80) 1.99 (1.03–3.88) 2.25 (1.14–4.44) [0.009]	Smoking, education level, alcohol consumption, physical activity	WC also associated
	129 660 Men Incidence	BMI, quintiles < 23.6 23.6–25.3 25.4–27.0 27.1–29.3 > 29.4 [P_{trend}]	 29 35 23 28 40	 1.00 1.07 (0.65–1.77) 0.67 (0.39–1.18) 0.84 (0.49–1.43) 1.22 (0.74–2.03) [0.51]		
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1971–1999	362 552 Men Incidence	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 444 448 94	 1.00 1.23 (1.08–1.42) 1.61 (1.27–2.04) [< 0.001]	Age, year, smoking, hypertension	
Reeves et al. (2007) Million Women Study United Kingdom 1995–2005	1.2 million Women Incidence	BMI < 22.5 22.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 per 10 kg/m^2	 119 165 155 106 178	 0.95 (0.79–1.14) 1.00 (0.86–1.17) 1.10 (0.94–1.28) 1.19 (0.99–1.44) 1.52 (1.31–1.77) 1.53 (1.27–1.84)	Age, region, SES, reproductive history, smoking, alcohol consumption, physical activity, HRT use	Association slightly weaker in never-smokers
Setiawan et al. (2007) Multiethnic Cohort USA 1993–2002	85 964 Women Incidence	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 38 52 37	 1.00 2.03 (1.31–3.15) 2.27 (1.37–3.74) [0.001]	Age, ethnicity, smoking, alcohol consumption, hypertension, physical activity	
	75 172 Men Incidence	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 77 93 50	 1.00 1.14 (0.84–1.55) 1.76 (1.20–2.58) [0.005]		

Table 2.2.16a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Adams et al. (2008) NIH-AARP cohort USA 1995–2003	214 906 Women Incidence	BMI 18.5–22.5 22.5–24.9 25–27.5 27.5–29.9 ≥ 30 [P_{trend}]	 17 33 46 27 64	 1.00 1.66 (0.92–2.98) 2.44 (1.39–4.26) 2.27 (1.23–4.20) 2.67 (1.53–4.66) [0.002]	Age, smoking, physical activity, protein intake, diabetes, hypertension	Similar association with BMI at age 50 yr; no association at age 18 yr or 35 yr. WC also associated
	312 500 Men Incidence	BMI 18.5–22.5 22.5–24.9 25–27.5 27.5–29.9 ≥ 30 [P_{trend}]	 28 88 169 127 152	 1.00 1.12 (0.73–1.72) 1.51 (1.01–2.26) 1.74 (1.15–2.63) 1.87 (1.24–2.82) [< 0.0005]		Similar association with BMI at age 50 yr; no association at age 18 yr or 35 yr. WC also associated
Jee et al. (2008) Cohort from National Health Insurance Corporation Republic of Korea 1992–2007	443 273 Women Incidence	BMI < 20 20–22.9 23–24.9 25–29.9 ≥ 30 [P_{trend}]	 22 95 100 100 14	 0.48 (0.28–0.82) 0.70 (0.49–0.99) 1.00 0.92 (0.64–1.31) 1.21 (0.58–2.53) [0.0042]	Age, smoking	
	770 556 Men Incidence	BMI < 20 20–22.9 23–24.9 25–29.9 ≥ 30 [P_{trend}]	 97 430 425 392 16	 0.64 (0.49–0.84) 0.67 (0.56–0.79) 1.00 1.11 (0.93–1.31) 1.38 (0.76–2.52) [< 0.0001]	Age, smoking	Association weaker in ever-smokers than in non-smokers
Song et al. (2008) Korean medical insurance cohort Republic of Korea 1993–2003	170 481 Women Incidence	BMI 21.0–22.9 23.0–24.9 25.0–26.9 27.0–29.9 ≥ 30.0 [P_{trend}]	 18 34 29 14 7	 1.00 1.74 (0.94–3.22) 1.74 (0.92–3.29) 1.37 (0.66–2.84) 2.61 (1.06–6.41) [< 0.05]	Age, height, smoking, alcohol consumption, physical activity, pay grade	

Table 2.2.16a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Wilson et al. (2009) ATBC cohort Finland 1985–2002	27 111 Men Incidence	BMI < 23.7 23.7–26.0 26.0–28.5 ≥ 28.5 [P_{trend}]	 41 70 65 69	 1.00 1.8 (1.3–2.7) 1.8 (1.2–2.7) 2.1 (1.4–3.1) [< 0.001]	Age, energy intake	
Sawada et al. (2010) Population sample of Japan Japan 1990–2006	46 837 Men Incidence	BMI < 21 21.0–22.9 23.0–24.9 25.0–26.9 ≥ 27.0	 22 20 21 18 20	 1.86 (1.01–3.45) 1.16 (0.62–2.16) 1.00 1.39 (0.73–2.63) 1.99 (1.04–3.81)	Age, area, tobacco use, alcohol consumption, physical activity, hypertension, diabetes	Analysis of data in women (n = 52 625) was based on very small number of cases; association unclear
Häggström et al. (2013) 3 cohorts Austria, Norway, Sweden 1994–2006	281 468 Women Incidence	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 24 28 61 66 84	 1.00 0.95 (0.52–1.74) 1.84 (1.08–3.13) 1.74 (1.02–2.94) 2.21 (1.32–3.70) [0.0002]	Age, time of measurement	
	278 920 Men Incidence	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 89 108 100 139 156	 1.00 1.11 (0.81–1.52) 0.94 (0.68–1.29) 1.28 (0.95–1.73) 1.51 (1.13–2.03) [0.001]		
Macleod et al. (2013) Population-based cohort USA 2000–2009	77 260 Women and men Incidence	BMI < 25 25–29.9 30–34.9 ≥ 35	 59 104 47 28	 1.00 1.23 (0.88–1.72) 1.20 (0.81–1.78) 1.71 (1.06–2.79)	Age, sex, race, smoking, alcohol consumption, hypertension, diabetes	
Bhaskaran et al. (2014) Clinical Practice Research Datalink United Kingdom 1987–2012	5.24 million Women and men Incidence	BMI per 5 kg/m^2	1906 total	 1.25 (1.17–1.33)	Age, year, sex, diabetes, SES, alcohol consumption, tobacco use	Similar findings for never-smokers

Table 2.2.16a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Sanfilippo et al. (2014) Women's Health Initiative cohort USA 1993–1998	156 774 Women Incidence	BMI 18.5–24.9 25–29.9 30–34.9 35–39.9 ≥ 40	 108 144 83 45 27	 1.00 1.32 (1.03–1.70) 1.47 (1.10–1.96) 1.91 (1.33–2.75) 2.48 (1.61–3.80)	Age, race/ethnicity, diastolic blood pressure	(See also Kabat et al., 2015) WC also associated with increased risk
Kabat et al. (2015) Women's Health Initiative cohort USA 1992–2013	143 901 Women Incidence	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	376 total	 1.00 0.89 (0.61–1.28) 1.21 (0.86–1.71) 1.36 (0.96–1.91) 1.73 (1.24–2.42) [< 0.0001]	Age, alcohol consumption, smoking, physical activity, age at menarche, age at first birth, parity, HRT use, family history of kidney cancer, ethnicity, education level	WC also associated with risk

ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; BMI, body mass index (in kg/m^2); CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HRT, hormone replacement therapy; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; RR, relative risk; SES, socioeconomic status; WC, waist circumference; yr, year or years

Table 2.2.16b Case–control studies of measures of body fatness and cancer of the kidney

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding Comments
Shapiro et al. (1999) USA (western Washington state) 1980–1995	238 (155 men, 83 women) 616 (261 men, 355 women) Population	Median BMI	Women:		Age, diabetes mellitus, hypertension Median BMI calculated using median weight recorded in medical records during the 5-yr period immediately before the reference date (2 yr before date of diagnosis and corresponding index date for controls)
		< 22.20	5	1.0	
		22.20–24.85	16	3.3 (1.1–9.7)	
		24.86–28.25	20	3.6 (1.3–10.3)	
		> 28.25	29	4.1 (1.5–11.8)	
		Top 10% (> 32.99)		6.0 (1.9–18.8)	
		Median BMI	Men:		
		< 24.59	23	1.0	
		24.59–26.39	27	1.1 (0.5–2.1)	
		26.40–28.88	26	1.0 (0.5–2.0)	
		> 28.88	45	1.8 (0.9–3.5)	
		Top 10% (> 31.85)		2.2 (1.0–5.0)	
Hu et al. (2003) Canada (8 provinces) 1994–1997	1279 (691 men, 588 women) 5370 (2696 men, 2674 women) Population	BMI 2 yr before study entry	Women:		10-year age group, province, education level, pack-years of smoking, alcohol consumption, total intake of meat, vegetables, and fruit
		< 18.5–24.9	221	1.0	
		25.0–29.9	200	1.5 (1.20–1.90)	
		30.0–34.9	100	2.5 (1.90–3.40)	
		35.0–39.9	31	2.7 (1.70–4.40)	
		≥ 40.00	33	3.8 (2.30–6.40)	
		BMI 2 yr before study entry	Men:		
		< 18.5–24.9	147	1.0	
		25.0–29.9	369	2.20 (1.70–2.70)	
		30.0–34.9	144	2.80 (2.20–3.80)	
		35.0–39.9	21	1.90 (1.10–3.30)	
		≥ 40.00	8	3.70 (1.50–9.40)	

Table 2.2.16b (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding Comments
Chiu et al. (2006) USA 1986–1990	406 (261 men, 145 women) 2434 (1601 men, 833 women) Population	BMI in 60s	Men:		All respondents: age, total energy intake, intake of red meat, intake of vegetables, hypertension, education level, smoking, family history of kidney cancer, proxy status; women only: marital status Analyses for BMI at age 20 yr and age 40 yr gave very similar results to BMI at age 60 yr
		≤ 23.48	49	1.0	
		23.49–25.17	33	0.6 (0.3–1.1)	
		25.18–27.35	34	0.6 (0.3–1.1)	
		27.36–30.07	27	0.8 (0.4–1.7)	
		≥ 30.08	20	0.4 (0.2–1.0)	
		[P_{trend}]		[0.2]	
		BMI in 60s	Women:		
		≤ 22.20	23	1.0	
		22.21–24.32	18	0.5 (0.2–1.4)	
		24.33–27.31	20	1.0 (0.4–2.5)	
		27.33–30.13	13	0.7 (0.3–2.1)	
		≥ 30.14	21	2.3 (0.9–6.0)	
		[P_{trend}]		[0.1]	
Brock et al. (2007) USA (Iowa) 1985–1989	406 (261 men, 145 women) 2434 (1601 men, 833 women) Population	BMI at age 20 yr			Age, sex, proxy status, pack-years of smoking Analysis also reported for men and women separately
		< 25	271	1.00	
		25–30	62	1.54 (1.10–2.17)	
		≥ 30	21	2.75 (1.51–5.01)	
		BMI at age 40 yr			
		< 25	180	1.00	
		25–30	130	1.36 (1.04–1.79)	
		≥ 30	51	2.08 (1.39–3.12)	
		BMI at age 60 yr			
		< 25	111	1.00	
		25–30	93	1.12 (0.81–1.55)	
		≥ 30	39	1.46 (0.94–2.28)	
Dal Maso et al. (2007) Italy 1992–2004	767 (494 men, 273 women) 1534 (988 men, 546 women) Hospital	BMI at age 30 yr			Calendar period of interview, years of education, smoking habits, family history of kidney cancer
		< 25	492	1.00	
		25– < 30	194	1.17 (0.95–1.45)	
		≥ 30	38	1.46 (0.95–2.25)	
		[P_{trend}]		[0.04]	
		BMI at age 50 yr			
		< 25	256	1.00	
		25– < 30	265	1.17 (0.94–1.45)	
		≥ 30	89	1.48 (1.07–2.03)	
		[P_{trend}]		[0.02]	

Table 2.2.16b (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding Comments
Dal Maso et al. (2007) (cont.)		BMI 1 yr before diagnosis			
		< 25	281	1.00	
		25– < 30	347	0.95 (0.78–1.16)	
		≥ 30	136	1.29 (0.99–1.69)	
		[P_{trend}]		[0.16]	
		By smoking status			
		Never-smokers:			
		< 25	39	1.00	
		25– < 30	62	1.25 (0.74–2.09)	
		≥ 30	82	1.83 (1.10–3.04)	
		Ever-smokers:			
		< 25	87	1.00	
		25– < 30	93	0.96 (0.66–1.41)	
		≥ 30	112	1.37 (0.95–1.98)	
		By histological type			
		Clear cell subtype:			
		< 25	71	1.00	
		25– < 30	89	0.99 (0.68–1.44)	
		≥ 30	121	1.40 (0.98–1.99)	
		Other subtype:			
		< 25	23	1.00	
		25– < 30	38	1.30 (0.73–2.30)	
		≥ 30	41	1.62 (0.92–2.85)	
Brennan et al. (2008) Czech Republic, Poland, Romania, Russian Federation (7 centres) 1998–2003	1097 (648 men, 449 women) 1476 (952 men, 524 women) Hospital	BMI 2 yr before interview	Men:		Age, smoking, history of hypertension, country
		< 25	191	1.00	
		25–27.5	166	1.19 (0.91–1.56)	
		27.5–29.99	125	1.32 (0.98–1.79)	
		30–35	133	1.70 (1.25–2.31)	
		> 35	32	1.72 (1.01–2.94)	
		[P_{trend}]		[0.001]	
		BMI 2 yr before interview	Women:		
		< 25	136	1.00	
		25–27.5	87	0.86 (0.60–1.25)	
		27.5–29.99	98	1.16 (0.80–1.70)	
		30–35	98	0.95 (0.66–1.38)	
		> 35	30	0.85 (0.49–1.48)	
		[P_{trend}]		[0.68]	

Table 2.2.16b (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding Comments
Beebe-Dimmer et al. (2012) USA 2002–2007	1214 (720 men, 494 women) 1234 (689 men, 545 women) Population	BMI 5 yr before interview			Age, education level, hypertension, family history of renal cancer, smoking history, study centre Analysis of BMI at age 21 yr gave similar results
		< 25.0	240	1.0	
		25.0–29.9	436	1.2 (0.9–1.5)	
		30.0–34.9	298	1.5 (1.2–2.1)	
		≥ 35	230	1.6 (1.1–2.2)	
		per 1 kg/m²		1.02 (1.01–1.04)	
		[P_{trend}]		[0.0013]	
Wang et al. (2012) China 2007–2009	250 299 Hospital	Current BMI			Univariate analysis
		< 25	157	1.00	
		≥ 25	93	1.94 (1.34–2.81)	
Purdue et al. (2013) USA (Detroit and Chicago; USKC study) and Europe (Czech Republic, Poland, Romania, Russian Federation; CEERCC study) 2002–2007	2314 2711 Population (USKC), hospital (CEERCC)	BMI a few years before interview			Study centre, age, sex, race, education level, BMI, smoking status, history of diagnosed hypertension, family history of kidney cancer Time before interview: 5 yr (USKC), 2 yr (CEERCC)
		Clear cell:	1524		
		per 5 kg/m²		1.2 (1.1–1.3)	
		Papillary:	237		
		per 5 kg/m²		1.1 (1.0–1.2)	
		Chromophobe:	80		
		per 5 kg/m²		1.2 (1.1–1.4)	
		Other/NOS:	367		
		per 5 kg/m²		1.0 (0.7–1.4)	

BMI, body mass index (in kg/m²); CEERCC, Central and Eastern European Renal Cell Cancer Study; CI, confidence interval; NOS, not otherwise specified; USKC, United States Kidney Cancer; yr, year or years

Table 2.2.16c Meta-analyses of measures of body fatness and cancer of the kidney

Reference	Total number of studies Sex	Exposure categories	Relative risk (95% CI)	Heterogeneity values
Bergström et al. (2001)	28 studies (6 cohort studies, 22 case–control studies; 16 population-based, 6 hospital-based) Men: 14 studies Women: 14 studies	BMI, per 1 kg/m^2 All Men Women	 1.07 (1.05–1.09) 1.07 (1.04–1.09) 1.07 (1.05–1.09)	 $P_{heterogeneity}$ = 0.03 $P_{heterogeneity}$ = 0.08 $P_{heterogeneity}$ = 0.24
Mathew et al. (2009)	28 studies (15 cohort studies, 13 case–control studies) Women	BMI, per 1 kg/m^2 Cohort studies Case–control studies	 1.06 (1.05–1.07) 1.07 (1.06–1.08)	 $P_{heterogeneity}$ = 0.081 $P_{heterogeneity}$ = 0.0643
Ildaphonse et al. (2009)	27 studies (13 cohort studies, 14 case–control studies) Men	BMI, per 1 kg/m^2 Cohort studies Case–control studies	 1.05 (1.04–1.06) 1.08 (1.06–1.09)	 $P_{heterogeneity}$ = 0.78 $P_{heterogeneity}$ = 0.4238
Wang & Xu (2014)	21 cohort studies Men and women	BMI, vs normal weight All: Pre-obesity Obesity Men: Pre-obesity Obesity Women: Pre-obesity Obesity	 1.28 (1.24–1.33) 1.77 (1.68–1.87) 1.22 (1.17–1.28) 1.63 (1.50–1.77) 1.38 (1.29–1.47) 1.95 (1.81–2.10)	BMI in adults was classified as follows: normal weight, 18.50–24.99; pre-obesity, 25.00–29.99; obesity, ≥ 30.00

BMI, body mass index (in kg/m^2); CI, confidence interval

Table 2.2.16d Mendelian randomization studies of measures of body fatness and cancer of the kidney

Reference	Characteristics of study population	Sample size	Exposure (unit)	Outcome	Odds ratio (95% CI); *P* value (with each unit increase in exposure) of the association between the exposure and outcome
Brennan et al. (2009)	Men and women from 15 centres in 6 countries in central and eastern Europe (Czech Republic, Hungary, Poland, Romania, Russian Federation, and Slovakia)	7067 (4015 cases and 3052 controls)	BMI (kg/m^2)	Kidney cancer	All subjects: 1.11 (0.91–1.37); $P = 0.31$ Subjects aged < 50 yr: 1.90 (1.16–2.27); $P = 0.0002$

BMI, body mass index (in kg/m^2); CI, confidence interval; OR, odds ratio; yr, year or years

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2.2.17 Cancer of the urinary bladder

Cancer of the urinary bladder accounts for approximately 3% of all cancers and is the ninth most common cancer worldwide. The incidence of urinary bladder cancer in men is approximately 4 times that in women. The average age of diagnosis is after age 70 years. Globally, incidence rates are highest in Europe and North America and lowest in Asia and Latin America.

The strongest risk factor is smoking, as was established several decades ago (IARC, 1986). Compared with never-smokers, smokers have a 6-fold increase in the risk of developing urinary bladder cancer (WCRF/AICR, 2015). Other risk factors include occupational exposure to aromatic amines and polyaromatic hydrocarbons.

About 90% of urinary bladder cancers are transitional cell carcinoma; the remainder are squamous cell carcinoma, adenocarcinoma, and small cell carcinoma.

(a) Cohort studies

See Table 2.2.17a (web only; available at: http://publications.iarc.fr/570).

A total of 23 prospective cohorts were identified that evaluated associations between BMI and either urinary bladder cancer incidence (19 studies) (Tulinius et al., 1997; Nagano et al., 2000; Tripathi et al., 2002; Samanic et al., 2004, 2006; Oh et al., 2005; Rapp et al., 2005; Cantwell et al., 2006; Holick et al., 2007; Reeves et al., 2007; Jee et al., 2008; Koebnick et al., 2008; Larsson et al., 2008; Prentice et al., 2009; Andreotti et al., 2010; Häggström et al., 2011; Bhaskaran et al., 2014; Roswall et al., 2014; Song et al., 2014) or urinary bladder cancer-related mortality (5 studies) (Calle et al., 2003; Batty et al., 2005; Fujino et al., 2007; Reeves et al., 2007; Parr et al., 2010) as the end-point. The large majority of these studies reported no significant association with urinary bladder cancer incidence or mortality. Two studies did show a positive association between BMI and risk of urinary bladder cancer. The NIH-AARP cohort (Koebnick et al., 2008) reported significantly increased associations with overweight (RR, 1.16; 95% CI, 1.03–1.29), obesity I (RR, 1.23; 95% CI, 1.06–1.43), and obesity II (RR, 1.30; 95% CI, 1.04–1.63) in men and women combined, compared with normal weight; stratified analysis indicated that these positive associations were limited to men. The EPIC study (Roswall et al., 2014) found a small but significant association for BMI in men only (RR per 2 kg/m^2, 1.05; 95% CI, 1.02–1.08), with a strong dose–response relationship. Findings from the Iowa Women's Health Study (Tripathi et al., 2002) demonstrated a statistically marginal inverse association between BMI and urinary bladder cancer incidence also in men only (P_{trend} = 0.06 after adjustments).

Almost all studies adjusted for smoking. Stratified analyses suggested that the associations were stronger in former smokers than in never-smokers. Four studies (Calle et al., 2003; Reeves et al., 2007; Koebnick et al., 2008; Bhaskaran et al., 2014) specifically stratified by never versus ever smoking status and statistically tested for interactions. None of those interactions were significant.

Several studies reported on the associations between BMI and urinary bladder cancer in Asian populations (Nagano et al., 2000; Oh et al., 2005; Fujino et al., 2007; Jee et al., 2008; Parr et al., 2010). No pattern of difference compared with European or North American populations was noted.

From a large meta-analysis for the association between BMI and urinary bladder cancer risk, based on 22 prospective cohort studies, the summary risk estimate was 1.03 (95% CI, 0.97–1.09) (WCRF/AICR, 2015). Two additional meta-analyses, of 11 cohort studies (Qin et al., 2013) and 15 cohort studies (Sun et al., 2015), reported summary risk estimates of positive

associations between BMI and urinary bladder cancer. [These differences in part reflect variations in study inclusion. In the meta-analysis by Sun et al., (2015), the summary estimate may have been disproportionally influenced by an incorrect data extraction of risk estimates from the FINRISK study (Song et al., 2014).]

