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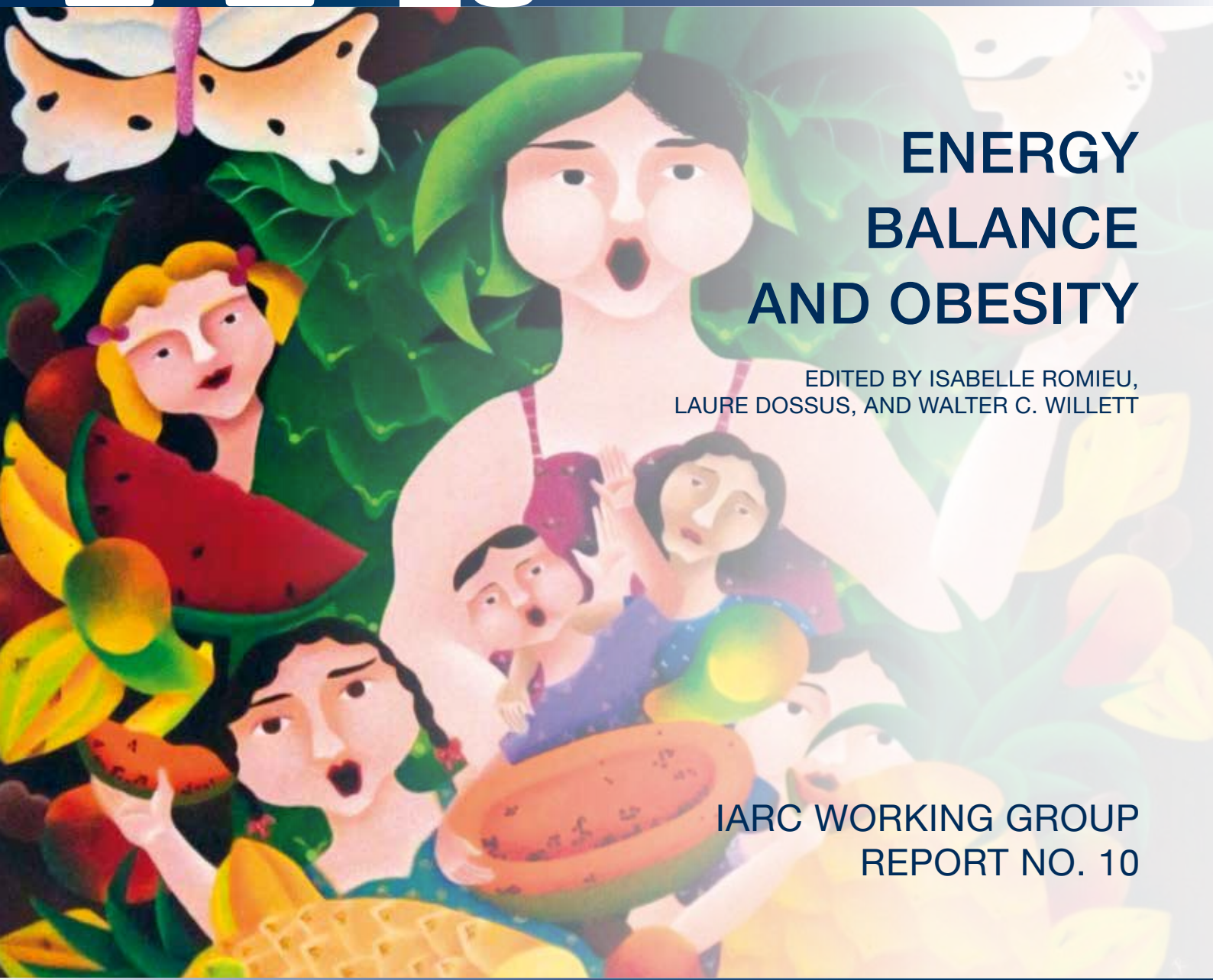

ENERGY BALANCE AND OBESITY

EDITED BY ISABELLE ROMIEU, LAURE DOSSUS, AND WALTER C. WILLETT

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International Agency for Research on Cancer
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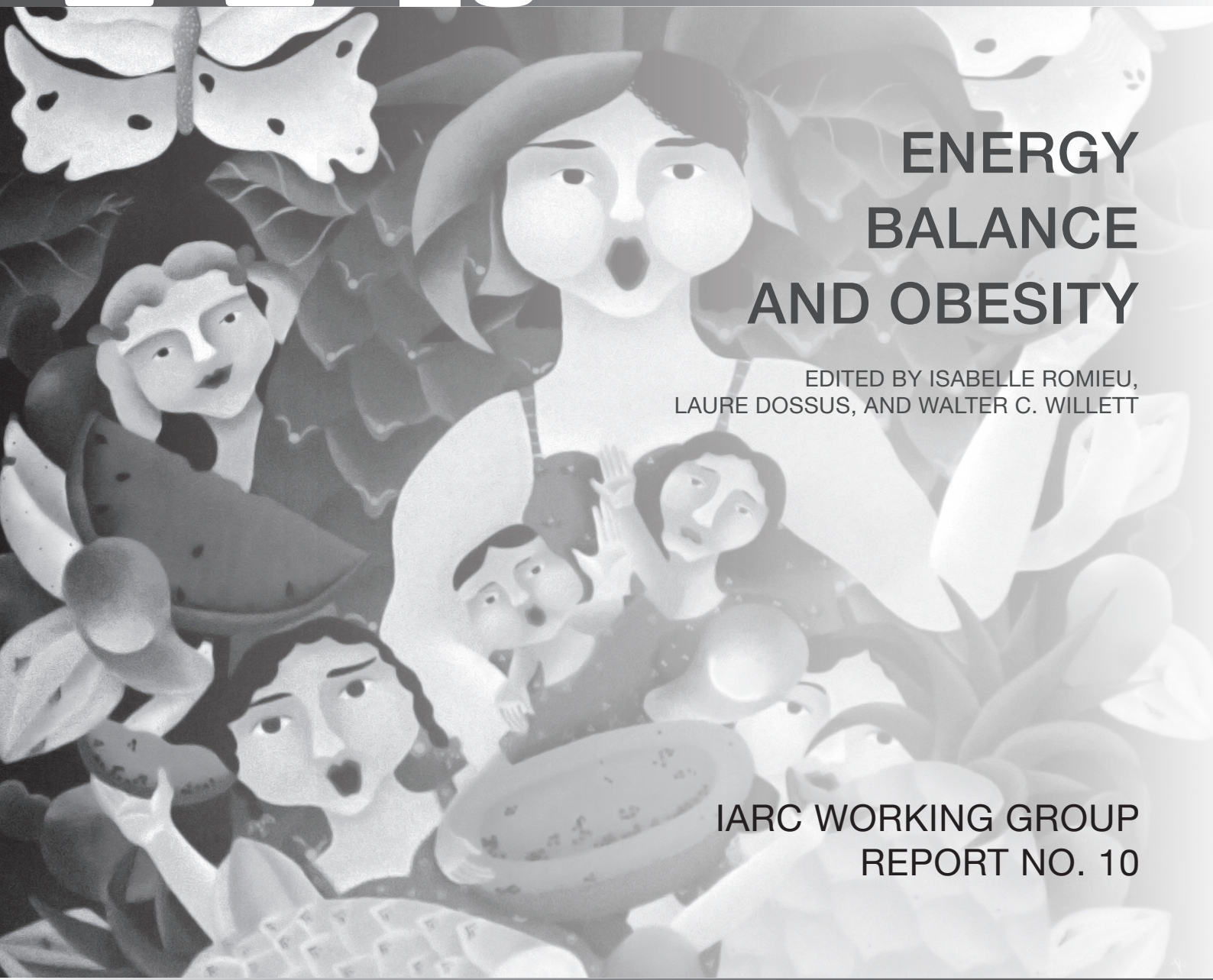