Three studies evaluated the relationship between waist circumference and urinary bladder cancer risk. Two studies (Tripathi et al., 2002; Larsson et al., 2008) found no significant association; the third study, based on the EPIC cohort (Roswall et al., 2014), found a small but significant association with waist circumference in men only (RR per 5 cm, 1.04; 95% CI, 1.01–1.08).

(b) Case–control studies

See Table 2.2.17b (web only; available at: http://publications.iarc.fr/570).

The four case–control studies that evaluated the relationship between BMI and urinary bladder cancer incidence (Pelucchi et al., 2002; Lin et al., 2010; MacKenzie et al., 2011; Attner et al., 2012) found no significant associations.

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2.2.18 *Primary tumours of the brain and central nervous system*

Primary tumours of the brain are a relatively uncommon group of heterogeneous neoplastic diseases with variable natural histories from benign to malignant. There are about 130 histological types arising from the many cell types that support and line the brain tissue and the central nervous system. Primary brain tumours occur across the age spectrum, from childhood through adulthood. The most common type, which arises from the glial cells, is called glioma and accounts for approximately 30% of all brain tumours in adults (Wiedmann et al., 2013). In turn, gliomas are of at least three types – astrocytoma, oligodendroglioma, and ependymoma – and are graded into four grades (1 and 2 are low-grade; 3 and 4, also known as glioblastoma multiforme, are high-grade) (Ricard et al., 2012).

The next most common group is meningioma, which accounts for approximately 20% of brain tumours. Many of these are benign and slow-growing, but – as occurs with other brain tumour types – benign tumours can undergo malignant transformation.

Established risk factors for brain tumours include hereditary conditions, such as neurofibromatosis, and ionizing radiation.

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and brain cancers, including meningioma, was *inadequate*.

(a) *Cohort studies of tumours of the brain and central nervous system combined*

Essentially all of the evidence of associations between measures of body fatness and primary brain tumours applies to tumours in adulthood.

Five large prospective cohort studies reported associations between BMI and cancers of the brain and central nervous system in terms of incidence or mortality without specifying the histological type (Table 2.2.18a; Calle et al., 2003; Oh et al., 2005; Samanic et al., 2006; Reeves et al., 2007; Bhaskaran et al., 2014). There is consistently no evidence of associations between BMI and the development of all brain tumours. [This observation was robust when restricting the analyses to non-smokers only (Reeves et al., 2007; Bhaskaran et al., 2014).]

(b) *Cohort studies of glioma*

Five cohort studies (all in European and North American populations) (Benson et al., 2008; Moore et al., 2009; Michaud et al., 2011; Edlinger et al., 2012; Wiedmann et al., 2013) reported on associations between baseline BMI and the development of glioma (Table 2.2.18a). There is consistently no evidence of associations between BMI and the development of glioma. One study stratified by low- and high-grade glioma and reported no difference.

The NIH-AARP cohort study (Moore et al., 2009) reported on the associations between recalled BMI at age 18 years and the development of glioma later in life and noted a positive association (P = 0.003) [the numbers of cases in the upper BMI categories were small; n = 11 for BMI of 30–34.9 kg/m^2, and no cases in the highest category of BMI ≥ 35 kg/m^2].

(c) *Cohort studies of meningioma*

Five cohort studies (all in European and North American populations) (Jhawar et al., 2003; Benson et al., 2008; Johnson et al., 2011; Michaud et al., 2011; Wiedmann et al., 2013) reported on associations between baseline BMI and the development of meningioma (Table 2.2.18a). All reported statistically significant or borderline significant positive associations, with increased risks ranging from 1.4 to 2.13.

Two cohort studies (Johnson et al., 2011; Michaud et al., 2011) reported on associations between baseline waist circumference and meningioma incidence. In both, significant positive associations were noted.

(d) Case–control studies

See Table 2.2.18b.

Two case–control studies (Cabaniols et al., 2011; Little et al., 2013) examined relationships between BMI and risk of glioma, and no associations were found. Two further case–control studies, one in women only (Claus et al., 2013) and the other in men only (Schildkraut et al., 2014), examined relationships between BMI and meningioma and found positive associations in both studies, similar to those found in the cohort studies.

A meta-analysis (Niedermaier et al., 2015), including 2982 meningioma cases from 12 cohort and case–control studies reported positive associations with meningioma: with normal weight as the reference group, the relative risk was 1.21 (95% CI, 1.01–1.43) for overweight and 1.54 (95% CI, 1.32–1.79) for obesity.

Table 2.2.18a Cohort studies of measures of body fatness and cancers of the brain and central nervous system

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Brain and central nervous system combined							
Calle et al. (2003) Cancer Prevention Study II population-based cohort USA 1982–1998	404 576 Men Mortality	Brain	BMI 18.5–24.9 25–29.9 30–34.9 35–39.9 [P_{trend}]	 370 461 68 – 	 1.00 0.98 (0.85–1.13) 0.79 (0.61–1.03) – [0.14]	Age, education level, smoking, physical activity, alcohol consumption, marital status, race, aspirin use, fat intake, vegetable intake; in women, also adjusted for HRT use	
	495 477 Women Mortality	Brain	BMI 18.5–24.9 25–29.9 30–34.9 35–39.9 ≥ 40 [P_{trend}]	 467 213 64 12 – 	 1.00 1.02 (0.87–1.21) 1.10 (0.84–1.44) 0.74 (0.42–1.32) – [0.96]		
Oh et al. (2005) Korean civil servants and teachers from the Korea National Health Insurance Corporation Republic of Korea 1992–2001	781 283 Men Incidence	Brain	BMI < 18.5 18.5–22.9 23.0–24.9 25.0–26.9 27.0–29.9 ≥ 30 [P_{trend}]	 4 105 69 32 21 3 	 1.07 (0.39–2.93) 1.00 1.09 (0.79–1.50) 0.84 (0.55–1.28) 1.47 (0.90–2.38) 1.79 (0.57–2.66) [0.241]	Age, smoking status, alcohol consumption, frequency of regular exercise, family history of cancer, area of residence	
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1971–1999	362 552 Men Incidence	Brain ICD-7: 193.0	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 519 353 46 	 1.00 1.03 (0.89–1.18) 0.86 (0.63–1.16) [> 0.5]	Age, year, smoking	

Table 2.2.18a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Reeves et al. (2007) Million Women Study United Kingdom 1995–2005	1.2 million Women Incidence	Brain ICD-10: C71	BMI < 22.5 22.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 per 10 kg/m^2	 113 133 143 83 99	 1.14 (0.95–1.38) 1.00 (0.84–1.19) 1.27 (1.08–1.50) 1.19 (0.96–1.47) 1.08 (0.88–1.32) 1.01 (0.81–1.26)	Age, region, SES, reproductive history, smoking, alcohol consumption, physical activity Where appropriate: time since menopause, HRT use	Similar results when restricting to never-smokers or excluding the first 2 yr of follow-up
	1.2 million Women Mortality		BMI < 22.5 22.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 per 10 kg/m^2	 123 143 158 90 131	 1.17 (0.98–1.40) 1.00 (0.85–1.18) 1.29 (1.10–1.51) 1.18 (0.96–1.45) 1.31 (1.10–1.56) 1.17 (0.95–1.43)		
Bhaskaran et al. (2014) United Kingdom Clinical Practice Research Database United Kingdom 1987–2012	5.24 million Men and women Incidence	Brain and central nervous system	BMI per 5 kg/m^2	2974	1.04 (0.99–1.10)	Age, diabetes status, smoking, alcohol consumption, calendar year, SES	Very similar risk estimates for never-smokers (n = 1359 incident cases)
Glioma							
Benson et al. (2008) Million Women Study United Kingdom 1996–2001	1 184 225 Women Incidence	Glioma ICD-O: 9380–9481	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 259 241 106	 1.00 1.20 (1.01–1.44) 1.07 (0.84–1.34) [0.10]	Height, SES, smoking, alcohol intake, parity, age (yr) at first birth, duration of OC use, physical activity, study region	
Moore et al. (2009) NIH-AARP cohort USA (8.2 years)	270 395 Men and women Incidence	Glioma ICD-O-3: 9380–9460	BMI < 18.5 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 4 82 95 46 9	 1.66 (0.59–4.64) 1.00 0.90 (0.67–1.22) 1.29 (0.89–1.86) 0.74 (0.37–1.48) [0.95]	Age at baseline, age squared, sex, race, highest level of education, marital status	

Table 2.2.18a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Moore et al. (2009) (cont.)			BMI at age 18 yr < 18.5 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 26 175 24 11 – 	 0.69 (0.45–1.05) 1.00 1.04 (0.67–1.59) 3.74 (2.03–6.90) – [0.003]		No significant associations observed with BMI at age 35 yr or at age 50 yr
Michaud et al. (2011) EPIC cohort From 1999 (8.4 years)	380 775 Men and women Incidence	Glioma ICD-O-2: 9380–9460, 9505	BMI < 20 20–24.9 25–29.9 ≥ 30 [P_{trend}]	 13 125 147 55 	 1.08 (0.60–1.92) 1.00 1.04 (0.81–1.34) 1.06 (0.76–1.48) [0.80]	Age, country, sex, education level	
			WC, quartiles Q1 Q2 Q3 Q4 [P_{trend}]	 73 82 73 90 	 1.00 0.90 (0.65–1.24) 0.82 (0.59–1.16) 0.97 (0.69–1.35) [0.81]	Age, country, sex, education level, height	
Edlinger et al. (2012) Metabolic Syndrome and Cancer Project (Me-Can) Austria, Norway, Sweden 1972–2005	578 462 Men and women Incidence	Low-grade glioma ICD-7: 193	BMI, quintiles Q1 Q2 Q3 Q4 Q5	 21 16 21 24 16	 1.00 0.69 (0.33–1.42) 0.90 (0.46–1.77) 1.00 (0.51–1.95) 0.66 (0.31–1.38)	Year of birth (in decades), cohort, smoking status	
		High-grade glioma ICD-7: 193	BMI, quintiles Q1 Q2 Q3 Q4 Q5	 65 72 82 99 92	 1.00 0.98 (0.68–1.43) 1.06 (0.73–1.52) 1.23 (0.87–1.75) 1.14 (0.80–1.64)		

Table 2.2.18a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Wiedmann et al. (2013) Nord-Trøndelag Health Study (HUNT 1 Study) Norway From 1991 (23.5 yr)	74 242 Men and women Incidence	Glioma ICD-O-3: 9380–9480	BMI < 20 20–24.9 25–29.9 ≥ 30 [P_{trend}]	 6 79 49 14	 0.67 (0.29–1.56) 1.00 0.88 (0.61–1.27) 1.04 (0.58–1.85) [0.87]	Age, sex	
Meningioma							
Jhawar et al. (2003) Nurses' Health Study USA 1.2 million person-years	121 700 Women Incidence	Meningioma (self-reported)	BMI < 22 22–24.9 ≥ 25 [P_{trend}]	 22 31 58	 1.00 1.10 (0.61–1.97) 1.61 (0.96–2.70) [0.06]	Age, menopausal status, postmenopausal HRT use	
Benson et al. (2008) Million Women Study United Kingdom 1996–2001	1 184 225 Women Incidence	Meningioma	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 154 120 84	 1.00 1.01 (0.79–1.29) 1.40 (1.08–1.87) [0.03]	Height, SES, smoking, alcohol intake, parity, age (yr) at first birth, duration of OC use, physical activity, study region	
Johnson et al. (2011) Iowa Women's Health Study USA 291 021 person-years	27 791 Women Incidence	Meningioma ICD-9: 192.1, 192.3, 225.2, 225.4, 237.6	BMI 18.5–24.9 25–29.9 30–34.0 ≥ 35 [P_{trend}] WC (in) < 30.25 30.26–33.50 33.51–37.75 > 37.75 [P_{trend}]	 41 36 35 13 22 20 35 44	 1.00 0.92 (0.59–1.44) 2.14 (1.36–3.36) 1.99 (1.06–3.71) [0.0007] 1.00 0.92 (0.50–1.69) 1.56 (0.92–2.67) 2.13 (1.28–3.56) [0.0006]	Age	BMI at age 18 yr and at age 30 yr not associated with risk

Table 2.2.18a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site or subtype (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Michaud et al. (2011) EPIC cohort From 1999 (8.4 yr)	380 775 Men and women Incidence	Meningioma	BMI			Age, country, sex, education level	
			< 20	7	1.00 (0.46–2.19)		
			20–24.9	70	1.00		
			25–29.9	87	1.34 (0.97–1.86)		
			≥ 30	39	1.48 (0.98–2.23)		
			[P_{trend}]		[0.05]		
		Meningioma	WC, quartiles			Age, country, sex, education level, height	
			Q1	32	1.00		
			Q2	45	1.18 (0.73–1.88)		
			Q3	41	1.06 (0.65–1.72)		
			Q4	66	1.71 (1.08–2.73)		
			[P_{trend}]		[0.01]		
Wiedmann et al. (2013) Nord-Trøndelag Health Study (HUNT 1 Study) Norway 23.5 yr	74 242 Men and women Incidence	Meningioma ICD-O-3: 9530–9539	BMI			Age, sex	When stratifying by sex, positive associations (borderline significant) observed in women only
			< 20	6	0.82 (0.35–1.92)		
			20–24.9	59	1.00		
			25–29.9	51	1.22 (0.83–1.80)		
			≥ 30	22	1.48 (0.89–2.45)		
			[P_{trend}]		[0.08]		

BMI, body mass index (in kg/m²); CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HRT, hormone replacement therapy; ICD, International Classification of Diseases; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; OC, oral contraceptive; SES: socioeconomic status; WC, waist circumference; yr, year or years

Table 2.2.18b Case–control studies of measures of body fatness and cancers of the brain and central nervous system

Reference Study location Period	Total number of cases Sex Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding
Glioma					
Cabaniols et al. (2011) France 2005	122 Men and women Hospital	BMI in recent past < 25 ≥ 25	 49	 1.00 0.70 (0.41–1.18)	Age, sex
Little et al. (2013) USA 2004–2012	643 Men Population	BMI in adulthood, recent past < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 8 133 311 191	 2.47 (0.63–9.70) 1.00 1.26 (0.94–1.69) 1.26 (0.91–1.75) [0.67]	Age, race, education level, state of residence
	460 Women Population	BMI in adulthood, recent past < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 10 203 136 111	 0.80 (0.34–1.87) 1.00 0.95 (0.70–1.29) 1.11 (0.98–1.03) [0.63]	
	643 Men Population	BMI at age 21 yr < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 34 391 182 29	 0.67 (0.41–1.09) 1.00 1.16 (0.89–1.52) 0.77 (0.45–1.31) [0.054]	
	460 Women Population	BMI at age 21 yr < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 69 324 39 23	 0.68 (0.48–0.96) 1.00 1.39 (0.85–2.27) 1.66 (0.85–3.23) [0.004]	

Table 2.2.18b (continued)

Reference Study location Period	Total number of cases Sex Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding
Meningioma					
Claus et al. (2013) USA 2006–2011	1127 Women Population	BMI < 23.4 23.4–26.6 26.6–30.9 ≥ 30.9 [P_{trend}]	 303 237 269 308	 1.00 1.06 (0.83–1.35) 1.13 (0.89–1.45) 1.29 (1.01–1.65) [0.04]	Race, education level, menopausal status, age at menopause, age at menarche, number of full-term pregnancies, age at first live birth, ever use of OC, ever use of HRT, ever use of fertility medications, smoking, alcohol consumption, breastfeeding, geographical location
Schildkraut et al. (2014) USA 2006–2012	456 Men Population	BMI < 25 25–29.9 30–34.9 ≥ 35	 84 206 102 58	 1.00 1.66 (1.17–2.34) 1.92 (1.28–2.90) 1.64 (1.02–2.64)	Age, race

BMI, body mass index (in kg/m²); CI, confidence interval; HRT, hormone replacement therapy; OC, oral contraceptive; yr, year or years

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2.2.19 Cancer of the thyroid

Cancer of the thyroid includes a variety of histological types, ranging from the most common group of differentiated cancers (papillary carcinoma and follicular carcinoma) to medullary carcinoma and anaplastic (undifferentiated) carcinoma. Globally, thyroid cancer incidence has been increasing during the past three decades; incidence rates in women are generally 2–3 times those in men. Known risk factors include exposure to radiation for all thyroid cancers, and iodine deficiency for follicular carcinoma.

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and thyroid cancer was *inadequate*. The 2007 WCRF review did not draw any conclusions about body fatness and thyroid cancer risk (WCRF/AICR, 2007).

(a) Cohort studies

The evidence from cohort studies since 2000 includes 15 publications (excluding analyses that were later updated and analyses based on fewer than 100 incident cases), including a large pooled analysis of 22 cohorts (Kitahara et al., 2016). Table 2.2.19a presents results from these studies for BMI at baseline, with comments on findings according to other measures of body fatness, such as weight changes over the life-course, waist circumference, or waist-to-hip ratio.

In general, the evidence from cohort studies supports a positive association between BMI and thyroid cancer, with most studies reporting a significantly increased risk at the highest versus lowest category of BMI and/or a significant dose–response relationship. However, in those studies that provided estimates for women and men separately, inconsistent findings were observed across studies. Almquist et al. (2011) found no association between BMI and thyroid cancer in either sex, but a positive trend across BMI quintiles in women only ($P_{trend} = 0.02$). In a Norwegian population-based cohort, Engeland et al. (2006) observed no association in men, but a positive association in women; the estimated relative risk for BMI ≥ 30 kg/m^2 compared with the reference BMI of 18–24.9 kg/m^2 was 1.29 (95% CI, 1.13–1.46). In the Radiologic Technologists Study in the USA (Meinhold et al. (2010), no association was observed in men, whereas the association in women was also positive (RR, 1.74; 95% CI, 1.03–2.94). A systematic review, including 11 studies, estimated the relative risk of thyroid cancer for obese compared with normal-weight individuals to be 1.53 (95% CI, 0.89–2.64) in men and 1.57 (95% CI, 1.13–2.19) in women (Schmid et al., 2015). Another systematic review (Zhang et al., 2014), including 16 cohort studies, estimated an overall relative risk of thyroid cancer of 1.29 (95% CI, 1.20–1.37) in relation to obesity, with similar risk estimates in men and in women [the Working Group noted that this study provided limited information]. A pooled analysis by Kitahara et al. (2016) of 22 cohorts including 2296 incident cases found a modest positive association between baseline BMI and thyroid cancer risk overall, and the association was stronger in men (RR per 5 kg/m^2, 1.17; 95% CI, 1.06–1.28) than in women (RR per 5 kg/m^2, 1.04; 95% CI, 1.00–1.09).

A total of four studies assessed the association between body fatness and thyroid cancer risk by histological subtype (Engeland et al., 2006; Kabat et al., 2012; Rinaldi et al., 2012; Kitahara et al., 2016). The association with BMI was similar for the papillary and follicular histological subtypes.

In the only study that assessed BMI at younger ages (Kitahara et al., 2016), thyroid cancer risk was similar for BMI in young adulthood (RR per 5 kg/m^2, 1.13; 95% CI, 1.02–1.25) and BMI later in adult life (RR per 5 kg/m^2, 1.06; 95% CI, 1.02–1.10); a positive association was also reported with BMI gain in adult life (RR per 5 kg/m^2, 1.07; 95% CI, 1.00–1.15), after adjustment for BMI.

Two studies assessed anthropometric measures of body fatness other than BMI. In the pooled analysis by Kitahara et al. (2016), a weaker positive association was found with waist circumference (RR per 5 cm, 1.03; 95% CI, 1.01–1.05) than with BMI (RR per 5 kg/m^2, 1.06; 95% CI, 1.02–1.10). In the EPIC cohort (Rinaldi et al., 2012), associations with waist circumference and waist-to-hip ratio were similar to those observed with BMI.

(b) Case–control studies

Six informative case–control studies were identified that evaluated the association between BMI and thyroid cancer, including two larger pooled analyses (Table 2.2.19b). One study (Cléro et al., 2010) that combined two of the five studies but that did not offer additional information was excluded. In two studies, the total number of cases in men was less than 50 (Guignard et al., 2007; Suzuki et al., 2008); therefore, only data for women are reported. Two studies (Guignard et al., 2007; Xu et al., 2014) were restricted to papillary carcinomas.

Overall, there appeared to be an association between elevated current BMI (in adulthood) and the occurrence of thyroid cancer. There was some indication that this relationship was stronger in women than in men. [However, this may reflect small case numbers in the studies, especially in men, related to the low prevalence of the disease.] Two of the studies evaluated the associations between BMI at age 18 years (Brindel et al., 2009) and at age 20 years (Suzuki et al., 2008) and thyroid cancer, and noted some evidence for an association with thyroid cancer occurrence.

Table 2.2.19a Cohort studies of measures of body fatness and cancer of the thyroid

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Samanic et al. (2004) United States Veterans cohort USA 1969–1996	4 500 700 Men Incidence or mortality	Obesity Non-obese Obese Non-obese Obese	 White men: 811 64 Black men: 156 13	 1.00 1.40 (1.09–1.81) 1.00 1.92 (1.09–3.40)	Age, calendar year	Obesity defined as discharge diagnosis of obesity: ICD-8: 277; ICD-9: 278.0 Cancers diagnosed within 1 yr of obesity diagnoses were excluded from the study In White men only, higher risk of adrenal thyroid cancer
Oh et al. (2005) Korea National Health Insurance Corporation cohort Republic of Korea 1992–2002	781 283 Men	BMI < 18.5 18.5–22.9 23–24.9 25–26.9 27–29.9 ≥ 30 [P_{trend}]	 3 72 70 53 28 – 	 0.82 (0.20–3.34) 1.00 1.52 (1.07–2.14) 2.00 (1.38–2.89) 2.23 (1.40–3.55) – [< 0.001]	Age, smoking, alcohol consumption, exercise, family history of cancer, area of residence	
Engeland et al. (2006) Norwegian population-based cohort Norway 1972–2003	963 523 Men Incidence	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 2 412 322 42 	 0.47 (0.12–1.87) 1.00 1.12 (0.97–1.30) 1.14 (0.82–1.56) [0.005]	Age	Association was similar for age 50–74 yr
	1 037 424 Women Incidence	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 30 1187 710 341 	 0.68 (0.47–0.98) 1.00 1.08 (0.98–1.20) 1.29 (1.13–1.46) [0.001]	Age	Association was similar for age 20–49 yr and stronger for age 50–74 yr (57% increased risk). Somewhat stronger associations for follicular carcinoma vs papillary carcinoma
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1971–1999	362 552 Men Incidence	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 89 73 9 	 1.00 1.24 (0.90–1.71) 0.98 (0.49–1.96) [0.48]	Age, calendar year, smoking	

Table 2.2.19a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Song et al. (2008) Female public servants Republic of Korea 1994–2003	170 481 Women	BMI < 18.5 18.5–20.9 21–22.9 23–24.9 25–26.9 27–29.9 ≥ 30 per 1 kg/m^2	 3 40 89 115 93 59 11	 0.35 (0.11–1.10) 0.78 (0.52–1.16) 1.00 1.05 (0.79–1.41) 1.08 (0.80–1.47) 1.02 (0.72–1.45) 0.70 (0.35–1.40) 1.02 (0.98–1.04)	Age, height, smoking, alcohol consumption, exercise, SES	
Clavel-Chapelon et al. (2010) E3N cohort (female teachers) France 1990–2005	91 909 Women	BMI < 18.5 18.5–22 22–25 25–30 ≥ 30 [P_{trend}]	 3 99 129 62 24	 0.35 (0.11–1.12) 1.00 1.39 (1.07–1.81) 1.18 (0.86–1.63) 1.76 (1.12–2.76) [0.005]	Age, year of birth, history of benign thyroid conditions, smoking, iodine	Large body shape (Sörensen's silhouette) at baseline and at age 35–40 yr, but not at age 20–25 yr, associated with increased risk
Leitzmann et al. (2010) NIH-AARP cohort USA 1995–2003	484 326 Men and women Incidence	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 107 153 92	 1.00 1.27 (0.99–1.64) 1.39 (1.05–1.85) [0.007]	Age, sex, physical activity, race/ethnicity, education level, smoking, alcohol consumption, OC use	For WC, positive association in men but not in women. For waist-to-hip ratio, null association in either sex
Meinhold et al. (2010) Radiologic Technologists Study USA 1983–2006	21 207 Men Incidence	BMI 18.5–24.9 25–29.9 30–34.5 ≥ 35 [P_{trend}]	 13 15 9 2	 1.00 0.89 (0.42–1.90) 1.91 (0.80–4.56) 2.14 (0.60–7.67) [0.11]	Year of birth, smoking, radiation exposure, history of benign thyroid conditions	
	69 506 Women Incidence	BMI < 18.5 18.5–24.9 25–29.9 30–34.5 ≥ 35 [P_{trend}]	 6 144 44 26 16	 0.96 (0.42–2.18) 1.00 0.90 (0.64–1.27) 1.41 (0.92–2.16) 1.74 (1.03–2.94) [0.04]		

Table 2.2.19a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Almquist et al. (2011) 7 population-based cohorts Austria, Norway, and Sweden 2006–2016	289 866 Men Incidence	BMI, quintiles			Age, smoking	
		Q1	23	1.00		
		Q2	35	1.41 (0.83–2.39)		
		Q3	20	0.77 (0.42–1.41)		
		Q4	29	1.09 (0.63–1.89)		
		Q5	26	1.00 (0.57–1.77)		
		[P_{trend}]		[0.61]		
	288 834 Women Incidence	BMI, quintiles			Age, smoking	
		Q1	41	1.00		
		Q2	37	0.84 (0.54–1.31)		
		Q3	51	1.10 (0.73–1.68)		
		Q4	59	1.22 (0.81–1.84)		
		Q5	67	1.40 (0.93–2.09)		
		[P_{trend}]		[0.02]		
Kabat et al. (2012) Women's Health Initiative USA 1993–2011	144 319 Women Incidence	BMI			Age, age at first pregnancy, education level, smoking, alcohol consumption, exercise, history of benign thyroid conditions	Waist-to-hip ratio and weight change, null association. Similar associations for papillary carcinoma and follicular carcinoma
		< 25	92	1.00		
		25– < 30	99	1.06 (0.79–1.42)		
		30–35	71	1.40 (1.00–1.94)		
		≥ 35	32	0.97 (0.62–1.50)		
		[P_{trend}]		[0.39]		
Rinaldi et al. (2012) EPIC cohort Europe 1992–2009	343 765 Women Incidence	BMI			Age, centre, smoking	Only 58 incident cases identified in men (results not presented). Similar findings for papillary carcinoma only. WC and waist-to-hip ratio both positively associated with risk
		< 18.5	3	0.27 (0.09–0.84)		
		18.5–24.9	290	1.00		
		25–29.9	145	1.12 (0.91–1.38)		
		≥ 30	66	1.19 (0.89–1.59)		
		[P_{trend}]	4	[0.042]		
Bhaskaran et al. (2014) Clinical Practice Research Datalink United Kingdom 1987–2012	5.24 million Men and women Incidence	BMI per 5 kg/m^2	941	1.09 (1.00–1.19)	Age, sex, year, diabetes, alcohol consumption, smoking, SES	Similar association in never-smokers

Table 2.2.19a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Kitahara et al. (2016) Pooled analysis of 22 cohorts Asia, Australia, Europe, and North America 1979–2009	578 922 Men Incidence	BMI 15–18.4 18.5–24.9 25–29.9 ≥ 30 per 5 kg/m^2	 2 191 327 129	 0.66 (0.16–2.67) 1.0 1.23 (1.02–1.47) 1.35 (1.07–1.71) 1.17 (1.06–1.28)	Age, alcohol consumption, physical activity, race/ethnicity, marital status, education level, smoking	WC less associated. Similar associations for papillary carcinoma and follicular carcinoma
	774 373 Women Incidence	BMI 15–18.4 18.5–24.9 25–29.9 ≥ 30 per 5 kg/m^2 BMI at baseline per 5 kg/m^2 BMI in young adulthood per 5 kg/m^2 BMI gain in adult life per 5 kg/m^2	 29 995 615 356	 0.86 (0.59–1.24) 1.0 1.02 (0.93–1.14) 1.05 (0.92–1.19) 1.04 (1.00–1.09) 1.06 (1.02–1.10) 1.13 (1.02–1.25) 1.07 (1.00–1.15)		Similar associations for WC. Similar associations for papillary carcinoma and follicular carcinoma

BMI, body mass index (in kg/m^2); CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; OC, oral contraceptive; SES, socioeconomic status; WC, waist circumference; yr, year or years

Table 2.2.19b Case–control studies of measures of body fatness and cancer of the thyroid

Reference Study location Period	Total number of cases Sex Source of controls	Exposure categories	Exposed cases	Odds ratio (95% CI)	Adjustment for confounding	Comments
Dal Maso et al. (2000) Pooled analysis of 12 case–control studies China, Greece, Italy, Japan, Norway, Sweden, Switzerland, and USA	Men: 417 Women: 2056 Population and hospital	BMI, tertiles T1 T2 T3 [P_{trend}] BMI, tertiles T1 T2 T3 [P_{trend}]	NR NR 	Men: 1.0 0.8 (0.6–1.1) 1.0 (0.8–1.4) [0.71] Women: 1.0 1.0 (0.9–1.2) 1.2 (1.0–1.4) [0.04]	Age, history of radiation exposure	
Guignard et al. (2007) New Caledonia 1993–1999	Women: 279 Population	BMI <18.5 18.5–24.99 25.0–29.9 30.0–34.9 ≥ 35.0 [P_{trend}]	 7 80 87 61 41 	 0.99 (0.35–2.80) 1.00 1.18 (0.75–1.86) 1.92 (1.14–3.22) 1.85 (1.02–3.35) [0.01]	Age, reference year, ethnicity, smoking, number of full-term pregnancies, miscarriages, and irregular menstruations	Papillary and follicular carcinomas only The risk was greater in women aged > 50 yr Data for men NR because of the low number of cases
Suzuki et al. (2008) Japan 2001–2005	Women: 131 Hospital	Current BMI, tertiles 15.4–20.4 20.4–22.9 22.9–37.0 [P_{trend}] BMI at age 20 yr, tertiles 14.9–19.2 19.3–21.1 21.2–33.4 [P_{trend}]	 31 51 49 31 45 50 	 1.00 1.01 (0.59–1.74) 1.48 (0.86–2.57) [0.141] 1.00 1.42 (0.85–2.38) 1.18 (0.69–2.01) [0.526]	Age, smoking habits, drinking habits, regular exercise, family history of thyroid cancer, past history of thyroid diseases, total non-alcohol energy intake, referral pattern to the hospital, menopausal status, age at menarche, parity, HRT use	Papillary and follicular carcinomas only Null associations with BMI or weight change since age 20 yr Data for men NR because of the low number of cases

Table 2.2.19b (continued)

Reference Study location Period	Total number of cases Sex Source of controls	Exposure categories	Exposed cases	Odds ratio (95% CI)	Adjustment for confounding	Comments
Brindel et al. (2009) French Polynesia 1979–2004	Men: 23 Women: 177 Population; matched by date of birth and sex	BMI before diagnosis			Height, ethnicity, education level, smoking, interviewer, radiation to head or neck before age 15 yr In women, also adjusted for number of full-term pregnancies, menopausal status	
			Men:			
		< 18.5	0	–		
		18.5–24.9	7	1.0		
		25.0–29.9	11	5.9 (0.8–40.8)		
		30.0–34.9	2	3.1 (0.2–42.1)		
		≥ 35.0	3	3.2 (0.3–39.2)		
			Women:			
		< 18.5	7	0.8 (0.3–2.4)		
		18.5–24.9	74	1.0		
		25.0–29.9	44	3.5 (1.7–7.4)		
		30.0–34.9	25	1.2 (0.6–2.6)		
		≥ 35.0	27	3.0 (1.3–7.1)		
		BMI at age 18 yr				
			Men:			
		< 18.5	1	0.05 (0.0–1.0)		
		18.5–24.9	16	1.0		
		25.0–29.9	3	0.8 (0.1–6.3)		
		≥ 30.0	2	4.8 (0.2–113)		
			Women:			
		< 18.5	26	0.6 (0.3–1.2)		
		18.5–24.9	117	1.0		
		25.0–29.9	32	3.7 (1.6–8.4)		
		≥ 30.0	5	1.2 (0.3–5.2)		
Xu et al. (2014) Pooled analysis Germany, Italy, USA 1993–2013	Men: 557 Women: 1360 Hospital	BMI			Age, sex, race/ethnicity, study centre	Papillary carcinoma only. Body fat percentage (calculated by the formula of Deurenberg) also associated with increased risk, overall and by sex
		< 18.5	35	0.82 (0.52–1.30)		
		18.5–24.9	581	1.00		
		25–29.9	422	1.67 (1.38–2.03)		
		≥ 30	319	3.91 (3.02–5.05)		
		[P_{trend}]		[0.001]		

Table 2.2.19b (continued)

Reference Study location Period	Total number of cases Sex Source of controls	Exposure categories	Exposed cases	Odds ratio (95% CI)	Adjustment for confounding	Comments
Xhaard et al. (2015) France 2005–2010	Men and women: 761 Population	BMI	All:		Stratified by sex, region, and age and adjusted for education level, ethnicity, smoking status, family history of thyroid cancer, and number of pregnancies (in women only)	No differences in risk were observed when restricting to papillary carcinomas (n = 676 cases)
		< 18.5	52	1.00		
		18.5–24.9	496	1.15 (0.77–1.71)		
		25–29.9	138	1.23 (0.77–1.96)		
		≥ 30	72	1.56 (0.92–2.66)		
		[P_{trend}]		[0.09]		
		BMI	Women:			
		< 18.5	45	1.00		
		18.5–24.9	384	1.25 (0.82–1.90)		
		25–29.9	102	1.50 (0.89–2.51)		
		≥ 30	65	1.78 (1.01–3.14)		
		[P_{trend}]		[0.03]		

BMI, body mass index (in kg/m²); CI, confidence interval; HRT, hormone replacement therapy; NR, not reported; yr, year or years

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2.2.20 *Haematopoietic malignancies of lymphoid origin*

Haematopoietic malignancies are a heterogeneous group of cancers that arise from the blood, the bone marrow, and lymphoid tissue, and the cells of origin are either lymphoid or myeloid. Historically, haematopoietic cancers were grouped into five major categories: Hodgkin lymphoma, non-Hodgkin lymphoma (NHL), multiple myeloma (also referred to as plasma cell myeloma), acute leukaemia, and chronic leukaemia. However, these historical groupings do not reflect the current understanding of etiology and pathogenesis or current clinical practice. In 2001, the World Health Organization (WHO) introduced a new classification system (Jaffe et al., 2001), which was subsequently updated (Swerdlow et al., 2008) and is considered the reference standard for classification of these malignancies. The WHO classification has been adopted worldwide, and the terminology has been incorporated into the third edition of the International Classification of Diseases for Oncology (ICD-O-3) (WHO, 2013).

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and cancers of the haematopoietic system (e.g. NHL, multiple myeloma) was *inadequate*. In the current review are included epidemiological studies of BMI, weight, or waist circumference at baseline in relation to risk of the more common types of haematopoietic malignancies for which the body of evidence was substantial enough to review. These include Hodgkin lymphoma, NHL, B-cell lymphoma overall, chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, multiple myeloma, T-cell lymphoma, leukaemia overall, acute myeloid leukaemia (AML), and chronic myeloid leukaemia (CML). Also included are findings from prospective studies with at least 50 cases for any specific subtype, meta-analyses or pooled analyses from prospective and case–control studies, and findings from case–control studies with at least 50 cases that were not included in a meta-analysis or pooled analysis. For malignancies for which there was evidence suggesting a relationship between BMI or weight at baseline and risk, the Working Group also weighed into their evaluation studies that assessed weight change and weight during young adulthood in relation to risk. Not all studies separated the haematopoietic cancers according to the current WHO classification system. Therefore, findings are presented about relationships between BMI and both individual haematological cancers and groups of cancers.

Table 2.2.20a and Table 2.2.20b (both web only, available at: http://publications.iarc.fr/570) present data for cohort and case–control studies, respectively, for subsites with *inadequate* evidence; Table 2.2.20c and Table 2.2.20d present the corresponding studies for subsites with *sufficient* or *limited* evidence.

(a) Hodgkin lymphoma

There are at least four individual prospective studies and one meta-analysis of BMI at baseline in relation to incidence of Hodgkin lymphoma (Table 2.2.20a, web only, available at: http://publications.iarc.fr/570). Results from three prospective studies in men (i.e. the United States Veterans cohort, the NIH-AARP cohort, and the Swedish Construction Worker cohort) showed increased risks (Samanic et al., 2004, 2006; Lim et al., 2007), none of which were statistically significant, whereas a Norwegian cohort study found a positive association in women but not in men (Engeland et al., 2007). [Most studies had limited statistical power, particularly at the high end of the BMI categories.] However, in the meta-analysis of five studies, obesity was

associated with a statistically significant 41% higher risk of Hodgkin lymphoma compared with normal BMI (Larsson & Wolk, 2011).

Only three case–control studies with at least 50 cases have evaluated the relationship between BMI and risk of Hodgkin lymphoma (Table 2.2.20b, web only, available at: http://publications.iarc.fr/570). The largest study, including 618 cases from the Scandinavian Lymphoma Etiology Study and 3187 population controls, did not find a relationship between BMI and risk of Hodgkin lymphoma in individuals younger or older than 45 years, assessed separately because of the bimodal distribution of the disease (Chang et al., 2005). A second large study, including 567 cases and 697 controls, also did not find a relationship between BMI and risk of Hodgkin lymphoma in subgroups defined by sex and age (Li et al., 2013). However, a smaller study of 216 cases and 216 matched controls, which considered BMI 5 years before cancer diagnosis, found an increased risk of Hodgkin lymphoma with BMI ≥ 30 kg/m^2 compared with normal BMI in men, but not in women (Willett & Roman, 2006).

(b) Non-Hodgkin lymphoma

There are at least 21 individual prospective studies and 4 meta-analyses or pooled analyses of BMI and/or weight at baseline in relation to NHL (Table 2.2.20a, web only, available at: http://publications.iarc.fr/570). There were no associations of either BMI or weight with NHL incidence or mortality in 12 individual prospective studies (Samanic et al., 2004, 2006; Fujino et al., 2007; Maskarinec et al., 2008; Song et al., 2008; Andreotti et al., 2010; De Roos et al., 2010; Kanda et al., 2010; Hemminki et al., 2011; Kabat et al., 2012; Bertrand et al., 2013; Bhaskaran et al., 2014). The other nine studies found positive associations in men and/or women (Calle et al., 2003; Oh et al., 2005; Rapp et al., 2005; Chiu et al., 2006; Engeland et al., 2007; Lim et al., 2007; Reeves et al., 2007; Troy et al., 2010; Chu et al., 2011). Three meta-analyses showed a positive association between BMI and NHL incidence and/or mortality (Larsson & Wolk, 2007a, 2011; Renehan et al., 2008), whereas one pooled analysis found no association (Whitlock, et al., 2009). [The inconsistent evidence from individual prospective studies and meta-analyses may be due to the variation in histological subtypes included in a classification of NHL.]

No association between waist circumference and NHL incidence was seen in the Women's Health Initiative in the USA (Kabat et al., 2012). However, in a cohort in Taiwan, China, high abdominal obesity (waist circumference ≥ 90 cm in men and ≥ 80 cm in women) was associated with an 86% higher risk of fatal NHL compared with lower waist circumference (Chu et al., 2011).

A total of 11 hospital-based or population-based case–control studies have evaluated the relationship between BMI and risk of any NHL (Table 2.2.20b, web only, available at: http://publications.iarc.fr/570). A meta-analysis of six of these reports published in 2004 and 2005 (Pan et al., 2004; Skibola et al., 2004; Bosetti et al., 2005; Cerhan et al., 2005; Chang et al., 2005; Willett et al., 2005) reported a relative risk of NHL of 1.22 (95% CI, 1.00–1.50) in individuals with BMI ≥ 30 kg/m^2 (Larsson & Wolk, 2007a). A subsequent pooled analysis from the InterLymph Consortium included data from 10 000 cases of NHL and 16 000 controls drawn from 18 case–control studies identified through the International Lymphoma Epidemiology Consortium (Willett et al., 2008). That study did not find a relationship between BMI and risk of NHL, with a relative risk of NHL of 0.84 (95% CI, 0.72–0.99) in individuals with BMI of 30–39.9 kg/m^2 and a relative risk of 0.63 (95% CI, 0.40–0.99) in those with BMI ≥ 40 kg/m^2.

(c) B-cell lymphoma

The association between excess body fatness and the incidence of B-cell lymphoma was examined in three individual prospective

studies (Table 2.2.20a, web only, available at: http://publications.iarc.fr/570) [notably, under the current classification, this includes all B-cell malignancies previously included under NHL]. Although no association was found with BMI and/or weight in men or in women in the EPIC cohort (Britton et al., 2008), there were statistically significant positive trends with weight in the California Teachers Study (Lu et al., 2009) and with BMI in the Cancer Prevention Study II Nutrition Cohort (Patel et al., 2013).

In the one study that assessed waist circumference, there was no association with the incidence of B-cell lymphoma in either men or women (Britton et al., 2008).

(d) Subtypes of B-cell lymphoma

(i) Chronic lymphocytic leukaemia/small lymphocytic lymphoma

Most of the individual prospective studies (Table 2.2.20a, web only, available at: http://publications.iarc.fr/570) found no associations of BMI and/or weight at baseline with the incidence of CLL or CLL/SLL (Ross et al., 2004; Samanic et al., 2006; Engeland et al., 2007; Lim et al., 2007; Lu et al., 2009; Pylypchuk et al., 2009; Kabat et al., 2012; Bertrand et al., 2013; Patel et al., 2013; Saberi Hosnijeh et al., 2013). However, in the United States Veterans study, the largest individual prospective study, the risk of CLL was 30% higher in obese White men and 72% higher in obese Black men compared with non-obese men (Samanic et al., 2004). In the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial in the USA, baseline weight, but not BMI, was positively associated with risk ($P_{trend} < 0.215$) (Troy et al., 2010). Although an earlier meta-analysis of three cohort studies suggested a 25% higher risk of CLL for obesity versus normal weight (Larsson & Wolk, 2008), an updated meta-analysis of six prospective studies found no association between BMI as a continuous measure and incidence of CLL/SLL (Larsson & Wolk, 2011).

No association between waist circumference and CLL/SLL incidence was found in the three studies that examined this relationship (Ross et al., 2004; Kabat et al., 2012; Saberi Hosnijeh et al., 2013).

Five case–control studies with at least 50 cases assessed the relationship between BMI and risk of CLL/SLL (Table 2.2.20b, web only, available at: http://publications.iarc.fr/570) and found no association between BMI and CLL/SLL risk (Chang et al., 2005; Pan et al., 2005; Morton et al., 2008; Chen et al., 2011; Kelly et al., 2012).

(ii) Diffuse large B-cell lymphoma

Associations of baseline BMI and/or weight with risk of DLBCL have been examined in at least nine individual prospective studies and two meta-analyses (Table 2.2.20c). Most individual prospective studies found no evidence of an association (Lim et al., 2007; Britton et al., 2008; Maskarinec et al., 2008; Lu et al., 2009; Pylypchuk et al., 2009; Kabat et al., 2012; Bertrand et al., 2013). However, two large studies in the USA did report statistically significant trends between baseline weight (Troy et al., 2010) or BMI (Patel et al., 2013) and DLBCL incidence. Both meta-analyses also showed statistically significant positive associations. One meta-analysis reported a relative risk per 5 kg/m^2 increase of 1.13 (95% CI, 1.02–1.26) (Larsson & Wolk, 2011). In the other meta-analysis, both overweight and obesity in men and women were associated with increased risk (Castillo et al., 2014).