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Foreword

Recent estimates indicate that worldwide about three quarters of a billion people are obese, and that by 2025 approximately one in five of all adults will be obese. Many more adults are and will be overweight. This trend is accompanied by a major disease burden, including diabetes, cardiovascular disease, and cancer. Characterizing the increased risk of cancer among individuals who are overweight or obese is one of the major successes in etiological cancer research in the past two decades. The global cancer burden in 2012 associated with high body mass index was estimated to be 481 000 cases, translating to 3.6% of all new cancers in adults. The contribution was greater in women than men and in countries with very high and high Human Development Index. A recent IARC report (Lauby-Secretan et al., N Engl J Med. 2016; 375(8):794–8) concluded that there was sufficient evidence for a cancer-preventive effect of avoidance of weight gain for 13 different types of cancer.

Describing the problem is an important step, but it is not enough. While knowledge of the risks has progressed, there is far less progress in understanding how to combat the problem. For some populations the challenge is to reverse an existing problem, whereas other populations still have the opportunity to avoid repeating the changes in patterns that have occurred elsewhere. To inform these efforts, several important research gaps are evident, including: better characterizing the drivers of overweight and obesity (energy balance, dietary composition, physical inactivity, social environment, marketing and pricing of unhealthy foods, etc.); understanding the mechanisms by which these factors act and thus how they may be countered; elucidating the health effects of overweight and obesity at different times in the life-course; and the stark need to develop and evaluate behavioural and policy interventions to prevent or reverse overweight and obesity at all ages.

This IARC Working Group Report summarizes and evaluates the available scientific evidence on what is driving the obesity epidemic. The report reviews the important characteristics of a healthy diet, the biological and physiological pathways modulated by dietary components, and the effects of physical activity. The major impacts of the food environment, marketing of unhealthy foods, and urbanization are also highlighted. All the evidence points to the requirement for a multisectoral approach to reverse the rise in the prevalence of obesity in all age groups and in all populations. There can be few greater challenges to public health in the coming decades.

The intention of our Agency is that this volume will provide a valuable scientific evidence base for the next steps in research and for the subsequent translation of research into policy by other national and international bodies.

Dr Christopher P. Wild
Director, International Agency for Research on Cancer

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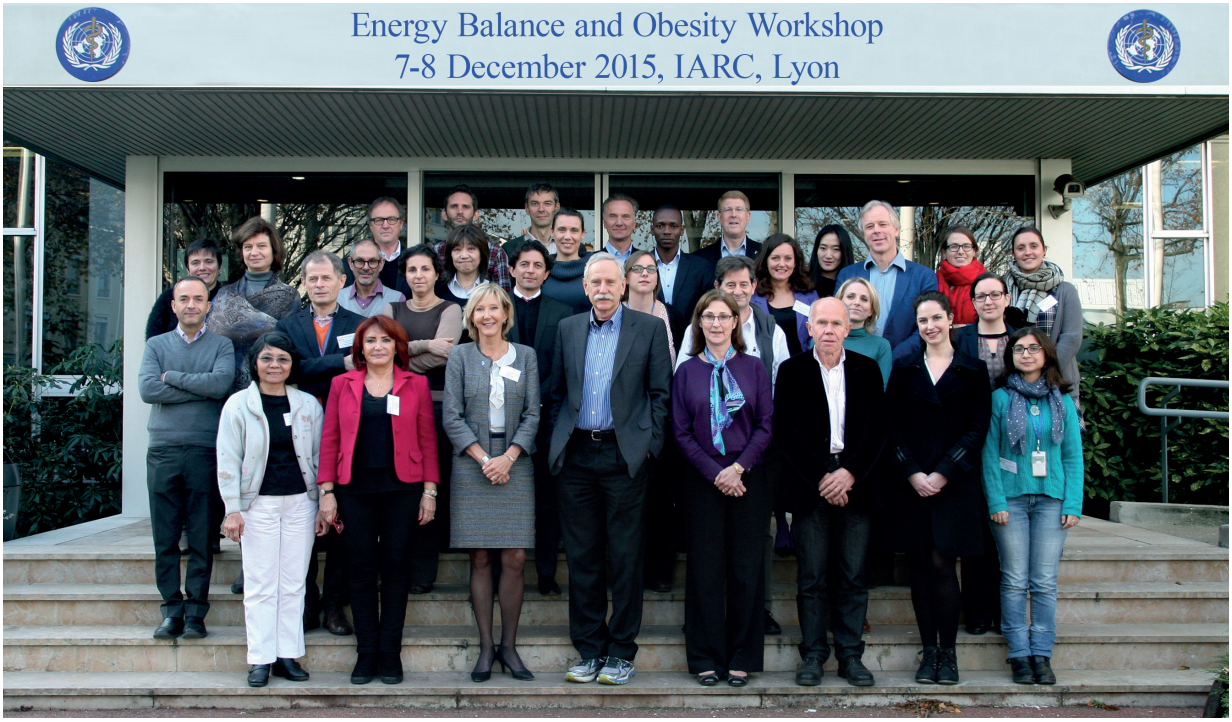

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Executive summary

The International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) convened a Working Group meeting in Lyon in December 2015 to review the evidence regarding energy balance and obesity and to consider the following scientific questions:

- Are the drivers of the obesity epidemic related only to energy excess and/or do specific foods or nutrients play a major role in this epidemic?
- What are the factors that modulate these associations?
- Which types of data and/or studies will further improve our understanding?

This IARC Working Group Report provides summaries of the evidence from the literature as well as the Working Group's conclusions and recommendations to tackle the global epidemic of obesity.

A summary of the topics addressed and the conclusions and recommendations of the Working Group has been published in *Cancer Causes & Control* [1].

Prevalence of overweight and obesity

Obesity is now well recognized as a disease in its own right, one that is largely preventable through changes in lifestyle, especially diet. Obesity is also a major risk factor associated with increased morbidity and mortality from many noncommunicable diseases (NCDs). Obesity has increasingly been considered to be a life-course condition, with its roots being established during pregnancy and with an intergenerational cycle, overlapping with the secular trend.