Six individual studies assessed the association between BMI or weight in early adulthood and incidence of DLBCL. In the two large studies in the USA, there were statistically significant positive associations of weight at age 20 years ($P_{trend} = 0.013$) (Troy et al., 2010) and of young adult BMI in men and women combined ($P_{trend} = 0.02$) (Bertrand et al., 2013) with risk of DLBCL. However, in none of the four other studies was BMI and/or body weight at age 18 years (Lu et al., 2009; Patel et al., 2013), at

age 20 years (Pylypchuk et al., 2009), or at age 21 years (Maskarinec et al., 2008) associated with DLBCL incidence. Similarly, adult weight gain was not associated with risk of DLBCL in any of the studies that examined this association (Maskarinec et al., 2008; Troy et al., 2010; Patel et al., 2013).

In the EPIC cohort, there was a 2-fold (RR, 2.03; 95% CI, 0.96–4.28) higher incidence of DLBCL for waist circumference ≥ 102 cm versus < 102 cm in men (based on only 21 cases in the group with high waist circumference), and no association in women (Britton et al., 2008). Similarly, there was no association between waist circumference and risk of DLBCL in the Women's Health Initiative in the USA (Kabat et al., 2012).

A pooled analysis of 19 case–control studies from the InterLymph Consortium of 4667 cases of DLBCL and 22 639 controls found a significant positive association between risk of DLBCL and young adult BMI, but not usual adult BMI (Cerhan et al., 2014). A case–control study from the National Enhanced Cancer Surveillance System in Canada, including 419 cases of DLBCL, found an odds ratio for individuals with BMI ≥ 30 kg/m^2 of 1.35 (95% CI, 0.99–1.83) (Pan et al., 2005). Another case–control study, by Chen et al., (2011), including 245 cases of DLBCL, did not find a relationship between BMI and risk of DLBCL (Table 2.2.20d).

(iii) Follicular lymphoma

None of the nine individual prospective studies (Lim et al., 2007; Britton et al., 2008; Maskarinec et al., 2008; Lu et al., 2009; Pylypchuk et al., 2009; Troy et al., 2010; Kabat et al., 2012; Bertrand et al., 2013; Patel et al., 2013) or the one meta-analysis (Larsson & Wolk, 2011) showed any evidence of an association between BMI and/or weight and the incidence of follicular lymphoma (Table 2.2.20a, web only, available at: http://publications.iarc.fr/570).

Waist circumference was also not associated with the incidence of follicular lymphoma in the two studies that examined this relationship (Britton et al., 2008; Kabat et al., 2012).

The largest study evaluating the association between BMI and follicular lymphoma (Table 2.2.20b, web only, available at: http://publications.iarc.fr/570) was a pooled analysis of 3530 cases and 22 639 population controls from 19 case–control studies in the InterLymph Consortium, which found no relationship between BMI and risk of follicular lymphoma (Linet et al., 2014). Two additional case–control studies not included in the pooled analysis also found no association between adult BMI and risk of follicular lymphoma (Pan et al., 2005; Chen et al., 2011).

Therefore, the relationship between BMI and risk of NHL varies by subtype, with a positive association seen in some studies limited to the risk of DLBCL, but not in studies assessing the risk of any NHL or of follicular lymphoma.

(e) Multiple myeloma

In the individual prospective studies that examined the association of baseline BMI and/or weight with multiple myeloma incidence or mortality (Table 2.2.20c), most found positive associations for at least one measure of excess body fatness at baseline (Calle et al., 2003; Samanic et al., 2004; Blair et al., 2005; Birmann et al., 2007; Engeland et al., 2007; Fujino et al., 2007; Reeves et al., 2007; Troy et al., 2010; Hofmann et al., 2013). In particular, a positive association was observed in the largest studies. In the United States Veterans cohort of more than 4 million men, the risk of multiple myeloma was 22% higher in obese White men and 26% higher in obese Black men compared with non-obese men (Samanic et al., 2004). Similarly, the Million Women Study in the United Kingdom found positive associations between BMI and multiple myeloma incidence and mortality (31% and 56% increase, respectively, per 10 kg/m^2) (Reeves et al., 2007). In a Norwegian cohort study of more than 2 million men and women whose height and weight were measured at baseline in 1963, there

were statistically significant dose-related positive associations between BMI and risk of multiple myeloma in men (RR, 1.14 for overweight and 1.28 for obesity vs normal BMI; $P_{trend} < 0.001$) and in women (RR, 1.12 for overweight, 1.23 for grade I, 1.42 for grade II, and 1.57 for grade III obesity vs normal BMI; $P_{trend} < 0.001$) (Engeland et al., 2007). One study found an inverse association (Samanic et al., 2006), and several studies found no association (Oh et al., 2005; Fernberg et al., 2007; Pylypchuk et al., 2009; De Roos et al., 2010; Lu et al., 2010; Kanda et al., 2010; Patel et al., 2013; Bhaskaran et al., 2014).

Several meta-analyses or pooled analyses of excess body fatness in relation to multiple myeloma incidence and/or mortality have been conducted (Larsson & Wolk, 2007b; Renehan et al., 2008; Parr et al., 2010; Wallin & Larsson, 2011; Teras et al., 2014). No association between BMI and multiple myeloma mortality was found in the Asia-Pacific Cohort Study Collaboration (Parr et al., 2010). However, in the meta-analysis by Wallin & Larsson (2011), which included studies worldwide, overweight and obesity were associated with a statistically significantly increased risk of multiple myeloma incidence (RR, 1.12 for overweight and 1.21 for obesity, based on 15 studies) and mortality (RR, 1.15 for overweight and 1.54 for obesity, based on 5 studies). The two earlier meta-analyses (Larsson & Wolk, 2007b; Renehan et al., 2008) found statistically significant positive associations of a similar magnitude. Consistent with these findings, in a pooled analysis of data from 20 prospective studies (Teras et al., 2014), there was a statistically significant positive association between BMI and multiple myeloma mortality (RR per 5 kg/m^2 increase in BMI, 1.09).

Given the observed associations between baseline BMI and risk of multiple myeloma, associations with young adult BMI and with BMI change were also examined. Several studies found no association between young adult BMI and risk of multiple myeloma (Fujino et al., 2007; Pylypchuk et al., 2009; De Roos et al., 2010; Lu et al., 2010; Patel et al., 2013), whereas in two large studies young adult BMI was positively associated with risk (Troy et al., 2010; Hofmann et al., 2013). In the large pooled analysis by Teras et al. (2014) there was a statistically significant positive association between increasing levels of young adult BMI (beginning in the overweight category) and multiple myeloma mortality, although there was no association for change in BMI during adulthood.

High waist circumference was associated with increased multiple myeloma incidence in one prospective study of postmenopausal women (Blair et al., 2005), but not in two other studies (Britton et al., 2008; Lu et al., 2010). In the large pooled analysis by Teras et al. (2014), there was a statistically significant positive association between waist circumference and multiple myeloma mortality in men and women combined (RR per 5 cm increase, 1.06).

Five case–control studies have evaluated the relationship between BMI and the risk of multiple myeloma, four of which were included in a meta-analysis (Larsson & Wolk, 2007b; Table 2.2.20d). An increased risk of multiple myeloma was reported in individuals who were overweight (RR, 1.43; 95% CI, 1.23–1.68) and those who were obese (RR, 1.82; 95% CI, 1.47–2.26). One additional study reported no significant association (Wang et al., 2013).

(f) T-cell lymphoma

In the Cancer Prevention Study II Nutrition Cohort (Table 2.2.20a, web only, available at: http://publications.iarc.fr/570), there was a positive association between BMI and the incidence of T-cell lymphoma ($P_{trend} = 0.013$) (Patel et al., 2013). However, in two European cohort studies there was no association (Lukanova et al., 2006; Lim et al., 2007). In the Cancer Prevention Study II Nutrition Cohort, BMI at age 18 years was not associated with the incidence of T-cell lymphoma (Patel et al., 2013).

Table 2.2.20c Cohort studies of measures of body fatness and haematopoietic malignancies of lymphoid origin with *sufficient* or *limited* evidence

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Diffuse large B-cell lymphoma							
Lim et al. (2007) NIH-AARP cohort USA 1995–2003	473 984 Men and women Incidence	DLBCL ICD-O-2: 9680–9684, 9688, 9710–9712, 9715	BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 119 141 61 21	 1.00 0.92 (0.72–1.18) 1.10 (0.81–1.51) 1.17 (0.73–1.88) [0.42]	Age, ethnicity, education level, alcohol intake, cigarette smoking, height, physical activity	
Britton et al. (2008) EPIC cohort 10 European countries 1993–1998	141 425 Men Incidence	DLBCL	BMI < 25 25–29.9 ≥ 30 [P_{trend}] Weight (kg) < 72.7 72.7–79.8 79.9–87.7 ≥ 87.8 [P_{trend}] WC (cm) < 102 ≥ 102	 24 37 10 19 13 20 19 44 21	 1.00 0.83 (0.39–1.76) 0.94 (0.56–1.59) [0.63] 1.00 0.59 (0.29–1.20) 0.90 (0.46–1.74) 0.86 (0.42–1.77) [1.00] 1.00 2.03 (0.96–4.28)	Age, study centre	Also examined height, hip circumference, and waist-to-hip ratio
	230 558 Women Incidence	DLBCL	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 30 31 12	 1.00 1.27 (0.63–2.55) 1.54 (0.92–2.57) [0.28]	Age, study centre	Also examined height, hip circumference, and waist-to-hip ratio

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Britton et al. (2008) (cont.)			Weight (kg)				
			< 72.7	14	1.00		
			72.7–79.8	12	0.78 (0.35–1.69)		
			79.9–87.7	21	1.32 (0.66–2.68)		
			≥ 87.8	26	1.62 (0.81–3.25)		
			[P_{trend}]		[0.06]		
			WC (cm)				
			< 88	47	1.00		
			≥ 88	21	0.88 (0.42–1.85)		
Maskarinec et al. (2008) Multiethnic Cohort 1993–2002	87 079 Men Incidence	DLBCL ICD-O-3: 9675, 9680, 9684	BMI at baseline			Age, ethnicity, education level, alcohol consumption	
			< 22.5	23	0.65 (0.35–1.21)		
			22.5–24.9	44	1.00		
			25.0–29.9	60	0.90 (0.56–1.43)		
			≥ 30.0	23	0.78 (0.40–1.52)		
			[P_{trend}]		[0.69]		
			BMI at age 21 yr				
			< 18.5	14	0.56 (0.27–1.15)		
			18.5–24.9	105	1.00		
			25.0–29.9	17	0.78 (0.41–1.48)		
			≥ 30.0	5	1.03 (0.36–2.91)		
			[P_{trend}]		[0.51]		
			Weight (lb) at baseline				
			< 152.0	47	1.00		
			152.0–170.0	37	1.97 (1.16–3.36)		
			170.1–192.0	32	1.36 (0.75–2.49)		
			> 192.0	35	1.87 (0.95–3.68)		
			[P_{trend}]		[0.12]		
			Weight (lb) at age 21 yr				
			< 130.0	43	1.00		
			130.0–145.0	34	0.87 (0.50–1.53)		
			145.1–165.0	38	1.24 (0.64–2.41)		
			> 165.0	27	1.26 (0.63–2.50)		
			[P_{trend}]		[0.33]		

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Maskarinec et al. (2008) (cont.)			Annual weight change (lb)				
			0 or loss	32	1.00		
			≤ 1	89	1.07 (0.62–1.86)		
			> 1	31	1.14 (0.56–2.34)		
			[P_{trend}]		[0.69]		
	105 972 Women Incidence	DLBCL ICD-O-3: 9675, 9680, 9684	BMI at baseline			Age, ethnicity, education level, alcohol consumption, age at first birth	
			< 22.5	27	1.41 (0.66–3.00)		
			22.5–24.9	30	1.00		
			25.0–29.9	43	1.06 (0.58–1.96)		
			≥ 30.0	28	1.45 (0.75–2.82)		
			[P_{trend}]		[0.80]		
			BMI at age 21 yr				
			< 18.5	16	1.02 (0.50–2.10)		
			18.5–24.9	91	1.00		
			25.0–29.9	11	1.08 (0.50–2.33)		
			≥ 30.0	4	0.94 (0.25–3.55)		
			[P_{trend}]		[1.00]		
			Weight (lb) at baseline				
			< 125.0	26	1.00		
			125.0–143.0	38	0.74 (0.40–1.38)		
			143.1–167.0	35	1.35 (0.67–2.75)		
			> 167.0	30	1.20 (0.57–2.52)		
			[P_{trend}]		[0.40]		
			Weight (lb) at age 21 yr				
			< 105.0	22	1.00		
			105.0–118.0	34	0.70 (0.35–1.41)		
			118.1–127.0	34	0.97 (0.48–1.96)		
			> 127.0	33	1.10 (0.53–2.29)		
			[P_{trend}]		[0.44]		
			Annual weight change (lb)				
			0 or loss	19	1.00		
			≤ 1	85	0.56 (0.21–1.55)		
			> 1	28	0.93 (0.34–2.54)		
			[P_{trend}]		[0.85]		

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Lu et al. (2009) California Teachers Study USA 1995–2007	121 216 Women Incidence	DLBCL	BMI at baseline			Weight, height, age at menarche, and physical activity	Also included results for height and physical activity
			< 20	17	1.42 (0.83–2.42)		
			20–24.9	64	1.00		
			25–29.9	41	1.07 (0.72–1.59)		
			≥ 30	26	1.37 (0.86–2.16)		
			[P_{trend}]		[0.50]		
			BMI at age 18 yr				
			< 19.5	37	0.98 (0.62–1.56)		
			19.5–20.7	36	1.00		
			20.8–22.4	32	0.90 (0.56–1.45)		
			> 22.4	43	1.23 (0.79–1.92)		
			[P_{trend}]		[0.30]		
			Weight (kg) at baseline				
			< 56.7	33	1.24 (0.76–2.03)		
			56.7– < 63.5	33	1.00		
			63.5– < 73.0	40	0.90 (0.57–1.43)		
			≥ 73.0	42	1.08 (0.68–1.72)		
			[P_{trend}]		[0.81]		
			Weight (kg) at age 18 yr				
			< 52.6	33	0.88 (0.54–1.41)		
			52.6– < 57.2	45	1.00		
			57.2– < 61.7	30	1.16 (0.72–1.84)		
			≥ 61.7	40	1.23 (0.79–1.92)		
			[P_{trend}]		[0.19]		
Pylypchuk et al. (2009) Netherlands Cohort Study on Diet and Cancer The Netherlands 1986–1999	5000 Men and women Incidence	DLBCL ICD-O-3: 9675, 9680, 9684	BMI			Age, sex	Case–cohort design
			< 18.5	3	1.91 (0.58–6.30)		
			18.5–24.9	112	1.00		
			25–29.9	101	1.16 (0.88–1.53)		
			≥ 30	8	0.62 (0.30–1.30)		
			[P_{trend}]		[0.77]		
			per 4 kg/m^2		0.92 (0.77–1.10)		

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Pylypchuk et al. (2009) (cont.)			BMI at age 20 yr				
			< 20	39	0.96 (0.61–1.50)		
			20–21.4	43	1.00		
			21.5–22.9	41	0.99 (0.64–1.54)		
			23–24.9	43	1.35 (0.88–2.10)		
			≥ 25	16	1.29 (0.71–2.35)		
			[P_{trend}]		[0.12]		
			per 4 kg/m²		1.20 (0.98–1.47)		
Troy et al. (2010) PLCO Trial USA 1993–2006	142 982 Men and women Incidence	DLBCL	BMI at baseline			Age, race/ ethnicity, education level	
			< 18.5	4	–		
			18.5–24.9	58	1.00		
			25–29.9	87	1.07 (0.76–1.50)		
			≥ 30	63	1.58 (1.10–2.27)		
			[P_{trend}]		[0.056]		
			BMI at age 20 yr				
			< 18.5	17	1.22 (0.74–2.02)		
			18.5–24.9	157	1.00		
			25–29.9	35	1.19 (0.82–1.73)		
			≥ 30	1	–		
			[P_{trend}]		[0.230]		
			Weight change (kg) per 10 yr				
			Loss	10	0.70 (0.35–1.39)		
			Gain 0–2	53	1.00		
			Gain 2.1–4	66	1.13 (0.78–1.63)		
			Gain 4.1–6	46	1.32 (0.88–1.97)		
			Gain ≥ 6	37	1.41 (0.91–2.18)		
			[P_{trend}]		[0.114]		
			Weight (kg) at baseline, quartiles (sex-specific)				
			Men: Women:				
			< 77.4 < 61.5	51	1.00		
			77.4–85.5 61.5–70.0	46	1.05 (0.71–1.57)		
			85.6–95.5 70.1–80.0	54	1.18 (0.81–1.74)		
			> 95.5 > 80.0	63	1.63 (1.12–2.37)		
			[P_{trend}]		[< 0.01]		

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Troy et al. (2010) (cont.)			Weight (kg) at age 20 yr, quartiles (sex-specific) Men: / Women: < 64.2 / < 51.9 64.2–72.7 / 51.9–54.5 72.8–79.5 / 54.6–59.1 > 79.5 / > 59.1 [P_{trend}]	 40 41 66 65	 1.00 1.26 (0.81–1.95) 1.46 (0.98–2.17) 1.67 (1.12–2.50) [0.013]		
Larsson & Wolk (2011) Meta-analysis Multiple locations 1999–2010	6 studies Men and women Incidence	DLBCL	BMI per 5 kg/m²	NR	 1.13 (1.02–1.26)		
Kabat et al. (2012) Women's Health Initiative USA 1993–2009	158 975 Women Incidence	DLBCL ICD-O-3: 9678–9680, 9684	BMI at baseline < 25 25– < 30 30– < 35 ≥ 35 [P_{trend}] Weight (kg) at baseline < 62.0 62.0– < 70.4 70.4– < 81.6 ≥ 81.6 [P_{trend}] WC (cm) at baseline < 76.1 76.1– < 84.6 84.6– < 95.0 > 95.0 [P_{trend}]	 99 115 55 33 73 79 80 70 70 80 68 84	 1.00 1.23 (0.93–1.62) 1.11 (0.78–1.58) 1.30 (0.85–1.99) [0.25] 1.00 1.09 (0.78–1.51) 1.11 (0.79–1.56) 1.05 (0.72–1.52) [0.77] 1.00 1.13 (0.82–1.58) 1.02 (0.72–1.44) 1.28 (0.91–1.81) [0.25]	Age, smoking, alcohol consumption, education level, ethnicity, physical activity, energy intake, substudy	Also included estimates for height, hip circumference, waist-to-hip ratio, and weight/BMI at ages 18 yr, 35 yr, and 50 yr

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Bertrand et al. (2013) Nurses' Health Study and Health Professionals Follow-up Study USA 1976–2008	163 184 Men and women Incidence	DLBCL	Adult BMI per 5 kg/m^2 [P_{trend}]	[261]	 1.10 (0.91–1.33) [0.31]	Age, height, smoking, physical activity, race	
			Young adult BMI per 5 kg/m^2 [P_{trend}]	[241]	 1.29 (1.05–1.57) [0.02]		
	46 390 Men Incidence	DLBCL	Adult BMI 15–22.9 23–24.9 25–26.9 27–29.9 30–45 per 5 kg/m^2 [P_{trend}]	 11 25 23 17 10	 1.00 1.57 (0.75–3.28) 1.58 (0.75–3.34) 1.65 (0.75–3.64) 2.18 (0.88–5.40) 1.30 (0.92–1.82) [0.14]	Age, height, smoking, physical activity, race	
			Young adult BMI 15–18.4 18.5–22.9 23–24.9 25–29.9 30–45 per 5 kg/m^2 [P_{trend}]	 4 40 19 17 4	 1.36 (0.46–4.02) 1.00 0.94 (0.54–1.64) 1.16 (0.65–2.08) 2.70 (0.93–7.86) 1.29 (0.89–1.88) [0.18]		
	116 794 Women Incidence	DLBCL	Adult BMI 15–22.9 23–24.9 25–26.9 27–29.9 30–45 per 5 kg/m^2 [P_{trend}]	 60 38 31 23 33	 1.00 0.97 (0.64–1.46) 1.06 (0.69–1.65) 0.85 (0.52–1.38) 1.36 (0.88–2.10) 1.04 (0.88–1.23) [0.65]	Age, height, smoking, physical activity, race	

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Bertrand et al. (2013) (cont.)			Young adult BMI				
			15–18.4	14	0.71 (0.40–1.24)		
			18.5–22.9	104	1.00		
			23–24.9	18	0.99 (0.60–1.64)		
			25–29.9	17	1.26 (0.75–2.11)		
			30–45	4	1.39 (0.51–3.81)		
			per 5 kg/m^2		1.28 (1.01–1.63)		
			[P_{trend}]		[0.04]		
Patel et al. (2013) Cancer Prevention Study II Nutrition Cohort USA 1992–2007	152 423 Men and women Incidence	DLBCL	BMI at baseline			Age, sex, family history of haematopoietic cancer, education level, smoking status, physical activity, alcohol consumption	
			< 18.5	1	0.28 (0.04–1.97)		
			18.5– < 25	159	1.00		
			25– < 30	199	1.30 (1.05–1.61)		
			≥ 30	85	1.62 (1.23–2.12)		
			[P_{trend}]		[0.0001]		
			BMI at age 18 yr				
			< 18.5	52	0.86 (0.64–1.17)		
			18.5– < 22.5	245	1.00		
			22.5– < 25	88	1.07 (0.83–1.38)		
			25– < 30	44	1.01 (0.72–1.42)		
			≥ 30	7	1.30 (0.60–2.80)		
			[P_{trend}]		[0.32]		
			Adult weight change (lb)				
			Loss > 5	11	0.60 (0.32–1.10)		
			Loss 5 to gain 20	147	1.00		
			Gain 21–40	142	0.97 (0.77–1.22)		
			Gain 41–60	83	0.97 (0.74–1.28)		
			Gain > 60	52	1.11 (0.80–1.54)		
			[P_{trend}]		[0.25]		

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Castillo et al. (2014) Meta-analysis of 10 cohorts, 6 case–control	NR Men and women Incidence	DLBCL	BMI Overweight Obese		 1.14 (1.04–1.24) 1.29 (1.16–1.43)		
	NR Men Incidence	DLBCL	BMI Overweight Obese		 1.27 (1.09–1.47) 1.40 (1.00–1.95)		
	NR Women Incidence	DLBCL	BMI Overweight Obese		 1.22 (1.07–1.38) 1.34 (1.16–1.54)		
Multiple myeloma							
Calle et al. (2003) Cancer Prevention Study II USA 1982–1998	495 477 Women Mortality	Multiple myeloma	BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 341 187 72 20	 1.00 1.12 (0.93–1.34) 1.47 (1.13–1.91) 1.44 (0.91–2.28) [0.004]	Age, race, education level, smoking, physical activity, alcohol consumption, marital status, aspirin use, fat and vegetable consumption	
	404 576 Men Mortality		BMI 18.5–24.9 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 259 368 70 11	 1.00 1.18 (1.01–1.39) 1.44 (1.10–1.89) 1.71 (0.93–3.14) [0.002]		
Samanic et al. (2004) United States Veterans cohort USA 1969–1996	4 500 700 Men Incidence	Multiple myeloma ICD-9: 203	Obesity Non-obese Obese Non-obese Obese	White men: 2817 204 Black men: 1509 89	 1.00 1.22 (1.05–1.40) 1.00 1.26 (1.02–1.56)	Age, calendar year	Obesity defined as discharge diagnosis of obesity: ICD-8: 277; ICD-9: 278.0
Blair et al. (2005) Iowa Women's Health Study USA 1986–2001	37 083 Women Incidence	Multiple myeloma	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 30 37 28	 1.0 1.3 (0.78–2.0) 1.5 (0.92–2.6) [0.10]	Age	Also included analyses of height, waist-to-hip ratio, and hip circumference

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Blair et al. (2005) (cont.)			Weight (lb) < 138 138–160 ≥ 161 [P_{trend}] WC (in) < 31.75 31.76–36.25 ≥ 36.26 [P_{trend}]	 19 40 36 19 37 39 	 1.0 2.0 (1.1–3.4) 1.9 (1.1–3.4) [0.04] 1.0 1.9 (1.1–3.2) 2.0 (1.1–3.5) [0.02]		
Oh et al. (2005) Korea National Health Insurance Corporation Republic of Korea 1992–2001	781 283 Men Incidence	Multiple myeloma	BMI < 18.5 18.5–22.9 23–24.9 25–26.9 27–29.9 ≥ 30 [P_{trend}]	 2 36 45 14 6 0 	 1.19 (0.29–4.96) 1.00 1.72 (1.11–2.68) 0.96 (0.51–1.77) 0.98 (0.30–3.32) – [0.61]	Age, smoking, alcohol intake, physical activity, family history of cancer, urban/ rural residence	
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1958–1999	362 552 Men Incidence	Multiple myeloma ICD-7: 203	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 231 201 20 	 1.00 0.96 (0.79–1.16) 0.58 (0.37–0.93) [0.06]	Attained age, calendar year, smoking	
Birmann et al. (2007) Nurses' Health Study and Health Professionals Follow-up Study combined USA 1980–2002	136 623 Men and women Incidence	Multiple myeloma	BMI < 22 22–24.9 25–29.9 ≥ 30 [P_{trend}]	 28 64 84 39 	 1.0 1.2 (0.8–1.9) 1.3 (0.9–2.0) 1.5 (0.9–2.5) [0.11]	Age, sex, physical activity, cohort	

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Birmann et al. (2007) (cont.) Nurses' Health Study	89 663 Women Incidence		BMI < 22 22–24.9 25–29.9 ≥ 30 [P_{trend}]	 21 32 53 23	 1.0 1.1 (0.7–2.0) 1.6 (1.0–2.7) 1.2 (0.7–2.2) [0.43]	Age, physical activity	
Health Professionals Follow-up Study	46 960 Men Incidence		BMI < 22 22–24.9 25–29.9 ≥ 30 [P_{trend}]	 7 32 31 16	 1.0 1.3 (0.5–2.9) 1.0 (0.4–2.2) 2.4 (1.0–6.0) [0.07]	Age, physical activity	
Engeland et al. (2007) Norwegian cohort Norway 1963–2001	963 709 Men Incidence	Plasma cell myeloma	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 11 1596 1417 209	 0.69 (0.38–1.25) 1.00 1.14 (1.06–1.22) 1.28 (1.10–1.47) [< 0.001]	Age, birth cohort	
	1 038 010 Women Incidence		BMI < 18.5 18.5–24.9 25–29.9 30–34.9 35–39.9 ≥ 40 [P_{trend}]	 24 1161 1125 436 110 26	 0.85 (057–1.27) 1.00 1.12 (1.03–1.22) 1.23 (1.10–1.38) 1.42 (1.17–1.74) 1.57 (1.06–2.31) [< 0.001]		
Fernberg et al. (2007) Swedish construction workers Sweden 1971–2004	336 381 Men Incidence	Multiple myeloma	BMI 18.5–25 25.1–30 > 30	 256 236 27	 1.00 1.04 (0.86–1.24) 0.70 (0.46–1.06)	Attained age, snuff use, daily tobacco smoking	

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Fujino et al. (2007) Japan Collaborative Cohort Study Japan NR	NR Men Mortality	Multiple myeloma	BMI			Age, area of study	[No information provided on follow-up or number of people in study]
			< 18.5	3	0.96 (0.29–3.16)		
			18.5–24	36	1.00		
			25–29	5	0.70 (0.27–1.80)		
			≥ 30	0	N.A		
			Weight (kg)				
			< 55	12	1.00		
			55–62	20	1.51 (0.73–3.11)		
			≥ 63	15	1.41 (0.64–3.12)		
			Weight (kg) at age 20 yr				
			< 55	25	1.00		
			55–60	12	0.91 (0.38–2.14)		
			≥ 61	10	0.98 (0.40–2.42)		
	NR Women Mortality	Multiple myeloma	BMI			Age, area of study	[No information provided on follow-up or number of people in study]
			< 18.5	2	0.59 (0.14–2.48)		
			18.5–24	31	1.00		
			25–29	7	0.77 (0.34–1.77)		
			≥ 30	4	4.34 (1.51–12.5)		
			Weight (kg)				
			< 49	18	1.00		
			49–54	12	0.93 (0.44–1.96)		
			≥ 55	17	1.17 (0.59–2.33)		
			Weight (kg) at age 20 yr				
			< 47	24	1.00		
			47–52	9	0.76 (0.32–1.81)		
			≥ 53	11	0.87 (0.38–1.97)		
Larsson & Wolk (2007b) Meta-analysis Multiple locations 1994–2007	9 cohort studies Men and women Incidence	Multiple myeloma	BMI per 5 kg/m^2	6987 total	1.11 (1.03–1.19)		

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Larsson & Wolk (2007b) (cont.)	9 cohort studies Men and women Mortality		BMI per 5 kg/m²	1492 total	 1.19 (1.12–1.28)		
	9 cohort studies Men and women Incidence and mortality		BMI Normal Overweight Obese per 5 kg/m²	8479 total	 1.00 1.12 (1.07–1.18) 1.27 (1.15–1.41) 1.14 (1.09–1.20)		Similar values for BMI per 5 kg/m² for men and women separately
Reeves et al. (2007) Million Women Study United Kingdom 1996–2005	1 222 630 Women Incidence	Multiple myeloma ICD-10: C90	BMI < 22.5 22.5–24.9 25–27.4 27.5–29.9 ≥ 30 per 10 kg/m²	 76 127 118 73 97	 0.80 (0.64–1.00) 1.00 (0.84–1.19) 1.11 (0.92–1.32) 1.11 (0.88–1.40) 1.16 (0.95–1.42) 1.31 (1.04–1.65)	Age, geographical region, SES, reproductive history, smoking status, alcohol intake, physical activity	
	1 222 630 Women Mortality		BMI < 22.5 22.5–24.9 25–27.4 27.5–29.9 ≥ 30 per 10 kg/m²	 46 63 68 38 69	 0.99 (0.74–1.32) 1.00 (0.78–1.28) 1.26 (0.99–1.59) 1.13 (0.82–1.55) 1.63 (1.28–2.08) 1.56 (1.15–2.10)		
Britton et al. (2008) EPIC cohort 10 European countries 1993–1998	141 425 Men Incidence	Multiple myeloma	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 43 72 24	 1.00 1.33 (0.79–2.23) 1.17 (0.80–1.72) [0.26]	Age, study centre	Also examined height, hip circumference, and waist-to-hip ratio; analyses by weight and WC gave similar results
	230 558 Women Incidence	Multiple myeloma	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 59 49 21	 1.00 0.93 (0.55–1.56) 1.06 (0.72–1.58) [0.89]	Age, study centre	Also examined height, hip circumference, and waist-to-hip ratio; analyses by weight and WC gave similar results

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Renehan et al. (2008) Meta-analysis Multiple locations 1966–2007	7 studies Men Incidence	Multiple myeloma	BMI per 5 kg/m²		1.11 (1.05–1.18)		
	6 studies Women Incidence		BMI per 5 kg/m²		1.11 (1.07–1.15)		
Pylypchuk et al. (2009) Netherlands Cohort Study on Diet and Cancer The Netherlands 1986–1999	5000 Men and women Incidence	Multiple myeloma ICD-O-3: 9731, 9732, 9734	BMI < 25 25–29.9 ≥ 30 [P_{trend}] per 4 kg/m²	 135 126 18 	 1.00 1.23 (0.95–1.58) 1.13 (0.68–1.88) [0.17] 1.13 (0.97–1.31)	Age, sex	Case–cohort design Similar results for BMI at age 20 yr
De Roos et al. (2010) Women's Health Initiative USA 1994–2008	81 219 Women Incidence	Multiple myeloma	BMI at enrolment < 25 25–29.9 30–34.9 ≥ 35 [P_{trend}]	 39 35 10 7 	 1.00 1.03 (0.65–1.63) 0.66 (0.33–1.33) 0.83 (0.37–1.87) [0.37]	Age, minority race, education level, region of the USA, smoking	Similar results for BMI at age 18 yr, age 35 yr, and age 50 yr
Kanda et al. (2010) Japanese men and women Japan 1992–2006	94 547 Men and women Incidence	Plasma cell myeloma ICD-O-3: 9731, 9732	BMI < 18.5 18.5–22.9 23.0–24.9 25–29.9 ≥ 30 per 1 kg/m² Weight (kg), quartiles (sex-specific) Men: / Women: 30–57 / 27–49 58–63 / 50–53 64–69 / 54–59 70–115 / 60–98 per 5 kg	 2 33 29 22 2 22 21 25 20 	 0.56 (0.13–2.36) 0.70 (0.42–1.15) 1.00 0.79 (0.45–1.38) 0.76 (0.18–3.20) 1.01 (0.95–1.09) 1.00 1.05 (0.57–1.93) 1.35 (0.74–2.46) 1.14 (0.59–2.21) 1.06 (0.93–1.22)	Age, sex, study area, pack-years of smoking, alcohol consumption	Also included estimates for height Similar results for weight at baseline and at age 20 yr

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Lu et al. (2010) California Teachers Study USA 1995–2007	121 216 Women Incidence	Multiple myeloma	BMI at baseline < 20 20–24.9 25–29.9 ≥ 30 [P_{trend}] Weight (lb) at baseline < 131 131–154 ≥ 155 [P_{trend}]	 9 55 28 14 38 36 32 	 0.92 (0.45–1.86) 1.00 0.83 (0.53–1.31) 0.86 (0.48–1.55) [0.55] 1.00 0.85 (0.54–1.36) 0.71 (0.43–1.16) [0.18]	Height, race	Also included estimates for hip circumference, waist-to-hip ratio, waist-to-height ratio, and height Similar results for BMI at age 18 yr, for weight at age 18 yr, and for WC
Parr et al. (2010) Asia-Pacific Cohort Studies Collaboration 1961–1999 Average follow-up 4 yr	326 387 Men and women Mortality	Myeloma ICD-9: 203 ICD-10: C90	BMI < 18.5 18.5–24.9 25–29.9 ≥ 30 per 5 kg/m² [P_{trend}]	 3 12 19 25 10 	 1.94 (0.57–6.68) 1.00 (0.70–1.43) 0.87 (0.54–1.41) 1.20 (0.59–2.43) 1.05 (0.73–1.50) [0.78]	Age, sex, smoking	
Troy et al. (2010) PLCO Trial USA 1993–2006	142 982 Men and women Incidence	Plasma cell myeloma	BMI at baseline < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}] BMI at age 20 yr < 18.5 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 2 57 112 66 12 173 41 12 	 – 1.00 1.45 (1.05–2.01) 1.69 (1.18–2.41) [< 0.01] 0.71 (0.40–1.29) 1.00 1.33 (0.94–1.88) 3.08 (1.71–5.54) [< 0.001]	Age, race/ ethnicity, education level	

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Troy et al. (2010) (cont.)			Weight change (kg) per 10 yr				
			Loss	16	1.00 (0.56–1.78)		
			Gain 0–2	52	1.00		
			Gain 2.1–4	78	1.40 (0.98–2.00)		
			Gain 4.1–6	51	1.48 (1.00–2.20)		
			Gain > 6	42	1.55 (1.02–2.36)		
			[P_{trend}]		[0.216]		
Wallin & Larsson (2011) Meta-analysis Multiple locations	15 studies Men and women Incidence	Multiple myeloma ICD-O-3: 9732/3	BMI	NR			
			Overweight		1.12 (1.07–1.18)		
			Obesity		1.21 (1.08–1.35)		
			per 5 kg/m^2		1.12 (1.08–1.16)		
	5 studies Men and women Mortality	Multiple myeloma ICD-O-3: 9732/3	BMI	NR			
			Overweight		1.15 (1.05–1.27)		
			Obesity		1.54 (1.35–1.76)		
			per 5 kg/m^2		1.21 (1.13–1.30)		
Hofmann et al. (2013) NIH-AARP cohort USA 1995–1996	305 618 Men and women Incidence	Multiple myeloma ICD-O-3: 9732	BMI at baseline			Age, sex, race	Analyses also for women and men separately
			< 18.5	1	0.30 (0.04–2.17)		
			18.5–22.49	53	1.0		
			22.5–24.9	99	1.02 (0.73–1.43)		
			25–29.9	207	1.09 (0.80–1.48)		
			30–34.9	82	1.26 (0.89–1.78)		
			≥ 35	34	1.55 (1.01–2.39)		
			[P_{trend}]		[0.008]		
			BMI at age 50 yr				
			< 18.5	3	0.78 (0.25–2.49)		
			18.5–22.49	73	1.00		
			22.5–24.9	129	1.14 (0.85–1.52)		
			25–29.9	193	1.16 (0.88–1.54)		
			30–34.9	45	1.23 (0.84–1.80)		
			≥ 35	18	1.77 (1.05–2.99)		
			[P_{trend}]		[0.04]		

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Hofmann et al. (2013) (cont.)			BMI at age 35 yr				
			< 18.5	7	0.77 (0.36–1.66)		
			18.5–22.49	136	1.00		
			22.5–24.9	159	1.42 (1.12–1.79)		
			25–29.9	131	1.27 (0.99–1.63)		
			30–34.9	22	1.41 (0.89–2.22)		
			≥ 35	8	2.53 (1.24–5.18)		
			[P_{trend}]		[0.004]		
			BMI at age 18 yr				
			< 18.5	55	0.93 (0.69–1.25)		
			18.5–22.49	237	1.00		
			22.5–24.9	86	1.12 (0.88–1.44)		
			≥ 25	64	1.38 (1.04–1.82)		
			[P_{trend}]		[0.015]		
Patel et al. (2013) Cancer Prevention Study II Nutrition Cohort USA 1992–2007	152 423 Men and women Incidence	Multiple myeloma	BMI at baseline			Age, sex, family history of haematopoietic cancer, education level, smoking status, physical activity, alcohol consumption	
			< 18.5	1	0.32 (0.04–2.30)		
			18.5– < 25	144	1.00		
			25– < 30	149	1.00 (0.79–1.26)		
			≥ 30	58	1.17 (0.86–1.60)		
			[P_{trend}]		[0.25]		
			BMI at age 18 yr				
			< 18.5	44	0.89 (0.64–1.24)		
			18.5–< 22.5	197	1.00		
			22.5–< 25	66	1.01 (0.75–1.34)		
			25– < 30	31	0.92 (0.61–1.37)		
			≥ 30	7	1.77 (0.82–3.84)		
			[P_{trend}]		[0.37]		

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Patel et al. (2013) (cont.)			Adult weight change (lb)				
			Loss > 5	10	0.77 (0.40–1.47)		
			Loss 5 to gain 20	105	1.00		
			Gain 21–40	133	1.25 (0.96–1.61)		
			Gain 41–60	68	1.08 (0.79–1.47)		
			Gain > 60	28	0.81 (0.53–1.24)		
			[P_{trend}]		[0.85]		
Bhaskaran et al. (2014) Clinical Practice Research Datalink United Kingdom 1987–2012	5 243 978 Men and women Incidence	Multiple myeloma ICD-10: C90	BMI per 5 kg/m^2 [P_{trend}]	2969	 1.03 (0.98–1.09) [0.15]	Age, sex, diabetes, smoking, alcohol consumption, SES, calendar year	
Teras et al. (2014) Pooled analysis of 20 cohorts Multiple locations 1970–2002	1 564 218 Men and women Mortality	Multiple myeloma ICD-9: 203; ICD-10: C90	BMI at baseline			Race, sex, education level, marital status, alcohol consumption, physical activity, smoking	
			15.0–18.4	15	1.21 (0.71–2.06)		
			18.5–20.9	85	1.02 (0.79–1.32)		
			21.0–22.9	171	1.00		
			23.0–24.9	302	1.22 (1.01–1.47)		
			25.0–27.4	351	1.15 (0.95–1.38)		
			27.5–29.9	215	1.24 (1.01–1.52)		
			30.0–34.9	178	1.23 (0.99–1.52)		
			≥ 35	71	1.52 (1.15–2.02)		
			per 5 kg/m^2		1.09 (1.03–1.16)		
			Young adult BMI				
			15.0–18.4	121	0.99 (0.80–1.23)		
			18.5–20.9	319	0.91 (0.78–1.07)		
			21.0–22.9	275	1.00		
			23.0–24.9	160	1.04 (0.85–1.26)		
			25.0–27.4	92	1.11 (0.87–1.40)		
			27.5–29.9	31	1.49 (1.03–2.16)		
			≥ 30.0	26	1.82 (1.22–2.73)		
			per 5 kg/m^2		1.22 (1.09–1.35)		

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories		Exposed cases	Relative risk (95% CI)	Covariates	Comments
Teras et al. (2014) (cont.)			BMI gain					
			≤ –2.5		34	1.12 (0.77–1.64)		
			–2.5 to < 0		67	0.84 (0.64–1.10)		
			0–2.5		221	1.00		
			2.5–4.9		266	1.04 (0.87–1.24)		
			5.0–7.4		220	1.17 (0.96–1.41)		
			7.5–9.9		113	1.10 (0.87–1.38)		
			≥ 10		103	1.17 (0.92–1.50)		
			per 1 kg/m²			1.06 (0.98–1.14)		
	647 478 Men and women Mortality		WC (cm), quartiles (sex-specific)				Race, sex, education level, marital status, alcohol consumption, physical activity, smoking	Also provided estimates for waist-to-hip ratio and height
			Men:	Women:				
			< 90	< 70	112	1.00		
			90–99	70–79	216	1.28 (1.01–1.62)		
			100–109	80–89	153	1.32 (1.02–1.71)		
			≥ 110	≥ 90	108	1.47 (1.10–1.96)		
			per 5 cm			1.06 (1.02–1.10)		
	656 771 Men Mortality		BMI at baseline				Race, education level, marital status, alcohol consumption, physical activity, smoking	Also provided estimates for waist-to-hip ratio and height
			15.0–18.4		1	–		
			18.5–20.9		17	0.97 (0.57–1.67)		
			21.0–22.9		63	1.00		
			23.0–24.9		176	1.37 (1.03–1.83)		
			25.0–27.4		219	1.20 (0.90–1.59)		
			27.5–29.0		130	1.29 (0.95–1.75)		
			30.0–34.9		93	1.28 (0.93–1.78)		
			≥ 35		24	1.48 (0.91–2.38)		
			per 5 kg/m²			1.11 (1.00–1.22)		
			Young adult BMI					
			15.0–18.4		40	0.85 (0.60–1.21)		
			18.5–20.9		136	0.91 (0.73–1.15)		
			21.0–22.9		155	1.00		
			23.0–24.9		92	0.88 (0.68–1.14)		
			25.0–27.4		62	1.00 (0.74–1.34)		
			27.5–29.0		21	1.47 (0.93–2.32)		
			≥ 30.0		10	1.36 (0.72–2.59)		
			per 5 kg/m²			1.15 (0.98–1.35)		