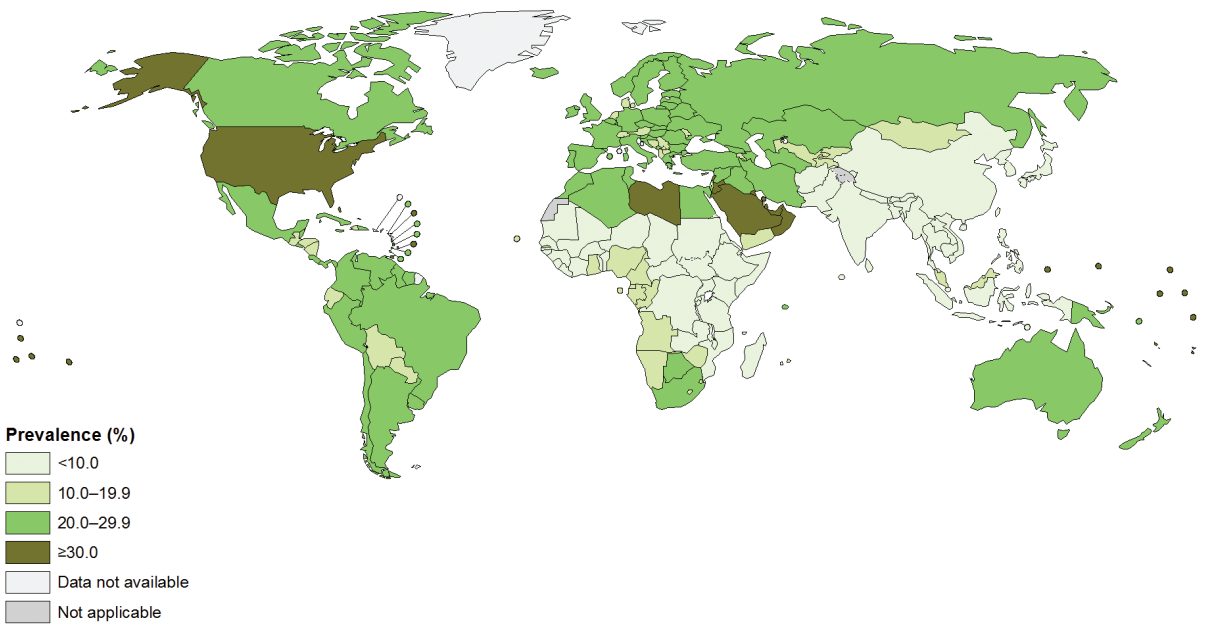
Obesity rates have been constantly increasing during the past 30 years. The worldwide prevalence of obesity in adults nearly doubled between 1980 and 2014 [2]. In 2014 there were 41 million overweight children younger than 5 years in the world, about 10 million more than there were in 1990. In 2014, almost half of all overweight children younger than 5 years lived in Asia, and one quarter lived in Africa. The number of overweight children in lower-middle-income countries has more than doubled since 1990, from 7.5 million to 15.5 million [3].

In 2014, 39% of adults aged 18 years and older (38% of men and 40% of women) were overweight. The prevalence of obesity in high-income countries (HICs) and upper-middle-income countries is more than double that in low-income countries (Fig. 1), and an increasing number of countries are affected.

The double burden of malnutrition

The double burden of malnutrition is the coexistence of undernutrition (including macronutrient and micronutrient deficiencies) and overnutrition in the same population across the life-course. In most regions, undernutrition and overnutrition coexist in the same country, in the same community, or even in the same household.

Fig. 1. The prevalence of obesity (body mass index ≥ 30 kg/m^2) in adults aged 18 years and older, for both sexes, in 2014 (age-standardized estimates). Source: WHO Global Health Observatory.



Although the prevalence of stunting and wasting in preschool children in low- and middle-income countries (LMICs) has declined, the rapid rise in rates of overweight/obesity in both children and adults is striking. The hidden hunger index indicates persistent problems. Hot spots and severe problems have been found in most countries in sub-Saharan Africa and South Asia and in some countries in South-East Asia.

Rapid economic development and urbanization in LMICs have resulted in rapidly changing dietary patterns. Increasingly, there is a shift away from traditional plant-based diets to less-nutrient-dense diets with consumption of highly processed foods and sugar-sweetened beverages, with a simultaneous reduction in physical activity levels across all ages. For many LMICs, government policy does not address these drivers of the double burden of malnutrition. Hence, many LMICs face a triple burden of malnutrition, with persistence of undernutrition, micronutrient deficiencies, and overnutrition, and the resulting rapidly increasing rates of obesity and related NCDs, including cancer.

The nutrition transition in LMICs provides an important opportunity to study the rapid changes in dietary patterns and physical activity levels, and to fill the gaps in our knowledge about whether these factors can explain the increases in cancer risk observed across different populations, so that programmes and policies can be strategically designed.

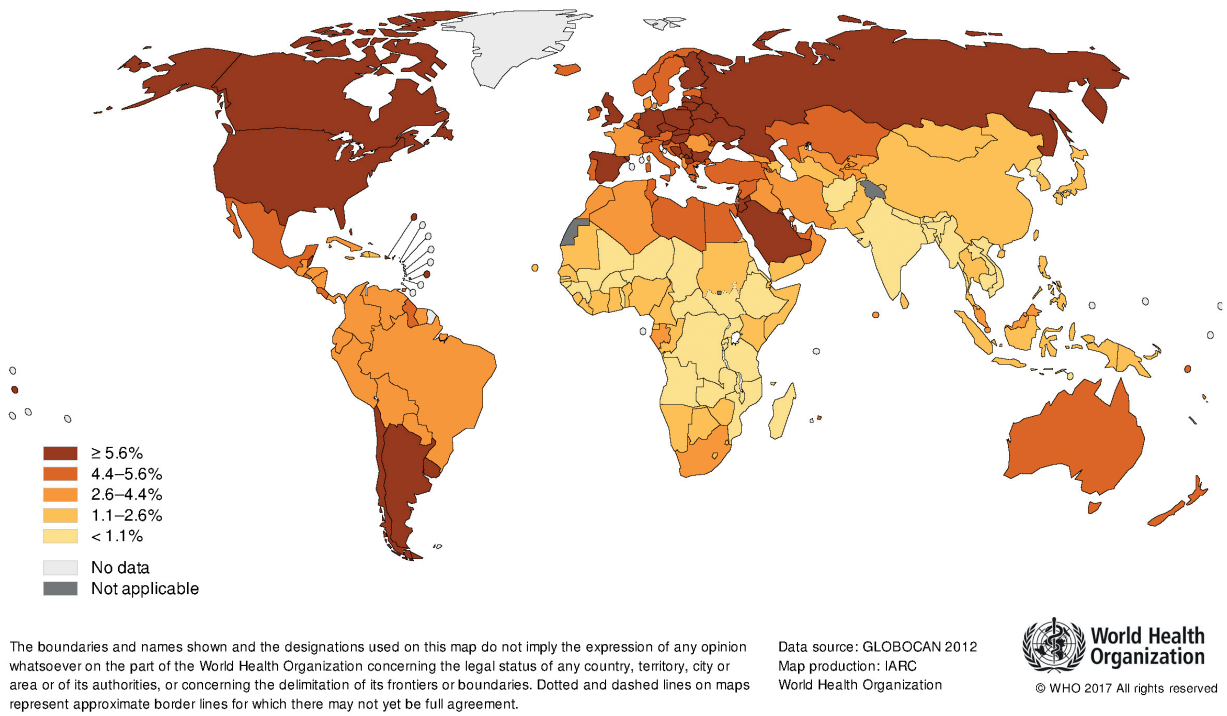
Obesity and cancer

The increase in the global burden of cancer may be explained partly by demographic changes; however, changes in lifestyle factors and globalization related to diet (increased consumption of highly processed foods and sugar-sweetened beverages) and increases in sedentary behaviour are also increasingly being recognized as major contributors to the rising prevalence of obesity and the increasing cancer burden.

The World Cancer Research Fund (WCRF) has reviewed the evidence linking diet, physical activity, body composition, and cancer worldwide in a systematic way [4]. From the WCRF review, there is convincing evidence for the role of obesity as a causal factor for several types of cancer, including cancers of the colorectum, endometrium, kidney, oesophagus, postmenopausal breast, gallbladder, and pancreas, and advanced prostate cancer.

A recent evaluation of the global cancer burden linked to obesity estimated that 481 000 or 3.6% of all new cancer cases in adults in 2012 were attributable to high body mass index (BMI) [5]. Cancers of the corpus uteri, postmenopausal breast, and colon accounted for

Fig. 2. The percentage of all cancer cases (at all anatomical sites) attributable to excess body mass index (BMI), for both sexes, in 2012. Source: Arnold et al. (2015) [31].



63.6% of cancers attributable to high BMI (about 10% of all cancers). Although the attributable burden was larger in HICs, high BMI appears to play a substantial role in Latin America, the Middle East and North Africa, and South Africa (Fig. 2). Furthermore, taking into account both current population mean BMI and the BMI changes over time, a larger increase in the population attributable fraction was observed in the Middle East and North Africa and in Latin America and the Caribbean, pointing to the importance of the cumulative effects of overweight and obesity in cancer etiology. Because there is a time lag between the development of obesity and the appearance of related comorbidity, it can be expected that the burden of obesity-related disease will increase markedly and will continue to do so for some time.

Recent progress in elucidating the mechanisms underlying the obesity–cancer link suggests that obesity exerts pleomorphic effects on pathways related to tumour development and progression. Therefore, there are multiple opportunities for primary, secondary, and tertiary prevention of obesity-related cancers. It is now known that obesity can affect each of the well-established hallmarks of cancer, but obesity-associated perturbations in systemic metabolism and inflammation, and the interactions of these perturbations with cancer cell energetics, are emerging as the primary drivers of obesity-associated cancer development and progression.

Interventions to prevent and control the rise in the prevalence of obesity are needed in order to control the rapid increase in the burden of NCDs, including cancer.

Energy intake and energy expenditure

Energy balance is the result of equilibrium between energy intake and energy expenditure. When energy intake exceeds energy expenditure, the excess energy is deposited as body tissue [6]. Such positive energy balance is a normal feature of growth during childhood, and of pregnancy, when accumulation of body tissue is physiological. During adulthood, the maintenance of stable body weight depends on the energy derived from food and drink (energy intake) being equal to the total energy expenditure over time.

Total energy expenditure is the sum of the basal metabolic rate, the energy expended in physical activity, and the energy expended in digestion of foods and absorption and assimilation of nutrients (diet-induced thermogenesis). The main determinant of the basal metabolic rate is the mass of lean tissue, and the main modifiable determinant of energy expenditure is physical activity. For weight loss, total energy expenditure must exceed energy intake, and for weight gain, energy intake must exceed energy expenditure [7].

Recommended levels of physical activity are about 30–60 minutes per day of moderate to vigorous activity [8, 9]. There is increasing evidence that time spent at very low activity levels (sedentary time) is important in energy balance and risk of NCDs, including cancer and cardiovascular disease, independent of the amount of moderate to vigorous activity [10–12].

Measuring dietary intake and energy expenditure is a challenge in epidemiology. In particular, assessment of energy intake sometimes has considerable measurement errors and may be subject to selection biases, such as the tendency of overweight and obese people to underestimate their intake. Although some objective measures exist for assessing energy expenditure or physical activity, such tools are not available for energy intake. Thus, assessment of energy balance by calculating the difference between intake and expenditure is not practically useful.

Over time the best marker of positive or negative energy balance is *change in body weight*. However, because change in body weight cannot distinguish between loss or gain of lean or fat mass, in the absence of specific measures of body composition, interpretation of weight change in an individual rests on assumptions about the nature of tissues lost or gained, i.e. the relative proportions of lean and fat tissue [13]. However, for most people, weight gain during adulthood is driven largely by gain in fat mass, and therefore change in body weight is a highly useful measure of medium- to long-term energy balance.

Measurement of adiposity

Several measures of overweight and obesity have been used in epidemiological studies. However, it is important to be aware that such measures are imperfect markers of the internal physiological processes that are the actual correlates of cancer development.

BMI (defined as the quotient between weight in kilograms and height in metres squared) is the most commonly used marker of body composition in epidemiological studies, because of the simplicity of assessment and the high precision and accuracy. However, it does not differentiate between lean and adipose tissue or take into account fat distribution, which varies across individuals, among ethnicities, and throughout the lifespan. Waist circumference and waist–hip ratio are useful tools to identify abdominal obesity but cannot clearly differentiate between visceral and subcutaneous fat compartments [14, 15].

Other measures that can be used in medium- or large-scale studies include skin-fold thickness and bioelectrical impedance analysis. More direct measures of body composition are available, such as air displacement plethysmography, underwater weighing (hydrodensitometry), dual-energy X-ray absorptiometry, ultrasonography, computed tomography, and magnetic resonance imaging [16, 17]. Although these methods are highly reproducible and valid [18], because of high costs and lack of portability, their use is limited to small-scale studies that require a high level of accuracy. Their use in large-scale epidemiological studies tends to be as reference methods [19].

Determinants of obesity

Factors that influence energy balance can be considered as relating to the host (i.e. people), the environment (i.e. the set of external factors to which people are exposed), and the vector (i.e. foods and drinks). These factors interact in a complex way to influence eating and drinking patterns as well as activity behaviours. Although these factors are experienced at the individual level as the acceptability, availability, and affordability of foods, drinks, and activity behaviours, their roots lie in policies and actions that determine the environment, which may be local, national, or international [20]. Such factors include food and drink prices (and relative prices) in relation to people's economic status, cultural and socioeconomic factors, availability of foods, different levels of food processing, advertising and marketing of foods and drinks, and the type and amount of options for eating meals outside the home, as well as the impact of the urban environment on the likelihood of people adopting active behaviours during everyday life.

For any individual, constitutional factors – genetic and/or arising from early-life exposures – can determine the degree of susceptibility to obesity [21, 22]. Apart from these largely non-modifiable factors, other characteristics may influence energy balance – in particular, the amount of energy expended in physical activity. Increasing energy expenditure might be expected not to influence energy balance, because of appetite control mechanisms that feed back and tend to maintain balance. However, there is evidence that at the low levels of activity characteristic of many HICs and increasingly of LMICs, this feedback operates imperfectly and does not suppress appetite to the low levels necessary to maintain energy balance [23].