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Teras et al. (2014) (cont.)			BMI gain				
			≤ –2.5	11	1.04 (0.55–1.97)		
			–2.5 to < 0	33	0.96 (0.65–1.42)		
			0–2.5	117	1.00		
			2.5–4.9	147	1.04 (0.81–1.33)		
			5 0–7.4	108	1.05 (0.80–1.38)		
			7.5–9.9	60	1.18 (0.85–1.64)		
			≥ 10	40	1.20 (0.82–1.76)		
			per 1 kg/m²		1.07 (0.94–1.21)		
			WC (cm)				
			< 90	62	1.00		
			90–99	144	1.25 (0.93–1.69)		
			100–109	83	1.26 (0.90–1.77)		
			≥ 110	38	1.38 (0.91–2.08)		
			per 5 cm		1.06 (1.01–1.12)		
	907 447 Women Mortality		BMI at baseline			Race, education level, marital status, alcohol consumption, physical activity, smoking	Also provided estimates for waist-to-hip ratio and height
			15.0–18.4	14	1.39 (0.79–2.43)		
			18.5–20.9	68	1.01 (0.75–1.38)		
			21.0–22.9	108	1.00		
			23.0–24.9	126	1.08 (0.83–1.39)		
			25.0–27.4	132	1.11 (0.86–1.44)		
			27.5–29.0	85	1.20 (0.90–1.60)		
			30.0–34.9	85	1.18 (0.89–1.58)		
			≥ 35	47	1.51 (1.06–2.15)		
			per 5 kg/m²		1.07 (0.99–1.16)		
			Young adult BMI				
			15.0–18.4	81	1.11 (0.84–1.47)		
			18.5–20.9	183	0.94 (0.75–1.19)		
			21.0–22.9	120	1.00		
			23.0–24.9	68	1.31 (0.97–1.76)		
			25.0–27.4	30	1.28 (0.86–1.91)		
			27.5–29.0	10	1.42 (0.75–2.71)		
			≥ 30.0	16	2.32 (1.37–3.92)		
			per 5 kg/m²		1.27 (1.10–1.47)		

Table 2.2.20c (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Teras et al. (2014) (cont.)			BMI gain				
			≤ –2.5	23	1.16 (0.72–1.89)		
			–2.5 to < 0	34	0.75 (0.51–1.10)		
			0–2.5	104	1.00		
			2.5–4.9	119	1.02 (0.78–1.33)		
			5.0–7.4	112	1.28 (0.98–1.68)		
			7.5–9.9	53	1.00 (0.71–1.40)		
			≥ 10	63	1.12 (0.81–1.56)		
			per 1 kg/m²		1.04 (0.95–1.15)		
			WC (cm)				
			< 70	50	1.00		
			70–79	72	1.32 (0.90–1.94)		
			80–89	70	1.42 (0.94–2.13)		
			≥ 90	70	1.54 (1.00–2.36)		
			per 5 cm		1.05 (1.00–1.11)		

BMI, body mass index (in kg/m²); CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; EPIC, European Prospective Investigation into Cancer and Nutrition; ICD, International Classification of Diseases; ICD-O, International Classification of Diseases for Oncology; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; NR, not reported; PLCO Trial, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; RR, relative risk; SES, socioeconomic status; WC, waist circumference; yr, year or years

Table 2.2.20d Case–control studies of measures of body fatness and haematopoietic malignancies of lymphoid origin with *sufficient* or *limited* evidence

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding
Diffuse large B-cell lymphoma					
Pan et al. (2005) Canada 1994–1997	419 from National Enhanced Cancer Surveillance System 3106 Population	Adult BMI 2 yr before interview/diagnosis 18.5– < 25 25– < 30 ≥ 30 [P_{trend}]	 162 184 69 	 1.00 1.37 (1.09–1.73) 1.35 (0.99–1.83) [0.015]	Age, province, sex, education level, pack-years of smoking, alcohol consumption, exposure to some chemicals, occupational exposures, physical activity, energy intake
Chen et al. (2011) USA 1996–2000	245 868 Population	Usual adult BMI assessed via interview < 25 25–30 > 30	 77 56 28	 1.0 1.5 (1.0–2.2) 1.1 (0.7–1.8)	Age, race, total energy intake
Cerhan et al. (2014) Pooled analysis from InterLymph Consortium of 19 case–control studies Europe, Japan, North America	4667 22 639	Young adult BMI 15– < 18.5 18.5– < 22.5 22.5– < 25 25– < 30 30–50 [P_{trend}] Usual adult BMI 15– < 18.5 18.5– < 22.5 22.5– < 25 25– < 30 30– < 35 35–50 [P_{trend}]	 64 517 276 226 54 33 722 850 1310 419 175 	 0.93 (0.69–1.24) 1.00 1.11 (0.93–1.31) 1.47 (1.22–1.77) 1.58 (1.12–2.23) [0.002] 0.58 (0.39–0.85) 1.00 0.91 (0.81–1.03) 0.93 (0.83–1.04) 0.95 (0.82–1.10) 1.06 (0.86–1.30) [0.042]	
Multiple myeloma					
Larsson & Wolk (2007b) Meta-analysis of 4 case–control studies Studies published in 1994–2007	1166 total 8247 total	BMI ≤ 25 25–29.9 ≥ 30	 	 1.00 1.43 (1.23–1.68) 1.82 (1.47–2.26)	Note: the reference category was ≤ 25 in all but 3 studies

Table 2.2.20d (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding
Wang et al. (2013) USA 1985–1992	278 from Los Angeles County Multiple Myeloma Case–Control Study 278 Population	Self-reported BMI 1 yr before cancer diagnosis or at time of interview			Sex, age ± 5 yr, race
			All:		
		< 25	116	1.00	
		25–29.9	98	0.75 (0.51–1.10)	
		30–34.9	43	0.98 (0.59–1.62)	
		≥ 35	21	1.86 (0.84–4.14)	
			Men:		
		< 25	58	1.00	
		25–29.9	65	0.85 (0.52–1.39)	
		30–34.9	19	0.96 (0.46–2.01)	
		≥ 35	8	1.80 (0.51–6.30)	
			Women:		
		< 25	58	1.00	
		25–29.9	33	0.62 (0.34–1.17)	
		30–34.9	24	0.92 (0.45–1.88)	
		≥ 35	11	1.56 (0.55–4.40)	

BMI, body mass index (in kg/m^2); CI, confidence interval; yr, year or years

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2.2.21 Other haematopoietic malignancies

(a) Myeloid leukaemia

(i) Cohort studies

There have been only two prospective studies of BMI and/or weight in relation to total myeloid leukaemia incidence (Table 2.2.20a, web only, available at: http://publications.iarc.fr/570). In the Japan Collaborative Cohort Study, compared with BMI 18.5–24 kg/m^2, BMI ≥ 30 kg/m^2 was associated with a statistically significantly higher risk (Fujino et al., 2007). In the EPIC cohort, BMI was positively associated with risk in women (P_{trend} = 0.04), but no association was found in men (Saberi Hosnijeh et al., 2013).

Statistically significant positive associations between BMI and risk of AML were observed in postmenopausal women in the USA (Ross et al., 2004), in the United States Veterans cohort (Samanic et al., 2004), and in a Norwegian cohort (Engeland et al., 2007). However, there were no associations of BMI or weight with risk in other studies in European men (Samanic et al., 2006; Fernberg et al., 2007; Saberi Hosnijeh et al., 2013) or women (Saberi Hosnijeh et al., 2013). Of six individual prospective studies of BMI and/or weight in relation to CML incidence (Samanic et al., 2004, 2006; Engeland et al., 2007; Fernberg et al., 2007; Kabat et al., 2013; Saberi Hosnijeh et al., 2013), only one (Engeland et al., 2007) found clear evidence of a positive association. In a meta-analysis of prospective studies, obesity was associated with a statistically significant 52% higher risk of AML and a 26% higher risk of CML compared with normal weight (Larsson & Wolk, 2008).

Only two studies have examined associations of abdominal obesity with risk of myeloid leukaemia. In the Iowa Women's Health Study, waist circumference was positively associated with risk of AML (P_{trend} = 0.04) (Ross et al., 2004). Similarly, in the EPIC cohort, there was suggestive evidence for an association of waist circumference with risk of AML in women (P_{trend} = 0.06), but not in men (Saberi Hosnijeh et al., 2013). In that study, there were also no associations of waist circumference with CML incidence in either men or women (Saberi Hosnijeh et al., 2013).

(ii) Case–control studies

Three case–control studies have evaluated the relationship between BMI and the risk of developing various subtypes of leukaemia (Table 2.2.20b, web only, available at: http://publications.iarc.fr/570). In a study of 420 cases of AML from the Minnesota Cancer Surveillance System, Poynter et al. (2016) found a non-significant increase in risk of AML with high BMI in women only. Kasim et al. (2005) found an increased risk of all leukaemia, AML, and CML in obese versus normal-weight individuals in a case–control study of 1068 people with leukaemia from the Canadian Enhanced Survival Surveillance System. Finally, Strom et al. (2009) found a trend towards an increased risk of CML with BMI at age 25 years, at age 40 years, and at diagnosis in a case–control study of 253 cases of CML from MD Anderson Cancer Center in the USA.

(b) Leukaemia not otherwise specified

At least six individual cohort studies found no association between BMI and total leukaemia incidence or mortality (Table 2.2.20a, web only, available at: http://publications.iarc.fr/570; Oh et al., 2005; Samanic et al., 2006; Andreotti et al., 2010; De Roos et al., 2010; Saberi Hosnijeh et al., 2013; Batty et al., 2015). Conversely, positive associations were found in at least eight other studies, conducted in the Republic of Korea, Taiwan, China, the United Kingdom, and the USA (Calle et al., 2003, in men only; Ross et al., 2004; Samanic et al., 2004; Chiu et al., 2006; Reeves et al., 2007; Song et al., 2008; Chu et al., 2011; Bhaskaran et al., 2014). Positive associations in men and in women were found in a meta-analysis of seven

prospective studies (Renehan et al., 2008). In a meta-analysis of 10 studies in men and women combined, there was a 39% increased risk of leukaemia incidence for obese versus normal BMI (Larsson & Wolk, 2008). Similarly, in the Asia-Pacific Cohort Studies Collaboration, there was a positive association between BMI and leukaemia mortality (Parr et al., 2010). However, a pooled analysis of almost 1 million people found no association between BMI and leukaemia mortality (Whitlock et al., 2009).

Although waist circumference was not associated with total leukaemia incidence in the Iowa Women's Health Study (Ross et al., 2004) or in the EPIC cohort (Saberi Hosnijeh et al., 2013), in the MJ Health Screening Center study, in Taiwan, China, abdominal obesity (waist circumference of ≥ 90 cm in men and ≥ 80 cm in women) was associated with an 87% higher risk of death from leukaemia compared with lower waist circumference (Chu et al., 2011).

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2.2.22 Cancers of the head and neck

Head and neck cancer refers to a group of cancers that develop in (i) the oral cavity; (ii) the pharynx, including the nasopharynx, the oropharynx, and the hypopharynx; (iii) the larynx; (iv) the paranasal sinuses and the nasal cavity; and (v) the salivary glands.

Most head and neck cancers are squamous cell carcinomas. Because of the established associations of head and neck cancer with tobacco use, and because BMI is inversely associated with tobacco use, it is important that associations of BMI with risk of head and neck cancers carefully consider potential confounding and/or effect modification by tobacco use. Notably, only prospective studies with at least 50 cases for any specific site were included in this review.

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and cancers of the head and neck was *inadequate*.

(a) Cohort studies

See Table 2.2.22a (web only, available at: http://publications.iarc.fr/570).

(i) Cancer of the oral cavity

The association between BMI and risk of cancer of the oral cavity has been examined in two individual prospective studies (Bhaskaran et al., 2014; Etemadi et al., 2014) and in a large pooled analysis of data from 20 prospective studies (Gaudet et al., 2015). All of these studies adjusted for both tobacco use and alcohol consumption. In the United Kingdom data linkage study of more than 5 million men and women, there was a statistically significant inverse association (RR per 5 kg/m^2 increase in BMI, 0.81; 95% CI, 0.74–0.89; $P_{trend} < 0.0001$) (Bhaskaran et al., 2014). No significant association was observed in the NIH-AARP cohort study in the USA (Etemadi et al., 2014) or in the large pooled analysis (Gaudet et al., 2015).

In contrast, quartiles of waist circumference were positively associated with risk (RR for highest vs lowest quartile, 2.00; 95% CI. 1.24–3.23; $P_{trend} < 0.001$) in the NIH-AARP study (Etemadi et al., 2014). Similarly, in the large pooled analysis of 20 prospective studies, there was a 9% increase in risk (95% CI, 1.03–1.16) per 5 cm increase in waist circumference ($P_{trend} = 0.006$) (Gaudet et al., 2015).

(ii) Cancers of the pharynx (nasopharynx, oropharynx, and/or hypopharynx)

There was no association between BMI and risk of nasopharyngeal cancer in the only study that assessed this relationship (Samanic et al., 2004). Similarly, there is no evidence that BMI is associated with risk of oropharyngeal cancer incidence (Gaudet et al., 2012, 2015) or mortality (Gaudet et al., 2012), or with hypopharyngeal cancer incidence (Gaudet et al., 2015). In the NIH-AARP cohort, BMI < 18.5 kg/m^2 was associated with a higher risk of oropharyngeal and hypopharyngeal cancer incidence compared with BMI 18.5– < 25 kg/m^2 (Etemadi et al. 2014). [There were only three cases in the exposed group.]

Waist circumference was not associated with oropharyngeal or hypopharyngeal cancer incidence in the NIH-AARP cohort study (Etemadi et al., 2014) or in the large pooled analysis (Gaudet et al., 2015).

(iii) Cancer of the larynx

Since 2000, there have been two individual prospective studies (Samanic et al., 2004; Etemadi et al., 2014) and one large pooled analysis of 20 prospective studies (Gaudet et al., 2015) of the association between BMI and risk of cancer of the larynx (Table 2.2.22a, web only, available at: http://publications.iarc.fr/570). In the large study of more than 4.5 million United States Veterans, there was a statistically significantly lower risk

of laryngeal cancer for obese compared with non-obese White and Black men (Samanic et al., 2004). [Neither tobacco use nor alcohol consumption was included in the statistical model; therefore, confounding by these factors is likely.] In the NIH-AARP cohort study in the USA, in which both tobacco use and alcohol consumption were adjusted for in the model, BMI was not associated with risk of laryngeal cancer (Etemadi et al., 2014). Conversely, in the pooled analysis, there was a statistically significant positive association between BMI and risk (RR per 5 kg/m^2 increase, 1.42; 95% CI, 1.19–1.70) (Gaudet et al., 2015).

In the NIH-AARP study (Etemadi et al., 2014), there was no evidence of an association between waist circumference and risk of laryngeal cancer, whereas a weak positive association was reported in the pooled analysis (RR per 5 cm increase, 1.10; 95% CI, 0.99–1.22; P_{trend} = 0.08) (Gaudet et al., 2015).

(iv) Cancer of the oral cavity, pharynx, and larynx combined

In two studies, the Asia-Pacific Cohort Studies Collaboration (Parr et al., 2010) and the Cancer Prevention Study II (Gaudet et al., 2012), BMI was inversely associated with death from cancer of the oral cavity, pharynx, and larynx combined. In contrast, in the pooled analysis, an incremental increase in BMI of 5 kg/m^2 was associated with a 36% increase in risk (Gaudet et al., 2015). Results from the Agricultural Health Study (Andreotti et al., 2010) were inconclusive.

The association between waist circumference and the risk of cancer of the oral cavity, pharynx, and larynx combined was examined in the large pooled analysis of 20 prospective studies, and no evidence of association was observed (Gaudet et al., 2015).

(v) Cancer of the salivary glands

There has been only one study of the association between BMI and incidence of salivary gland cancer (Samanic et al., 2004). In that study, being obese was not associated with a higher incidence compared with being non-obese in either White men or Black men.

(vi) Cancer of the head and neck or upper aerodigestive tract

For head and neck cancer incidence overall, in the United States Veterans study there was a significantly lower risk for obese compared with non-obese Black men and White men, without adjustment for tobacco use or alcohol consumption (Samanic et al., 2004). Most other prospective studies found a weak inverse association or no association between BMI at baseline and incidence of head and neck cancer (Wolk et al., 2001; Gaudet et al., 2012; Hashibe et al., 2013; Etemadi et al., 2014). When the pooled analysis of data from 20 prospective studies was stratified by smoking status, BMI was positively associated with risk in never-smokers but was inversely associated with risk in current smokers (Gaudet et al., 2015).

BMI was inversely associated with head and neck cancer mortality ($P_{trend} = 3 \times 10^{-10}$) in the Cancer Prevention Study II in the USA (Gaudet et al., 2012), and in a smaller cohort study in Switzerland a weaker inverse association was found between BMI and death from cancer of the upper aerodigestive tract (Meyer et al., 2015).

In the only study that examined the association between BMI at younger ages and risk of head and neck cancer, no association was found with increased BMI at age 20 years or at age 50 years, or with percentage change in BMI from age 20 years or age 50 years to baseline (Hashibe et al., 2013).

Waist circumference was positively associated with risk of head and neck cancer incidence both in the NIH-AARP cohort study (Etemadi et al., 2014) and in the pooled analysis of 20 prospective studies, in which a 5 cm increase in waist circumference was associated with a 4% increase in risk (95% CI, 1.03–1.05) (Gaudet et al., 2015).

(b) Case–control studies

Since 2000, a total of seven independent case–control studies, conducted in Australia, China, Cuba, India, Europe, Sudan, and the USA, and one large multicentre case–control study (nine countries) have reported on the association of BMI with various combinations of cancers of the head and neck (Table 2.2.22b, web only, available at: http://publications.iarc.fr/570). In addition, Gaudet at al. (2010) and Lubin et al. (2010, 2011) performed pooled reanalyses of 15–17 case–control studies with stratification by smoking status, by alcohol consumption status, and by subsite (Table 2.2.22c, web only, available at: http://publications.iarc.fr/570).

In most studies, BMI was assessed on the basis of self-reported height and body weight, referring to either a recent period (mostly 1 or 2 years) before disease diagnosis or to a period in the more distant past (e.g. at age 30 years). All original studies adjusted for potential confounding by smoking or alcohol consumption, in addition to variable adjustments for other potential confounding factors.

Most of the studies found an inverse association of BMI with cancer risk. In several studies, compared with normal-weight individuals (18.5 kg/m^2 ≤ BMI < 25 kg/m^2), those who were overweight or obese had reduced risks of head and neck cancer (Rajkumar et al., 2003; Rodriguez et al., 2004; Kreimer et al., 2006; Peters et al., 2008; Radoï et al., 2013; Petrick et al., 2014 in African Americans only); being underweight (BMI < 18.5 kg/m^2) was associated with an approximately 2-fold increase in risk in two large-scale studies (French ICARE study, 689 cases and 3481 controls, Radoï et al., 2013; United States CHANCE study, 1289 cases and 1361 controls, Petrick et al., 2014). In the one study that additionally reported recalled body weight at age 30 years (Radoï et al., 2013), this inverse association was also observed for past BMI.

Four case–control studies stratified the analyses by smoking status. In one early study in the USA, the inverse association was more pronounced in current or ever-smokers than in never-smokers (Kabat et al., 1994). In two more recent studies in the USA, a similar pattern was observed in African Americans but not in Whites (Petrick et al., 2014) and in both HPV-positive and HPV-negative individuals (Tan et al., 2015). In contrast, the IARC Multicenter Oral Cancer Study, which included a total of 1670 cases and 1732 controls from nine countries worldwide, found statistically significant inverse associations of BMI (country-specific tertiles) with risk of oral and oropharyngeal squamous cell carcinomas in both tobacco users and never-users, as well as in alcohol consumers and never-drinkers (Kreimer et al., 2006). Similarly, a pooled reanalysis of the data from 17 case–control studies, which included a total of 12 716 cases and 17 438 controls (INHANCE consortium; Gaudet et al., 2010) (see Table 2.2.22c, web only, available at: http://publications.iarc.fr/570), found inverse relationships of BMI with the risk of cancers of the oral cavity, pharynx, and larynx, in men and women combined, in ever-smokers (for BMI ≥ 30 kg/m^2 vs 18.5– < 25 kg/m^2: OR, 0.38; 95% CI, 0.30–0.49) but not in never-smokers. Furthermore, the increase in risk in underweight (BMI < 18.5 kg/m^2) compared with normal-weight (18.5– < 25 kg/m^2) individuals was significant only in the smokers (OR, 2.13; 95% CI, 1.75–2.58) (Gaudet et al., 2010).

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2.2.23 Malignant melanoma

Malignant melanoma is the most lethal of the cancers of the skin. The incidence of melanoma varies between countries and is related to skin colour, with a higher risk for populations with lighter skin. Melanoma is known to be caused by exposure to ultraviolet radiation in people who are susceptible because of family history and/or who have a tendency to burn easily as a result of exposure to sunlight.

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that the evidence of an association between avoidance of weight gain and malignant melanoma was *inadequate*.

(a) Cohort studies

The evidence published since 2000 includes eight cohort studies (excluding analyses that were later updated and analyses based on fewer than 100 incident cases) (Table 2.2.23a, web only, available at: http://publications.iarc.fr/570) and one meta-analysis (Table 2.2.23b, web only, available at: http://publications.iarc.fr/570).

In most studies, there was no association between BMI and risk of melanoma (Calle et al., 2003; Rapp et al., 2005; Dennis et al., 2008; Pothiawala et al., 2012; Bhaskaran et al., 2014). However, findings by sex have not been consistent. In two studies in men only, the estimated relative risk for BMI ≥ 30 kg/m^2 was 1.35 (95% CI, 1.06–1.73) in Swedish construction workers (Samanic et al., 2006) and 1.29 (95% CI, 1.14–1.46) in White men in the United States Veterans cohort (Samanic et al., 2004). In the Million Women Study (Reeves et al., 2007), the risk was also significantly increased (RR per 10 kg/m^2, 1.24; 95% CI, 1.03–1.48). In a meta-analysis of cohort studies (Sergentanis et al., 2013), the estimated relative risk of obesity was 1.30 (95% CI, 1.17–1.45) in men (based on 7 studies) and 0.87 (95% CI, 0.70–1.08) in women (based on 6 studies).