Many factors relating to the foods and drinks consumed have been shown to influence the amount consumed or energy balance over the short to medium term, such as energy density and portion size [24, 25]. Long-term (> 1 year) experimental data on prevention of weight gain suggest that the change in body fatness that occurs when intake is modified appears to be mediated

via *changes in energy intakes* and that intake of naturally occurring fat does not have a significant impact on obesity [26]. In weight-loss trials, low-carbohydrate interventions led to significantly greater weight loss than did low-fat interventions [27]. Other aspects of diet quality, such as the degree of processing, have important effects on long-term weight gain [28, 29], presumably mediated primarily by influencing satiety and energy intake.

In addition, dietary habits and the physiology of the host influence the intestinal microbiota, and dysbiosis (an imbalanced microbiota) has been linked to obesity [30].

Childhood obesity is an important contributor to adult obesity, diabetes, and NCDs. The trends in childhood obesity rates and the large variations in the rates and trends between countries provide useful insights into the drivers of the epidemic. Multiple biological, behavioural, family, and societal factors affect a child's risk of developing obesity. Because children are different from adults, special efforts are needed to help them develop healthy eating patterns and physical activity behaviours and maintain an optimal body weight. Although genetic factors play a role in affecting individuals' susceptibility to developing obesity, environmental factors should be the key targets of intervention efforts to fight the epidemic, because they are modifiable.

A major challenge is to capture life-course exposure and identify windows of susceptibility. The growth patterns of infants and children can be altered by early exposure to poor diet, increased consumption of sugar-sweetened beverages, physical inactivity, tobacco smoke, and other environmental exposures, and these factors may result in altered metabolism, obesity, and a high risk of chronic diseases in adulthood. However, adolescents are an understudied group and merit further attention.

Further work on birth cohorts or other prospective studies in LMICs is likely to provide additional insights into developmental causes of obesity and NCDs. Although prospective studies are an important area of research, as are nutrition surveillance, intervention, and implementation research, resources and expanded research capacity are of the highest priority. Input from local research communities, health ministries, and policy-makers and appropriate funding or resource assignment are critical for the success of new efforts in LMICs.

Conclusions and recommendations

The global epidemic of obesity and the double burden of malnutrition are both related to poor diet quality, and therefore improvement in diet quality can address both of these challenges.

The benefits of a healthy diet in terms of adiposity are likely mediated by effects of diet quality on *energy intake*, which is *the main driver of weight gain*. Energy balance is best assessed by changes in body weight or in fat mass. Measures of energy intake and expenditure are not precise enough to capture small differences that are of individual and public health importance. The quality of the diet may exert its effect on energy balance through *complex hormonal and neural pathways* that influence *satiety* and possibly also through *other mechanisms*.

Dietary patterns characterized by higher intakes of fruits and vegetables, legumes, whole grains, nuts and seeds, and *unsaturated fat*, and lower intakes of refined starch, red meat, saturated and trans-fatty acids, and sugar-sweetened foods and beverages, consistent with a traditional Mediterranean diet and other measures of diet quality, can contribute to long-term weight control. Limiting consumption of sugar-sweetened beverages has a particularly important role in weight control. Specifically concerning weight-loss trials, the available evidence does not support the role of reducing the percentage of energy from fat on weight loss. However, the reductions in fat may not have been low enough to observe an effect in these trials. As a matter of general principle, the effects of single macronutrients cannot be adequately captured without specifying replacement or comparison sources of energy.

Genetic factors cannot explain the global epidemic of obesity. It is possible that factors such as genetics, epigenetics, and the microbiota can influence individual responses to diet and physical activity. Very few gene–diet interactions have been established. Understanding the mechanisms underlying the relationship of adiposity to cancer may offer the possibility of identifying targets for prevention or treatment independent of adiposity.

Short-term studies have not provided clear evidence of the benefit of physical activity for weight control, but meta-analyses of longer-term trials indicate a modest benefit for weight loss and weight maintenance. The combination of aerobic and resistance training seems to be optimal. Long-term epidemiological studies also support a mild benefit of physical activity on body weight. This includes benefits of walking and bicycle riding, which can be incorporated into daily life and be sustainable for the whole population. Physical activity has important health benefits independent of its effects on regulating body weight. In addition, long-term epidemiological studies show that sedentary behaviour (in particular television viewing) is related to increased risk of obesity, suggesting that limiting sedentary time has potential for preventing weight gain.

The major drivers of the obesity epidemic are the *food environment*,

marketing of unhealthy foods, and *urbanization*, and probably *reduction in physical activity levels*. Existing evidence on the relationships of diet, physical activity, and socioeconomic and cultural factors to body weight is largely from HICs. There is an important lack of data on diet, physical activity, and adiposity in most parts of the world, and this information needs to be collected in a standardized manner. In most settings, 24-hour recalls will be the most suitable method for dietary surveillance. Attention should be paid to data in subgroups, because mean values may obscure important disparities. The in utero and early childhood environment has important implications for lifetime adiposity, and early life offers an important window of opportunity for intervention. Observational data on determinants of body weight and intervention trials across the life-course to improve body weight are also required. To accomplish these goals, resources are needed to build capacity and to conduct translational research.

Gaining control of the obesity epidemic will require the engagement of many sectors, including education, health care, the media, worksites, agriculture, the food industry, urban planning, transportation, parks and recreation, and governments from local to national. Thus, there is an opportunity for all individuals to participate in this effort, whether at home or in establishing high-level policy. Evidence is now available that intensive multisectoral efforts can stop and partially reverse the rise in the prevalence of obesity, in particular among children.

References

1. Romieu I, Dossus L, Barquera S, Blottière HM, Franks PW, Gunter M, et al.; IARC Working Group on Energy Balance and Obesity (2017). Energy balance and obesity: what are the main drivers? Cancer Causes Control. 28(3):247–58. http://dx.doi.org/10.1007/s10552-017-0869-z PMID:28210884

2. WHO (2014). Global status report on noncommunicable diseases 2014. Geneva, Switzerland: World Health Organization. Available from: http://apps.who.int/iris/bitstream/10665/148114/1/9789241564854_eng.pdf?ua=1.

3. UNICEF, WHO, and World Bank Group (2015). Levels and trends in child malnutrition: UNICEF – WHO – World Bank Group joint child malnutrition estimates: key findings of the 2015 edition. New York, USA: United Nations Children's Fund; Geneva, Switzerland: World Health Organization; Washington (DC), USA: The World Bank. Available from: http://www.who.int/nutgrowthdb/jme_brochure2015.pdf?ua=1.

4. WCRF/AICR (2007). Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington (DC), USA: American Institute for Cancer Research. Available from: www.aicr.org/assets/docs/pdf/reports/Second_Expert_Report.pdf.

5. Arnold M, Pandeya N, Byrnes G, Renehan AG, Stevens GA, Ezzati M, et al. (2015). Global burden of cancer attributable to high body-mass index in 2012: a population-based study. Lancet Oncol. 16(1):36–46. http://dx.doi.org/10.1016/S1470-2045(14)71123-4 PMID:25467404

6. Anderson AS, Key TJ, Norat T, Scoccianti C, Cecchini M, Berrino F, et al. (2015).). European Code against Cancer 4th Edition: obesity, body fatness and cancer. Cancer Epidemiol. 39(Suppl 1):S34–45. http://dx.doi.org/10.1016/j.canep.2015.01.017 PMID:26205840

7. United Kingdom Scientific Advisory Committee on Nutrition (2011). Dietary reference values for energy. London, UK: The Stationery Office. Available from: https://www.gov.uk/government/publications/sacn-dietary-reference-values-for-energy.

8. United States Department of Health and Human Services (2015). Physical activity guidelines – adults. Office of Disease Prevention and Health Promotion. Available from: http://health.gov/paguidelines/guidelines/adults.aspx.

9. United Kingdom Department of Health (2015). Physical activity guidelines for adults (19–64 years). Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213740/dh_128145.pdf.

10. Healy GN, Wijndaele K, Dunstan DW, Shaw JE, Salmon J, Zimmet PZ, et al. (2008). Objectively measured sedentary time, physical activity, and metabolic risk: the Australian Diabetes, Obesity and Lifestyle Study (AusDiab). Diabetes Care. 31(2):369–71. http://dx.doi.org/10.2337/dc07-1795 PMID:18000181

11. Hu FB, Li TY, Colditz GA, Willett WC, Manson JE (2003). Television watching and other sedentary behaviors in relation to risk of obesity and type 2 diabetes mellitus in women. JAMA. 289(14):1785–91. http://dx.doi.org/10.1001/jama.289.14.1785 PMID:12684356

12. Liao Y, Liao J, Durand CP, Dunton GF (2014). Which type of sedentary behaviour intervention is more effective at reducing body mass index in children? A meta-analytic review. Obes Rev. 15(3):159–68. http://dx.doi.org/10.1111/obr.12112 PMID:24588966

13. Romero-Corral A, Somers VK, Sierra-Johnson J, Thomas RJ, Collazo-Clavell ML, Korinek J, et al. (2008). Accuracy of body mass index in diagnosing obesity in the adult general population. Int J Obes. 32(6):959–66. http://dx.doi.org/10.1038/ijo.2008.11 PMID:18283284

14. WHO (2011). Waist circumference and waist–hip ratio: report of a WHO Expert Consultation, Geneva, 8–11 December 2008. Geneva, Switzerland: World Health Organization. Available from: http://www.who.int/nutrition/publications/obesity/WHO_report_waistcircumference_and_waisthip_ratio/en/.

15. van der Kooy K, Leenen R, Seidell JC, Deurenberg P, Droop A, Bakker CJ (1993). Waist-hip ratio is a poor predictor of changes in visceral fat. Am J Clin Nutr. 57(3):327–33. PMID:8438766

16. Heymsfield SB, Lohman TG, Wang Z, Going SB, editors (2005). Human body composition. 2nd ed. Champaign (IL), USA: Human Kinetics.

17. McCrory MA, Gomez TD, Bernauer EM, Molé PA (1995). Evaluation of a new air displacement plethysmograph for measuring human body composition. Med Sci Sports Exerc. 27(12):1686–91. http://dx.doi.org/10.1249/00005768-199512000-00016 PMID:8614326

18. Glickman SG, Marn CS, Supiano MA, Dengel DR (2004). Validity and reliability of dual-energy X-ray absorptiometry for the assessment of abdominal adiposity. J Appl Physiol (1985). 97(2):509–14. http://dx.doi.org/10.1152/japplphysiol.01234.2003 PMID:15075304

19. Bandera EV, Maskarinec G, Romieu I, John EM (2015). Racial and ethnic disparities in the impact of obesity on breast cancer risk and survival: a global perspective. Adv Nutr. 6(6):803–19. http://dx.doi.org/10.3945/an.115.009647 PMID:26567202

20. World Cancer Research Fund/American Institute for Cancer Research (2009). Policy and action for cancer prevention. food, nutrition, and physical activity: a global perspective. Washington (DC), USA: American Institute for Cancer Research. Available from: www.wcrf-hk.org/sites/default/files/Policy_Report.pdf.

21. Zhao J, Bradfield JP, Li M, Wang K, Zhang H, Kim CE, et al. (2009). The role of obesity-associated loci identified in genome-wide association studies in the determination of pediatric BMI. Obesity (Silver Spring). 17(12):2254–7. http://dx.doi.org/10.1038/oby.2009.159 PMID:19478790

22. Godfrey KM, Sheppard A, Gluckman PD, Lillycrop KA, Burdge GC, McLean C, et al. (2011). Epigenetic gene promoter methylation at birth is associated with child's later adiposity. Diabetes. 60(5):1528–34. http://dx.doi.org/10.2337/db10-0979 PMID:21471513

23. Blundell JE, Gibbons C, Caudwell P, Finlayson G, Hopkins M (2015). Appetite control and energy balance: impact of exercise. Obes Rev. 16(Suppl 1):67–76. http://dx.doi.org/10.1111/obr.12257 PMID:25614205

24. Ello-Martin JA, Ledikwe JH, Rolls BJ (2005). The influence of food portion size and energy density on energy intake: implications for weight management. Am J Clin Nutr. 82(1 Suppl):236S–41S. PMID:16002828

25. Prentice AM (1998). Manipulation of dietary fat and energy density and subsequent effects on substrate flux and food intake. Am J Clin Nutr. 67(3 Suppl):535S–41S. PMID:9497166

26. Salas-Salvadó J, Bulló M, Babio N, Martínez-González MA, Ibarrola-Jurado N, Basora J, et al.; PREDIMED Study Investigators (2011). Reduction in the incidence of type 2 diabetes with the Mediterranean diet: results of the PREDIMED-Reus nutrition intervention randomized trial. Diabetes Care. 34(1):14–9. http://dx.doi.org/10.2337/dc10-1288 PMID:20929998

27. Tobias DK, Chen M, Manson JE, Ludwig DS, Willett W, Hu FB (2015). Effect of low-fat diet interventions versus other diet interventions on long-term weight change in adults: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 3(12):968–79. http://dx.doi.org/10.1016/S2213-8587(15)00367-8 PMID:26527511

28. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB (2011). Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med. 364(25):2392–404. http://dx.doi.org/10.1056/NEJMoa1014296 PMID:21696306

29. Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I, et al.; Dietary Intervention Randomized Controlled Trial (DIRECT) Group (2008). Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med. 359(3):229–41. http://dx.doi.org/10.1056/NEJMoa0708681 PMID:18635428

30. Cani PD, Delzenne NM (2009). Interplay between obesity and associated metabolic disorders: new insights into the gut microbiota. Curr Opin Pharmacol. 9(6):737–43. http://dx.doi.org/10.1016/j.coph.2009.06.016 PMID:19628432

31. Arnold M, Lam F, Ervik M, Soerjomataram I (2015). Cancer and obesity: global burden of cancer attributable to excess weight. Lyon, France: International Agency for Research on Cancer. Available from: http://gco.iarc.fr/obesity.