Three cohorts have examined weight at earlier ages in relation to risk of melanoma. In both the Nurses' Health Study and the Male Health Professionals Follow-Up Study, BMI at 10 years before baseline was not related to risk (Pothiawala et al., 2012); in the study of agricultural workers in the USA (Dennis et al., 2008), recalled BMI at age 20 years was positively associated, with an estimated relative risk for BMI ≥ 25 kg/m^2 of 2.55 (95% CI, 1.52–4.30).

(b) Case–control studies

The meta-analysis by Sergentanis et al. (2013) included 10 published case–control studies that evaluated the association between BMI and risk of melanoma (Table 2.2.23b, web only, available at: http://publications.iarc.fr/570). The association between BMI and melanoma was significant both in overweight men and in obese men, although there was considerable between-study heterogeneity. No such association was observed in women. When the cohort and case–control studies were combined, the pooled effect estimate was 1.31 (95% CI, 1.18–1.45) in overweight men and 1.31 (95% CI, 1.19–1.44) in obese men. In women, no association was observed in either category (Sergentanis et al., 2013). [There was evidence for confounding by exposure to sunlight in women.]

The pooled analysis of case–control studies (Olsen et al., 2008) assessed BMI in early adulthood and weight change in relation to risk of melanoma in women. There was no association between BMI in early adulthood and melanoma risk, but an elevated risk was associated with a weight gain of 2 kg or more during adult life (pooled OR, 1.5, 95% CI, 1.1–2.0) (see Table 2.2.23b, web only, available at: http://publications.iarc.fr/570).

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2.3. Excess body fatness in early life and subsequent cancer risk

WHO defines children as individuals younger than 19 years (WHO, 2016). The scope of this section includes children and young adults up to age 25 years, the age range collectively referred to as early life.

It is generally held that childhood obesity is strongly associated with obesity in adulthood. According to a recent systematic review (Simmonds et al., 2015), obese children are more than 5 times as likely as non-obese children to be obese as adults. However, childhood BMI is not a good predictor of the occurrence of obesity in adulthood; 80% of people older than 30 years who are obese were not obese in adolescence. Similarly, many obesity-related diseases occur in adults who had a healthy weight in childhood.

Few comprehensive reviews or meta-analyses are available on the topic of body shape and weight in early life and subsequent cancer risk. The literature review for this section identified three categories of studies: (i) prospective studies that directly measured weight and height in childhood and related these parameters with subsequent cancer occurrence; (ii) prospective cohort studies that determined body shape in early adulthood by recall and related these parameters with subsequent cancer occurrence; and (iii) studies that determined trajectories of body shape (from repeated determinations) from childhood to late adulthood and related these parameters with subsequent cancer occurrence.

[The Working Group considered that the relationship between weight at birth and subsequent cancer risk was beyond the scope of this *Handbook*.]

2.3.1 Weight and height measured in childhood

The few prospective studies that directly measured weight and height in childhood and related these parameters with subsequent cancer occurrence have been reviewed recently (Simmonds et al., 2015). These include data from the Helsinki Birth Cohort Study (ages 7 years and 15 years; Hilakivi-Clarke et al., 2001), the 1946 United Kingdom Medical Research Council National Survey of Health and Development (ages 2–15 years; De Stavola et al., 2004), the Copenhagen School Health Records Register (ages 7–15 years; Ahlgren et al., 2006; Aarestrup et al., 2014; Berentzen et al., 2014; Kitahara et al., 2014a, 2014b; Cook et al., 2015), the Norwegian health surveys (ages 14–19 years; Engeland et al., 2003; Bjørge et al., 2004, 2008), the Israeli army (ages 16–19 years; Levi et al., 2011; Leiba et al., 2013), and the Harvard Alumni Health Study (ages 18–21 years; Gray et al., 2012). [These cohorts have the advantage that height and weight were directly measured, but they have relatively small sample sizes. Because the baseline data were collected more than half a century ago, extrapolation to the current childhood and adolescent population may not apply, and it is not always clear whether these cohorts were representative of the general population.] The relationship between weight and height in childhood and subsequent cancer occurrence is presented separately for cancer of the breast (Table 2.3a) and for other cancers (Table 2.3b).

Table 2.3a lists study characteristics and breast cancer risk estimates from three studies (Hilakivi-Clarke et al., 2001; De Stavola et al., 2004; Ahlgren et al., 2006), which included a total of 3576 breast cancer cases. There was no evidence that excess weight directly measured in childhood is associated with subsequent breast cancer risk. Indeed, there is some evidence of an inverse association.

Table 2.3b lists, for boys and/or girls, study characteristics and risk estimates of mortality and incidence for the following types of cancer: colon cancer (Bjørge et al., 2008; Levi et al., 2011), rectal cancer (Levi et al., 2011), oesophageal adenocarcinoma (Cook et al., 2015), gastric non-cardia cancer (Levi et al., 2013), hepatocellular carcinoma (Berentzen et al., 2014), pancreatic cancer (Levi et al., 2012), ovarian cancer (Engeland et al., 2003), prostate cancer (Gray et al., 2012; Aarestrup et al., 2014; Batty et al., 2015), renal cancer (Bjørge et al., 2004; Leiba et al., 2013), urothelial cancer (Leiba et al., 2012), glioma (Kitahara et al., 2014a), and thyroid cancer (Farfel et al., 2014; Kitahara et al., 2014b). Although the number of studies per cancer type is small, for boys, excess weight in childhood and adolescence (generally expressed per increase of 1 or 2 standard deviations in BMI) was generally associated with increased risk of colon cancer (but not rectal cancer), oesophageal adenocarcinoma, hepatocellular carcinoma, pancreatic cancer, renal cancer, or urothelial cancer. There was no association with subsequent prostate cancer occurrence. For girls, there was evidence that excess weight in childhood and adolescence (generally expressed per increase of 1 or 2 standard deviations in BMI) was associated with increased risk of colon cancer (but not rectal cancer), oesophageal adenocarcinoma, hepatocellular carcinoma, and ovarian cancer. The association with renal cancer was uncertain [because of a large confidence interval]. No associations were seen for glioma or thyroid cancer in either sex.

2.3.2 Body shape in early adulthood determined by recall

A larger number of prospective cohort studies have determined body shape in early adulthood (ages 18–25 years) by recall, typically using the Sørensen scale (silhouette drawings), and converting the results to BMI values. [There is a risk of recall bias, but distributions of recalled BMI have been tested against BMI distributions from population data contemporaneous with the respective age strata and were found to be similar (Renehan et al., 2012). It is worth remembering that the mean values of BMI distributions of a cohort at ages 18–25 years are considerably lower than those in later adulthood. For example, in the NIH-AARP cohort, the mean BMI at age 18 years was 21.5 kg/m^2 in men and 20.8 kg/m^2 in women (Renehan et al., 2012). In addition, there is a survival bias, in that individuals have had to survive to baseline age (typically > 50) to participate in the cohort study. Finally, in these studies, risk estimates from multivariate analyses are commonly expressed as those from separate models adjusted for several potential confounders and as those from models adjusted for several potential confounders plus baseline (current-age) BMI. The latter models are of mechanistic relevance; for the purpose of a public health message in this *Handbook*, risk estimates from the former models are reported.]

These studies are dealt with in the individual cancer site-specific sections. Here, specific note is made in relation to breast cancer.

Prospective cohort studies of recalled BMI at ages 18–25 years and subsequent postmenopausal or premenopausal breast cancer risk are presented in Table 2.3c and Table 2.3d, respectively.

For BMI at ages 18–25 years determined by recall, several cohort studies showed no association (van den Brandt et al., 1997; Suzuki et al., 2011; Fagherazzi et al., 2013; Krishnan et al., 2013; Catsburg et al., 2014) or inverse associations (Ahn et al., 2007; Palmer et al., 2007; Baer et al., 2010; Kawai et al., 2010; White et al., 2012) with subsequent breast cancer risk. The same level of association was observed for postmenopausal (Table 2.3c) and premenopausal (Table 2.3d) women.

Some studies additionally evaluated BMI or weight at ages younger than 18 years determined

by recall: age at menarche in the French cohort (Fagherazzi et al., 2013), at age 12 years in the Iowa Women's Health Study (Bardia et al., 2008), and at ages 5 years and 10 years in the Nurses' Health Study (1988–2004) and the Nurses' Health Study II (1989–2005) cohorts (Baer et al., 2010) (data not shown in tables). These studies are consistent in showing that body fatness at ages 5–12 years or age at menarche is independently and inversely associated with subsequent premenopausal (Baer et al., 2010) and postmenopausal breast cancer (Bardia et al., 2008; Baer et al., 2010; Fagherazzi et al., 2013).

2.3.3 *Trajectories of body shape determined from early life*

Additional information may be gained by exploring weight changes with time and cancer risk. Recently, Song et al. (2016) reported combined analyses from the Nurses' Health Study (73 581 women) and the Health Professionals Follow-up Study (32 632 men) for several cancer sites (Table 2.3e). Using a data-driven latent class approach, they identified five distinct trajectories of body shape from age 5 years to age 60 years: maintained a lean body shape (lean-stable), started lean and experienced a moderate increase in body shape (lean-moderate increase), started lean and gained a substantial amount of weight (lean-marked increase), maintained a medium body shape (medium-stable), and started heavy and maintained or gained weight (heavy-stable/increase). Compared with women with the lean-stable trajectory, women with the lean-marked increase and the heavy-stable/increase trajectories had higher risks of colorectal, oesophageal, pancreatic, renal, and endometrial cancers. For postmenopausal breast cancer risk, early-life adiposity with no loss in later life (heavy-stable/increase trajectory) showed no association, whereas late-life adiposity (lean-marked increase trajectory) was positively associated. In men, excess body fatness during any life period was associated with a higher risk of colorectal cancer and oesophageal adenocarcinoma; in addition, the heavy-stable/increase trajectory was associated with a higher risk of pancreatic cancer and a lower risk of advanced prostate cancer.

In the French E3N cohort, Fagherazzi et al. (2013) evaluated the risk of breast cancer associated with body shape (using the Sørensen scale) at ages 8 years, age at menarche, 20–25 years, and 35–40 years. Six lifetime trajectories of body shape were derived, using a finite mixture modelling approach (Jones & Nagin, 2007). In this analysis, from age 8 years and/or at menarche, a constantly elevated body size was associated with a significantly decreased risk of ER-positive and PR-positive postmenopausal breast cancer (approximately 80% of breast cancers). No significant association with other body shape trajectories was found.

Table 2.3a Prospective studies of childhood cohorts where weight and height were directly measured and subsequent risk of cancer of the breast

Reference Cohort Period of study	Number at baseline (Birth cohort)	Number at follow-up	Number of breast cancers	Adult age at final follow-up (years)	Childhood age at measurement (years)	Relative risk (95% CI) per SD or unit increase in BMI
Hilakivi-Clarke et al. (2001) Helsinki Birth Cohort 1971–1995	3447 (1924–1933)	3447	177	Minimum, 38 (76% > 50)	7 15	0.91 (0.73–1.05) 0.85 (0.70–1.00)
De Stavola et al. (2004) United Kingdom Medical Research Council National Survey of Health and Development 1946–1999	2547 (March 1946)	2187	59	47–53	2 4 7 11 15	1.02 (0.78–1.33) 0.88 (0.67–1.14) 0.87 (0.66–1.15) 0.89 (0.68–1.18) 0.86 (0.65–1.14)
Ahlgren et al. (2006) Girls in Copenhagen, Denmark (Copenhagen School Health Records Register) Until 2001	161 063 (1930–1975)	117 415	3340	NR	14	0.97 (0.96–0.98)

BMI, body mass index (in kg/m^2); CI, confidence interval; NR, not reported; SD, standard deviation

Table 2.3b Prospective studies of childhood cohorts where weight and height were directly measured and subsequent risk of other cancers, by sex and by organ site

Reference Cohort	Number at baseline Period of recruitment	Number at follow-up	Number of cancers	Adult age at final follow-up (years)	Childhood age at measurement (years)	Relative risk (95% CI) per SD or unit increase in BMI
Boys						
Colon cancer: mortality						
Bjørge et al. (2008) Norwegian Cancer Registry	114 977 (1963–1975)	NR	97	Mean, 40	14–19	≥ 85th percentile vs 25th–75th percentile: 2.1 (1.1–4.1)
Colon cancer: incidence						
Levi et al. (2011) Israeli military cohort	1 109 864 (1947–1966)	NR	445	19–57	16–19	1.21 (1.07–1.38)[b]
Rectal cancer: incidence						
Levi et al. (2011) Israeli military cohort	1 109 864 (1947–1966)	NR	193	19–57	16–19	0.96 (0.88–1.10)[b]
Oesophageal adenocarcinoma: incidence						
Cook et al. (2015) Boys in Copenhagen, Denmark (Copenhagen School Health Records Register)	188 360 (1930–1989)	128 330	216	> 40	7 8 9 10 11 12 13	1.11 (0.95–1.30) 1.10 (0.94–1.29) 1.15 (0.98–1.35) 1.18 (1.00–1.38) 1.21 (1.03–1.42) 1.25 (1.07–1.47) 1.25 (1.06–1.46)
Gastric non-cardia: incidence						
Levi et al. (2013) Israeli military cohort	1 088 530 (1967/2005–2006)	NR	130	19–57	16–19	vs BMI 18.5–24.9: BMI 25–29.9: 0.98 (0.51–1.89) BMI ≥ 30: 2.62 (0.96–7.15)
Hepatocellular carcinoma: incidence						
Berentzen et al. (2014) Boys in Copenhagen, Denmark (Copenhagen School Health Records Register)	188 360 (1930–1980)	144 417	229	Median, 59	7 8 9 10 11 12 13	1.18 (1.01–1.37) 1.17 (1.00–1.37) 1.25 (1.07–1.47) 1.29 (1.10–1.51) 1.31 (1.12–1.53) 1.36 (1.16–1.59) 1.36 (1.17–1.60)
Pancreatic cancer: incidence						
Levi et al. (2012) Israeli military cohort	720 927 (1967–1995)	NR	98	29–56	16–19	1.17 (0.96–1.52)[b]

Table 2.3b (continued)

Reference Cohort	Number at baseline Period of recruitment	Number at follow-up	Number of cancers	Adult age at final follow-up (years)	Childhood age at measurement (years)	Relative risk (95% CI) per SD or unit increase in BMI
Prostate cancer: mortality						
Gray et al. (2012) Harvard Alumni Health Study	19 593 (1914–1952)	NR	NR	NR	Mean, 18.4	1.04 (0.93–1.16)
Prostate cancer: incidence						
Aarestrup et al. (2014) Boys in Copenhagen, Denmark (Copenhagen School Health Records Register)	188 360 (1930–1969)	133 647	3355	Median, 66.5 (range, 40–81)	7 8 9 10 11 12 13	1.04 (0.98–1.10) 1.04 (0.98–1.11) 1.02 (0.96–1.09) 1.03 (0.97–1.09) 1.02 (0.96–1.08) 1.02 (0.96–1.08) 1.02 (0.96–1.09)
Batty et al. (2015) Scottish Mental Health Survey Scotland, United Kingdom	2332 1947–2014	2332	109	Maximum, 77	11	0.97 (0.80–1.18)
Renal cancer: incidence						
Bjørge et al. (2004) Norwegian Cancer Registry	115 267 (1963–2001)	NR	109	Mean, 45	14–19	≥ 85th percentile vs 25th–75th percentile: 2.64 (1.48–4.70)
Leiba et al. (2013) Israeli military cohort	1 110 835 (1967–2005)	NR	274	Mean, 44	16–19	1.19 (1.04–1.37)[b]
Urothelial cancer:[a] *incidence*						
Leiba et al. (2012) Israeli military cohort	1 110 835 (1967–2005)	NR	661	Mean, 35	16–19	1.21 (1.06–1.38)[b]
Glioma: incidence						
Kitahara et al. (2014a) Boys in Copenhagen, Denmark (Copenhagen School Health Records Register)	188 360	162 295	355	> 40	7 8 9 10 11 12 13	1.01 (0.86–1.17) 1.04 (0.89–1.22) 1.03 (0.88–1.21) 1.02 (0.87–1.19) 1.02 (0.87–1.19) 1.00 (0.86–1.17) 1.04 (0.89–1.21)

Table 2.3b (continued)

Reference Cohort	Number at baseline Period of recruitment	Number at follow-up	Number of cancers	Adult age at final follow-up (years)	Childhood age at measurement (years)	Relative risk (95% CI) per SD or unit increase in BMI
Thyroid cancer: incidence						
Farfel et al. (2014) Israeli military cohort	1 145 865 (1967–2005)	NR	425	19–57	16–19	BMI, Q5 vs Q1: 1.19 (0.87–1.63)
Kitahara et al. (2014b) Boys in Copenhagen, Denmark (Copenhagen School Health Records Register)	165 978	162 632	64	> 40	7 8 9 10 11 12 13	1.22 (0.93–1.60) 1.24 (0.94–1.63) 1.23 (0.93–1.63) 1.21 (0.91–1.60) 1.24 (0.94–1.65) 1.25 (0.94–1.66) 1.25 (0.93–1.66)
Girls						
Colon cancer: mortality						
Bjørge et al. (2008) Norwegian Cancer Registry	111 701 (1963–1975)	NR	108	Mean, 43	14–19	≥ 85th percentile vs 25th–75th percentile: 2.0 (1.2–3.5)
Oesophageal adenocarcinoma: incidence						
Cook et al. (2015) Girls in Copenhagen, Denmark (Copenhagen School Health Records Register)	184 276 (1931–1971)	126 723	38	> 40	7 8 9 10 11 12 13	1.30 (0.90–1.87) 1.41 (0.97–2.06) 1.49 (1.02–2.16) 1.44 (0.99–2.11) 1.63 (1.12–2.36) 1.55 (1.07–2.26) 1.68 (1.15–2.44)
Hepatocellular carcinoma: incidence						
Berentzen et al. (2014) Girls in Copenhagen, Denmark (Copenhagen School Health Records Register)	184 276 (1930–1980)	141 467	62	Median, 60.2	7 8 9 10 11 12 13	1.20 (0.90–1.60) 1.12 (0.84–1.50) 1.12 (0.83–1.51) 1.03 (0.77–1.39) 1.05 (0.78–1.40) 1.15 (0.85–1.54) 1.23 (0.93–1.65)
Ovarian cancer						
Engeland et al. (2003) Norwegian Cancer Registry	NR (1963–1999)	111 883	7882	Mean, 41	14–19	1.22 (1.01–1.49)[b]

Table 2.3b (continued)

Reference Cohort	Number at baseline Period of recruitment	Number at follow-up	Number of cancers	Adult age at final follow-up (years)	Childhood age at measurement (years)	Relative risk (95% CI) per SD or unit increase in BMI
Renal cancer: incidence						
Bjørge et al. (2004) Norwegian Cancer Registry	111 954 (1963–2001)	NR	45	Mean, 45	14–19	≥ 85th percentile vs 25th–75th percentile: 1.48 (0.57–3.85)
Glioma: incidence						
Kitahara et al. (2014a) Girls in Copenhagen, Denmark (Copenhagen School Health Records Register)	184 276	158 130	253	> 40	7 8 9 10 11 12 13	0.96 (0.79–1.16) 0.95 (0.79–1.16) 0.95 (0.79–1.16) 0.87 (0.72–1.06) 0.93 (0.76–1.13) 0.91 (0.75–1.10) 1.01 (0.83–1.22)
Thyroid cancer: incidence						
Farfel et al. (2014) Israeli military cohort	478 445 (1989–2005)	NR	323	19–57	16–19	BMI, Q5 vs Q1: 1.14 (0.81–1.60)
Kitahara et al. (2014b) Girls in Copenhagen, Denmark (Copenhagen School Health Records Register)	161 262	158 453	171	> 40	7 8 9 10 11 12 13	1.13 (0.96–1.33) 1.12 (0.95–1.32) 1.18 (1.00–1.39) 1.14 (0.96–1.35) 1.11 (0.94–1.31) 1.09 (0.92–1.29) 1.13 (0.96–1.34)

BMI, body mass index (in kg/m^2); CI, confidence interval; NR, not reported; SD, standard deviation.

[a] Bladder, ureter, and renal pelvis.

[b] Taken from the systematic review and meta-analysis by Simmonds et al. (2015).

Table 2.3c Prospective cohort studies of BMI at ages 18–25 years determined by recall and subsequent risk of cancer of the breast in postmenopausal women

Reference Cohort Country	Total number in cohort	Follow-up period (years)	Baseline age (years)	Recall age (years)	Number of cases	Relative risk (95% CI)
van den Brandt et al. (1997) Netherlands Cohort Study The Netherlands	62 573	4.3	55–69	20	626	Per 8 kg/m²: 0.79 (0.58–1.08)
Ahn et al. (2007) NIH-AARP Diet and Health Study USA	99 039	3.9	50–71 All postmenopausal	18	2111	BMI ≥ 30.0 vs 18.5–22.4: HRT non-users 0.48 (0.27–0.86) HRT current users 0.65 (0.35–1.23)
Palmer et al. (2007) Black Women's Health Study USA	9542	10	21–69	18	442	BMI ≥ 25.0 vs < 20.0: 0.55 (0.37–0.82)
Baer et al. (2010) Nurses' Health Study (NHS) and NHS II USA	188 860	16	NHS, 30–55 NHS II, 25–42	20	4974	Per 1 kg/m²: 0.93 (0.90–0.95)
Kawai et al. (2010) Miyagi Cohort Study Japan	10 106	12.8	40–64	20	108	BMI ≥ 23.8 vs < 20.5: 0.44 (0.24–0.81)
Suzuki et al. (2011) Japan Public Health Cohort Study Japan	41 594	10	40–59	20	232	Per 5 kg/m²: 0.77 (0.59–1.02)
White et al. (2012) Multiethnic Cohort USA	82 971	NR	45–75	21	3030	BMI ≥ 30.0 vs < 20.0–24.9: 0.63 (0.43–0.91)
Fagherazzi et al. (2013) French E3N cohort France	81 089	NR	40–64	20–25	2828	Level ≥ 4 vs level 1:[a] 0.86 (0.74–1.00)
Krishnan et al. (2013) Melbourne Collaborative Cohort Study Australia	14 441	16.5	27–76 (99% 40–69)	18–21	668	Per 5 kg/m²: 0.90 (0.79–1.04)

Table 2.3c (continued)

Reference Cohort Country	Total number in cohort	Follow-up period (years)	Baseline age (years)	Recall age (years)	Number of cases	Relative risk (95% CI)
Catsburg et al. (2014) Canadian Study of Diet, Lifestyle and Health Canada	2210	12	67	20	541	BMI ≥ 30.0 vs 18.5–24.9: 0.21 (0.03–1.59)

BMI, body mass index (in kg/m^2); CI, confidence interval; HRT, hormone replacement therapy; NR, not reported

[a] Participants were asked to recall their body fatness by using a 9-level figure drawing, where level 1 represents the most lean and level 9 represents the most overweight.