Abbreviations

ACSM	American College of Sports Medicine
AICR	American Institute for Cancer Research
ALSPAC	Avon Longitudinal Study of Parents and Children
AMPK	adenosine monophosphate (AMP)-activated protein kinase
ASA24	automated self-administered 24-hour dietary recall
ATP	adenosine triphosphate
BMI	body mass index
BMI-H	BMI heritability
BMR	basal metabolic rate
CARDIA	Coronary Artery Risk Development in Young Adults
CI	confidence interval
CNVs	copy number variations
COHORTS	Consortium of Health-Orientated Research in Transitioning Societies
COSI	Childhood Obesity Surveillance Initiative
CV%	coefficient of variation
DALY	disability-adjusted life year
DBM	double burden of malnutrition
DEXA	dual-energy X-ray absorptiometry
DLW	doubly labelled water
DOHaD Society	International Society for Developmental Origins of Health and Disease
DPP	Diabetes Prevention Program
ECHO	Commission on Ending Childhood Obesity
EMA	European Medicines Agency
EPIC	European Prospective Investigation into Cancer and Nutrition
ER	estrogen receptor
FAO	Food and Agriculture Organization of the United Nations
FDA	United States Food and Drug Administration
FFQ	food frequency questionnaire
GI	glycaemic index
GIANT	Genetic Investigation of Anthropometric Traits
GWAS	genome-wide association studies
HERITAGE	Health, Risk Factors, Exercise Training, and Genetics

HICs	high-income countries
ICC	intraclass correlation coefficient
IGF-1	insulin-like growth factor-1
IGF-1R	IGF-1 receptor
IGFBP	IGF-binding protein
IL	interleukin
LMICs	low- and middle-income countries
Look AHEAD	Action for Health in Diabetes
MD	mean difference
MET	metabolic equivalent
MetaHIT	Metagenomics of the Human Intestinal Tract
MGRS	Multicentre Growth Reference Study
MTC	Mexican Teachers' Cohort
mTOR	mammalian target of rapamycin
NAFLD	non-alcoholic fatty liver disease
NAFPD	non-alcoholic fatty pancreatic disease
NASH	non-alcoholic steatohepatitis
NCDs	noncommunicable diseases
NCHS	United States National Center for Health Statistics
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NHANES	National Health and Nutrition Examination Survey
OR	odds ratio
PAHO	Pan American Health Organization
PAI-1	plasminogen activator inhibitor-1
PAL	physical activity level
PI3K	phosphatidylinositol-3 kinase
PPAR	peroxisome proliferator-activated receptor
PREDIMED	Prevención con Dieta Mediterránea
RCT	randomized controlled trial
RMR	resting metabolic rate
SD	standard deviation
SNPs	single nucleotide polymorphisms
STAT	signal transducer and activator of transcription
TNF-α	tumour necrosis factor-α
UI	uncertainty interval
UNICEF	United Nations Children's Fund
USDA	United States Department of Agriculture
VEGF	vascular endothelial growth factor
WAT	white adipose tissue
WC	waist circumference
WCRF	World Cancer Research Fund
WHO	World Health Organization
WHR	waist–hip ratio

CHAPTER 1.

Global trends in overweight and obesity

Chizuru Nishida, Elaine Borghi, Francesco Branca, and Mercedes de Onis

Obesity is now well recognized as a disease in its own right, one that is largely preventable through changes in lifestyle, especially diet. Obesity is also a major risk factor associated with increased morbidity and mortality from many noncommunicable diseases (NCDs).

Obesity in adulthood increases the likelihood of type 2 diabetes mellitus, hypertension, coronary heart disease, stroke, certain cancers, obstructive sleep apnoea, and osteoarthritis. It also negatively affects reproductive performance [1].

Overweight and obesity in childhood are associated with a higher probability of obesity in adulthood and may have devastating consequences for this very vulnerable age group. Children who are overweight or obese are at a higher risk of developing serious health problems, including type 2 diabetes, high blood pressure, asthma and other respiratory problems, sleep disorders, and liver disease. They may also suffer from psychological effects, such as low self-esteem, depression, and social isolation [2].

In 1997, the World Health Organization (WHO), recognizing the rapidly increasing prevalence of obesity and its overwhelming social, economic, and public health consequences, held, for the first time, an Expert Consultation on Obesity [3]. The Expert Consultation reviewed the global prevalence of obesity and trends in obesity in children and adults, factors contributing to the problem of obesity, and associated consequences of obesity. It also examined the health and economic consequences of obesity and their impact on development, and developed recommendations to assist countries in developing comprehensive public health policies and strategies for improving the prevention and management of obesity. Since then, WHO has organized several technical meetings to address various issues related to the prevention and control of obesity.

In 2012, 15 years after the first Expert Consultation on Obesity was held, the Sixty-fifth World Health Assembly endorsed the Comprehensive Implementation Plan on Maternal, Infant and Young Child Nutrition [4] together with the six global nutrition targets to be attained by 2025 [5]. One of the six global nutrition targets is to “ensure that there is no increase in childhood overweight”. To accelerate the efforts of WHO and to develop a comprehensive response to childhood obesity, the WHO Director-General established a high-level Commission on Ending Childhood Obesity (ECHO) in May 2014.

In 2013, the Sixty-sixth World Health Assembly endorsed the Global

Action Plan for the Prevention and Control of NCDs 2013–2020, including a set of nine voluntary global targets to be attained by 2025 and a global monitoring framework. One of the nine targets is to "halt the rise in diabetes and obesity", and one important indicator related to this target is obesity in adolescents. However, identifying obesity during adolescence is difficult, because of continual changes in body composition, differences in the age of onset of puberty, and differential rates of fat accumulation. Prompted by the increasing need to develop an appropriate single growth reference for screening and monitoring of school-aged children and adolescents, in 2007 WHO developed a growth reference for these population groups (aged 5–19 years), which is aligned with the WHO Child Growth Standards at age 5 years and with the recommended adult cut-off points for overweight and obesity at age 19 years [6]. In school-aged children and adolescents, the 2007 WHO classification system defines overweight as body mass index (BMI)-for-age > +1 standard deviation (SD) from the WHO growth reference median (equivalent to a BMI of 25 kg/m^2 at 19 years) and obesity as BMI-for-age > +2 SD from the median (equivalent to a BMI of 30 kg/m^2 at 19 years) [6].

Unfortunately, WHO has not yet been compiling the data for this age group systematically and comprehensively, except in the WHO European Region. The WHO European Childhood Obesity Surveillance Initiative (COSI) was established in 2007 by the action network on childhood obesity surveillance to provide regular and comparable data on overweight and obesity in primary schoolchildren. Selected schools in participating countries gather data according to an agreed protocol containing core items and consisting of national representative samples. At the global level, efforts are currently being made to fill this data gap, in particular for those aged 10–18 years, and to generate estimates for prevalence of overweight and obesity in adolescents, using data available in 2016.

Therefore, this chapter focuses on obesity only in children younger than 5 years and in adults.

Defining overweight and obesity in children younger than 5 years

In 1993, WHO undertook a comprehensive review of the uses and interpretation of anthropometric references. The review concluded that the United States National Center for Health Statistics (NCHS)/WHO child growth reference, which had been recommended for international use since the late 1970s, did not adequately represent early childhood growth and that new growth curves were necessary. In 1994, the Forty-seventh World Health Assembly endorsed this recommendation. In response, WHO undertook the Multicentre Growth Reference Study (MGRS) between 1997 and 2003 to generate new curves for assessing the growth and development of children worldwide.