Table 2.3d Prospective cohort studies of BMI at ages 18–25 years determined by recall and subsequent risk of cancer of the breast in premenopausal women

Reference Cohort Country	Total number in cohort	Follow-up period (years)	Baseline age (years)	Recall age (years)	Number of cancers	Relative risk (95% CI)
Palmer et al. (2007) Black Women's Health Study USA	42 538	10	21–69	18	491	BMI ≥ 25.0 vs < 20.0: 0.63 (0.46–0.87)
Baer et al. (2010); Michels et al. (2012) Nurses' Health Study (NHS) and NHS II USA	188 860	16	NHS, 30–55 NHS II, 25–42	20	2188	Per 1 kg/m^2: 0.89 (0.86–0.93)
Suzuki et al. (2011) Japan Public Health Cohort Study Japan	41 594	10	40–59	20	220	Per 5 kg/m^2: 0.78 (0.57–1.06)
Fagherazzi et al. (2013) French E3N cohort France	81 089	NR	40–64	20–25	745	Level ≥ 4 vs level 1:[a] 1.22 (0.88–1.69)
Catsburg et al. (2014) Canadian Study of Diet, Lifestyle and Health Canada	1110	14	45	20	556	BMI ≥ 30.0 vs 18.5–24.9: 0.96 (0.33–2.81)

BMI, body mass index (in kg/m^2); CI, confidence interval; NR, not reported

[a] Participants were asked to recall their body fatness by using a 9-level figure drawing, where level 1 represents the most lean and level 9 represents the most overweight.

Table 2.3e Relative risk of selected cancers according to trajectories of body shape from age 5 years to age 60 years in women and in men

Cancer type	Category of body shape trajectory[a]				
	Lean-stable	Lean-moderate increase	Lean-marked increase	Medium-stable	Heavy-stable/increase
Women					
Number of participants	13 183	18 405	18 217	23 288	11 699
Colorectal cancer	1.00	0.97 (0.80–1.17)	1.22 (1.00–1.49)	1.02 (0.85–1.22)	1.40 (1.13–1.74)
Oesophageal adenocarcinoma	1.00	1.02 (0.29–3.63)	2.56 (0.82–8.03)	1.04 (0.30–3.57)	2.19 (0.63–7.70)
Pancreatic cancer	1.00	1.18 (0.82–1.69)	1.36 (0.93–1.98)	1.15 (0.81–1.63)	1.39 (0.91–2.12)
Kidney cancer	1.00	1.26 (0.78–2.04)	1.89 (1.19–3.03)	1.05 (0.65–1.69)	1.92 (1.15–3.21)
Postmenopausal breast cancer	1.00	1.30 (1.17–1.45)	1.41 (1.26–1.58)	1.05 (0.94–1.17)	1.11 (0.97–1.28)
Endometrial cancer	1.00	0.99 (0.75–1.29)	1.57 (1.21–2.03)	0.94 (0.73–1.22)	2.08 (1.59–2.73)
Ovarian cancer	1.00	0.88 (0.66–1.16)	0.93 (0.70–1.25)	0.88 (0.67–1.15)	0.84 (0.59–1.19)
Men					
Number of participants	5946	6881	14 225	5725	4929
Colorectal cancer	1.00	1.36 (1.03–1.80)	1.23 (0.95–1.60)	1.26 (0.92–1.72)	1.47 (1.05–2.05)
Oesophageal adenocarcinoma	1.00	1.90 (0.67–5.34)	2.09 (0.80–5.48)	1.53 (0.48–4.84)	3.01 (1.04–9.13)
Pancreatic cancer	1.00	0.85 (0.54–1.35)	1.20 (0.81–1.78)	1.12 (0.70–1.80)	1.50 (0.92–2.46)
Kidney cancer	1.00	1.05 (0.67–1.64)	0.94 (0.63–1.43)	1.07 (0.66–1.74)	0.93 (0.53–1.64)
Advanced prostate cancer	1.00	1.16 (0.91–1.47)	0.97 (0.78–1.21)	1.00 (0.76–1.32)	0.67 (0.47–0.95)

[a] Trajectories of body shape: maintained a lean body shape (lean-stable); started lean and experienced a moderate increase in body shape (lean-moderate increase); started lean and gained a substantial amount of weight (lean-marked increase); maintained a medium body shape (medium-stable); started heavy and maintained or gained weight (heavy-stable/increase).

Source: Song et al. (2016). Data for women are from the Nurses' Health Study, and data for men are from the Health Professionals Follow-up Study.

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2.4 Excess body fatness in cancer survivors

2.4.1 Studies of weight at diagnosis and cancer outcomes

An increasing number of observational studies are focusing on the association between excess body fatness and prognosis in cancer survivors. Specifically, more than 100 individual reports have evaluated the relationship between BMI or body weight at the time of diagnosis of early-stage breast cancer and the risk of breast cancer recurrence, breast cancer-related mortality, and all-cause mortality.

A meta-analysis of 82 reports on this topic (all but 8 of which had a median follow-up of at least 5 years) incorporated data from 213 075 women (Chan et al., 2014). Women who were obese (BMI > 30.0 kg/m^2) at the time of diagnosis of breast cancer had a 35% increased risk (RR, 1.35; 95% CI, 1.24–1.47) of breast cancer-related mortality and a 41% increased risk of all-cause mortality compared with women who were of normal weight at the time of breast cancer diagnosis. The association between obesity and poor outcomes was seen in both postmenopausal and premenopausal breast cancer survivors, with summary relative risks for all-cause mortality in obese versus normal-weight women of 1.75 (95% CI, 1.26–2.41) in women with premenopausal breast cancer and 1.34 (95% CI, 1.18–1.53) in women with postmenopausal breast cancer.

In another study, the WCRF Continuous Update Project reviewed data on the association in female breast cancer survivors between weight and the risk of dying of breast cancer, second cancers, or any cause (WCRF/AICR, 2014). The report stressed the importance of taking into account the timing of weight measurement, focusing on three main time points: (i) before diagnosis; (ii) less than 12 months after diagnosis; and (iii) more than 12 months after diagnosis. Associations were observed between measures of adiposity and prognosis, but there were many pitfalls to interpretations, biases, and confounding. The evidence linking obesity to cancer survival was rated as "limited-suggestive", primarily because of concerns about the timing of baseline BMI analysis in relation to cancer diagnosis in some studies.

Fewer studies have evaluated the association between body fatness and cancer prognosis in other malignancies. A meta-analysis that evaluated the relationship between obesity and colorectal cancer outcomes included 16 reports that encompassed 58 917 individuals followed up for a median of 9.9 years (Lee et al., 2015). Obesity before diagnosis of colorectal cancer was associated with an increased risk of colorectal cancer-specific mortality (RR, 1.22; 95% CI, 1.00–1.35) and all-cause mortality (RR, 1.25; 95% CI, 1.14–1.36). Obesity after diagnosis of colorectal cancer was also associated with an increased risk of all-cause mortality (RR, 1.08; 95% CI, 1.03–1.13).

Excess body fatness has also been linked with biochemical recurrence of cancer (rising levels of prostate-specific antigen [PSA]) in men with early-stage prostate cancer treated with radical prostatectomy or external beam radiation. A meta-analysis of 26 studies, including 36 927 men, estimated a 16% increase in the risk of elevated PSA levels with each 5 kg/m^2 increase in BMI (RR, 1.16; 95% CI, 1.08–1.24) (Hu et al., 2014).

A meta-analysis of 14 studies that assessed BMI before or shortly after diagnosis in women with ovarian cancer estimated a hazard ratio for all-cause mortality of 1.17 (95% CI, 1.03–1.34) for obese versus non-obese patients (Protani et al., 2012). Another meta-analysis of 13 cohort studies of individuals with pancreatic cancer reported an adjusted hazard ratio for pancreatic cancer-related mortality of 1.06 (95% CI, 1.02–1.11) in overweight patients and of 1.31 (95%

CI, 1.20–1.42) in obese patients versus normal-weight patients (Majumder et al., 2015).

Meta-analyses and/or systematic reviews on obesity and cancer survival have also been conducted in patients with endometrial cancer (Arem & Irwin, 2013; Nakao et al., 2014) and with childhood leukaemia (Amankwah et al., 2015).

[It is unclear whether the relationship between obesity and increased risk of cancer-related mortality stems from differences in the biological aggressiveness or subtypes of cancers that develop in obese versus non-obese patients. Some studies have suggested that obese individuals are more likely to develop biologically aggressive cancers with poorer outcomes, or to have more advanced disease at the time of diagnosis. For example, studies have shown that obese individuals are at increased risk of developing biologically aggressive prostate cancers, but not of developing lower-grade prostate cancers (see Section 2.2.14). Some reports suggest that obese women are more likely to develop poorly differentiated and hormone receptor-negative breast cancers (Stark et al., 2010; Abdel-Maksoud et al., 2012), although other reports suggest that obese women are more likely to develop slower-growing hormone receptor-positive breast cancers (Borgquist et al., 2009; Canchola et al., 2012; Biglia et al., 2013). A few recent studies that have used genomic profiling techniques have suggested that obese women who develop hormone receptor-positive cancers are more likely to have luminal B cancers, which have been shown to have a worse prognosis, compared with luminal A cancers (Kwan et al., 2015; Ligibel et al., 2015). See Section 2.2.9 for more detailed data on risk estimates by subtype of breast cancer.]

2.4.2 Studies of weight change after cancer diagnosis and cancer outcomes

Fewer studies have investigated the association between weight change after cancer diagnosis and recurrence-free or overall survival.

A recent meta-analysis of 12 studies examined the association between weight gain after diagnosis of breast cancer and prognosis (Playdon et al., 2015). High weight gain after breast cancer diagnosis (> 10% of body weight at diagnosis) increased the risk of both all-cause mortality and breast cancer-specific mortality, whereas moderate weight gain (5–10%) did not (HR, 0.98; 95% CI, 0.83–1.15). The increased risk was observed among women with a BMI at diagnosis of less than 25 kg/m^2 and of 25 kg/m^2 or more. In an earlier analysis of a prospective cohort study of 5204 non-smoking women with early-stage breast cancer, those who gained more than 2 kg/m^2 had a significantly increased risk of death from breast cancer compared with women who maintained a stable weight; the relative risk of death from breast cancer was 1.35 (95% CI, 0.93–1.95) for weight gain of 0.5–2 kg/m^2 and 1.64 (95% CI, 1.07–2.51) for weight gain of more than 2 kg/m^2 (Kroenke et al., 2005). In contrast, in another study of 1692 women with early-stage breast cancer, no association was observed between weight gain and breast cancer recurrence or all-cause mortality, even among women who gained more than 10% of their baseline body weight (Caan et al., 2006).

2.4.3 Intervention trials of weight-loss intervention and dietary modification

No data were available to the Working Group about the impact of a weight-loss intervention on cancer recurrence, cancer-related mortality, or all-cause mortality in cancer survivors.

Two randomized trials assessed the impact of dietary modification on disease-free and overall survival in women with early-stage breast cancer.

The Women's Intervention Nutrition Study randomized 2400 women to a low-fat dietary intervention or usual care (control group) (Chlebowski et al., 2008). Patients assigned to the intervention group reduced their dietary fat intake for the duration of the 5-year intervention.

Intervention participants experienced an average weight loss of 6 lb (2.7 kg). An initial analysis of study results demonstrated a 24% reduction in breast cancer recurrence compared with the control group (HR, 0.76; 95% CI, 0.60–0.98) (Chlebowski et al., 2006), although the difference lost statistical significance with further follow-up (Chlebowski et al., 2008). Unplanned subset analysis suggested that the impact of the intervention differed in women with ER-positive cancers versus those with ER-negative cancers, with a hazard ratio for recurrence in the intervention group versus controls of 0.58 (95% CI, 0.37–0.91) in women with ER-negative cancers and 0.85 (95% CI, 0.63–1.14) in women with ER-positive cancers ($P_{interaction} = 0.15$). [The weight loss experienced by participants in the Women's Intervention Nutrition Study may have contributed to the reduced risk of cancer recurrence in intervention participants in that study.]

In contrast, the Women's Healthy Eating and Living study randomized 3088 women to a counselling programme for a diet very high in fruits and vegetables and low in fat or printed guidelines (Pierce et al., 2007). Adherence to the dietary intervention was good, with intervention participants increasing their daily intake of vegetables by 65% and of fruits by 25%, and reducing their daily intake of fat by 13%. [Of note, participants consumed on average seven servings of fruits and vegetables per day at baseline.] Participants randomized to the dietary intervention group did not lose weight compared with controls. The dietary intervention had no impact on rates of recurrence (HR for recurrence in intervention group vs controls, 0.96; 95% CI, 0.80–1.14).

[There were several differences between the trials, including in the degree of reduction in dietary fat intake achieved by intervention participants, the baseline diets, the delivery method of the dietary intervention, the timing of enrolment relative to breast cancer diagnosis, and the study population.]

Several ongoing studies are testing the hypothesis that weight loss after cancer diagnosis reduces the risk of cancer recurrence or progression in individuals with early-stage cancer (Courneya et al., 2008; Rack et al., 2010; Villarini et al., 2012; Crane et al., 2014; Parsons et al., 2014).

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2.5 Sustained weight loss and cancer risk: illustrative examples

Studies investigating whether weight loss protects against cancer occurrence are limited to a few observational studies on weight reduction in relation to breast cancer incidence and on the impact of intentional weight loss after bariatric surgery on cancer risk in morbidly obese patients.

2.5.1 Studies of weight loss and cancer risk

Few observational studies have been able to assess the impact of weight loss on cancer risk. Women from the Nurses' Health Study who had never used postmenopausal HRT and had lost 10 kg or more sustainably since menopause [duration not reported] had a lower risk of postmenopausal breast cancer than those who maintained their weight since menopause (RR, 0.43; 95% CI, 0.21–0.86) (Eliassen et al., 2006). However, no association was found between short-term (4-year) weight loss and subsequent cancer risk in the same cohort (Rosner et al., 2015). In contrast, regardless of use of postmenopausal HRT, adult weight loss was unrelated to postmenopausal breast cancer risk compared with stable weight in the NIH-AARP study (Ahn et al., 2007), the EPIC-PANACEA study (Emaus et al., 2014), and the Cancer Prevention Study II for the first 5 years of follow-up (Teras et al., 2011); however, in the Cancer Prevention Study II an inverse association was suggested in women who maintained a weight loss of 10 lb [4.5 kg] or more for the next 4 years. Similarly, in the Women's Health Initiative Dietary Intervention Trial, no effect of weight loss on postmenopausal breast cancer risk was found in overweight or obese women (Neuhouser et al., 2015).

[It is important to note that many of the published trials and observational studies were not designed to document weight loss, and weight change may reflect both intentional weight loss (with uncertainty about what exactly the intervention was) and unintentional weight loss (which is potentially illness-induced).]

2.5.2 Studies of bariatric surgery and cancer risk

Several prospective intervention trials or retrospective cohort studies (Christou et al., 2008; Adams et al., 2009; Sjöström et al., 2009; Ward et al., 2014) and reviews (Tee et al., 2013; Maestro et al., 2015) have evaluated the effect of bariatric surgery on cancer risk, comparing the risk of cancer in patients who underwent bariatric surgery with that in an obese control group who did not undergo surgery (Table 2.5). Overall, in most studies the risk of cancer at all sites in obese patients was significantly reduced after bariatric surgery. A 45% decrease in risk of all cancers combined was estimated in a recent meta-analysis (RR, 0.55; 95% CI, 0.41–0.73) (Tee et al., 2013). The extent of the cancer-protective effect of bariatric surgery seems to be more pronounced in women than in men: in the Swedish Obese Subjects study, after a median follow-up of more than 10 years, the relative risk was 0.58 (95% CI, 0.44–0.77) in women and 0.97 (95% CI, 0.62–1.52) in men (Sjöström et al., 2009). Also, there are broadly consistent inverse associations with the subsequent risk of female sex hormone-sensitive cancers, notably endometrial cancer and breast cancer (Adams et al., 2009; Tee et al., 2013; Ward et al., 2014). [However, there were methodological problems in the study designs because of confounding by indication, and failure to adequately capture the extent of body weight reduction after bariatric surgery.]

Studies using population-level registry data (i.e. standardized population cohorts) for comparison purposes have reported an increased incidence of colorectal cancer in obese men who underwent bariatric surgery compared with the expected risk in the general population (Östlund et al., 2010; Derogar et al., 2013). [Because the general population was used as comparator, the median BMI (not reported) would have been considerably less than that for the treatment group, and the observed increase in incidence might reflect the effect of the premature morbidly obese status rather than of the surgery itself. Therefore, any comparison with the general population may be misleading in the evaluation of the effects of bariatric surgery on subsequent cancer risk in obese patients.]

Table 2.5 Studies of obese patients who underwent bariatric surgery and subsequent cancer risk

Reference Location	Study design Mean follow-up (years)	Surgery group	Control group	Cancer site	Surgery cases (cohort) Control cases (cohort)	Relative risk (95% CI)	Adjustments Comments
Men and women							
Christou et al. (2008) Canada	Retrospective hospital-based Maximum, 5.0	Bariatric patients in regional database BMI not available	Diagnosis of "morbid obesity" from hospital records or prescription BMI unknown	All sites[a]	21 (1035) 487 (5746)	0.22 (0.14–0.35)	Age, sex, BMI
Adams et al. (2009) Utah, USA	Retrospective registry 12.5	Roux-en-Y gastric bypass Mean BMI, 44.9	State document applicants with a self-reported BMI > 35 Mean BMI, 47.4	All sites[b]	254 (6596) 477 (9442)	0.76 (0.65–0.89)	Age, sex, BMI Data also reported for the 31 individual cancer sites
				"Obesity-related sites"[c]	104 (6596) 253 (9442)	0.62 (0.49–0.78)	
				Colorectum	25 (6596) 52 (9442)	0.70 (0.43–1.15)	
Women							
Adams et al. (2009) Utah, USA	Retrospective registry Median, 12.5	Roux-en-Y gastric bypass Mean BMI, 44.9	State document applicants with a self-reported BMI > 35 Mean BMI, 47.4	All sites[b]	215 (5654) 412 (7872)	0.73 (0.62–0.87)	Age, BMI
				Breast	25 (5654) 52 (7872)	0.91 (0.67–1.24)	
				Premenopausal breast	49 (5654) 65 (7872)	0.93 (0.63–1.37)	
				Postmenopausal breast	24 (5654) 40 (7872)	0.96 (0.57–1.63)	
				Corpus uteri	14 (5654) 98 (7872)	0.22 (0.13–0.40)	
Sjöström et al. (2009) Sweden	Prospective intervention trial 10.9	Mean BMI, 42.2	Matched using 18 anthropometric, cardiovascular, and biochemical indices Mean BMI, 41.6	All sites[d]	79 (1420) 130 (1447)	0.58 (0.44–0.77)	Age, smoking, weight change, energy intake, and matching Also significantly reduced for melanoma and haematopoietic cancers
Ward et al. (2014) USA	Retrospective clinical data repository Unknown	All female patients with a history of bariatric surgery BMI unknown	All female admissions with an associated diagnosis of obesity BMI unknown	Corpus uteri	424 (103 797) 43 921 (7 328 061)	0.29 (0.26–0.32)	None

Table 2.5 (continued)

Reference Location	Study design Mean follow-up (years)	Surgery group	Control group	Cancer site	Surgery cases (cohort) Control cases (cohort)	Relative risk (95% CI)	Adjustments Comments
Men							
Adams et al. (2009) Utah, USA	Retrospective registry 12.5	Roux-en-Y gastric bypass Mean BMI, 44.9	State document applicants with a self-reported BMI > 35 Mean BMI, 47.4	All sites[b]	39 (942) 65 (1570)	1.02 (0.69–1.51)	Age, BMI
Sjöström et al. (2009) Sweden	Prospective intervention trial 10.9	Mean BMI, 40.6	Matched using 18 anthropometric, cardiovascular, and biochemical indices Mean BMI, 39.2	All sites[d]	39 (590) 39 (590)	0.97 (0.62–1.52)	Age, smoking, weight change, energy intake, and matching Results were not statistically significant for any of the individual cancer sites

[a] Includes colorectum, pancreas, breast, endometrium, kidney, melanoma, myeloma, and non-Hodgkin lymphoma.
[b] Includes 31 cancer sites and "other".
[c] Includes colorectum, oesophagus (adenocarcinoma), liver, gall bladder, pancreas, postmenopausal breast, corpus and uterus, kidney, non-Hodgkin lymphoma, leukaemia, and multiple myeloma.
[d] Includes colorectum, stomach, liver, pancreas, kidney, bladder, lung and bronchia, haematopoietic system, and melanoma for both sexes, and breast, cervix, and endometrium in women and prostate in men.
BMI, body mass index (in kg/m^2); CI, confidence interval

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