The MGRS included 1737 breastfed infants and young children (894 boys and 843 girls), who were from six geographically distinct sites (Brazil, Ghana, India, Norway, Oman, and the USA) and were raised in environments that did not constrain growth. Rigorous methods of data collection and standardized procedures across study sites yielded data of very high quality. These data were used to develop the WHO Child Growth Standards [7], which were released in 2006, replacing the previously recommended 1977 NCHS/WHO child growth reference.

Based on the WHO Child Growth Standards, in children younger than 5 years, overweight is defined as weight-for-height > +2 SD from the WHO Child Growth Standards median, and obesity as weight-for-height > +3 SD from the median. "At risk of overweight" is defined as weight-for-height > +1 SD and ≤ +2 SD from the median.

Trends in overweight and obesity in children younger than 5 years

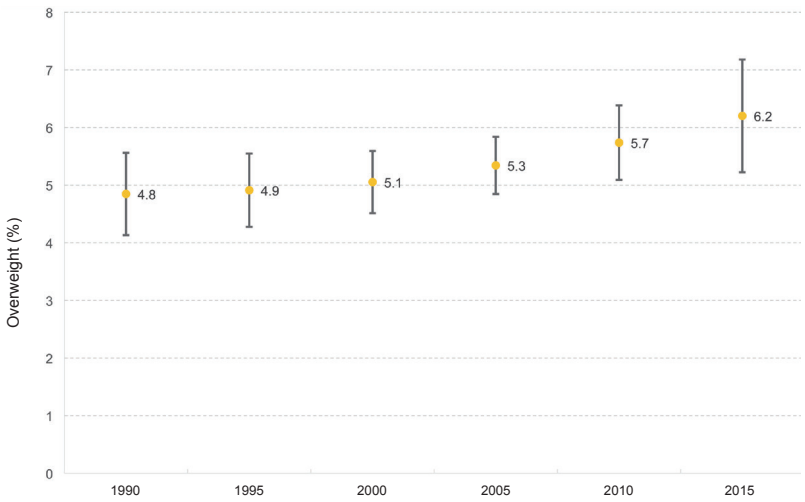
In September 2015, the United Nations Children's Fund (UNICEF), WHO, and the World Bank Group released updated joint child malnutrition estimates based on 778 national surveys, from 150 countries and territories, representing more than 90% of all children younger than 5 years globally. The prevalence of overweight in children younger than 5 years has been increasing steadily, from 4.8% in 1990 to 6.2% in 2015 (Fig. 1.1), despite overlapping 95% confidence intervals across the years [8]. In 2014 there were 41 million overweight children younger than 5 years in the world, about 10 million more than there were in 1990.

In 2014, almost half of all overweight children younger than 5 years lived in Asia, and one quarter lived in Africa. The number of overweight children younger than 5 years in Africa has nearly doubled since 1990. The number of overweight children in lower-middle-income countries has more than doubled since 1990, from 7.5 million to 15.5 million [8].

Classifying overweight and obesity in adults

BMI is calculated as the weight in kilograms divided by the square of the height in metres (kg/m^2). It is commonly used to classify overweight and obesity in adults. BMI values are age-independent and the same for both sexes. However, BMI

Fig. 1.1. Trend in the prevalence of overweight in children younger than 5 years (and 95% confidence intervals), according to the latest child malnutrition estimates from UNICEF, WHO, and World Bank Group (2015) [8].



may not correspond to the same degree of fatness in different populations, due, in part, to differences in body proportions.

Because BMI does not measure fat mass or fat percentage and because there are no clearly established cut-off points for fat mass or fat percentage that can be translated into cut-offs for BMI, the WHO Expert Committee on Physical Status: the Use and Interpretation of Anthropometry [9], which met in 1993, decided to express different levels of high BMI in terms of degrees of overweight rather than degrees of obesity, which would imply knowledge of body composition.

For adults, the 1993 Expert Committee [9] proposed a BMI classification with cut-off points of 25, 30, and 40 kg/m^2 for the three degrees of overweight as shown in Table 1.1.

This classification is based primarily on the association between BMI and mortality, and the following considerations are important in interpreting these cut-off points [9].

- The recommended cut-offs are appropriate for identifying the extent of overweight in individuals and populations, but they do not imply targets for intervention.
- The broad ranges of BMI do not imply that the individual can fluctuate within this range without consequence; for example, for an individual of height 1.75 m, the BMI range of 18.5–25 kg/m^2 covers a weight range of 20 kg. Weight gain in adult life may be associated with increased morbidity and mortality independently of the original degree of overweight.
- The cut-off points for degrees of overweight should not be interpreted in isolation but should always be interpreted in combination with other determinants of morbidity and mortality (disease, smoking, blood pressure, serum lipids, glucose intolerance, type of fat distribution, etc.).

The 1997 WHO Expert Consultation on Obesity [3] reiterated the BMI classification of overweight and obesity as shown in Table 1.2.

The classification shown in Table 1.2 is in agreement with the one recommended by the 1993 Expert Committee (Table 1.1), except that obesity is classified as a BMI ≥ 30 kg/m^2 and it also includes an additional subdivision at a BMI of 35.0–39.9 kg/m^2 in recognition of the fact that management options for dealing with obesity differ above a BMI of 35 kg/m^2.

Table 1.2 shows a simplistic relationship between BMI and the risk of comorbidity, which can be affected by a range of factors, including the nature of the diet, ethnicity, and activity level. The method used to establish BMI cut-off points has been largely arbitrary. Therefore, it was considered that perhaps population-specific BMI cut-off points may be required to more accurately identify overweight and obesity in different population groups, in particular in Asian populations.

To address this debate, WHO held an Expert Consultation in 2002 to review and assess the issues related to whether population-specific BMI cut-off points are needed in Asian populations [10]. The Expert Consultation reviewed the scientific

Table 1.1. Classification of BMI proposed by the 1993 WHO Expert Committee on Physical Status

Classification	BMI (kg/m^2)
Normal range	18.50–24.99
Grade 1 overweight	25.00–29.99
Grade 2 overweight	30.00–39.99
Grade 3 overweight	≥ 40.00

BMI, body mass index.

Source: Compiled from WHO (1995) [9].

Table 1.2. Classification of BMI proposed by the 1997 WHO Expert Consultation on Obesity

Classification	BMI (kg/m²)	Risk of comorbidities
Underweight	< 18.50	Low (but risk of other clinical problems increased)
Normal range	18.50–24.99	Average
Overweight	≥ 25.00	
Pre-obese	25.00–29.99	Increased
Obese class I	30.00–34.99	Moderate
Obese class II	35.00–39.99	Severe
Obese class III	≥ 40.00	Very severe

BMI, body mass index.

Source: Reprinted with permission from WHO (2000) [3].

evidence on the relationships between BMI, percentage of body fat, and health risks in Asian populations, which has suggested differences in these relationships compared with those observed in European populations. The Expert Consultation concluded that the proportion of Asian people who are at a risk of developing type 2 diabetes and cardiovascular disease is substantial at BMI levels below the existing WHO BMI cut-off point for overweight (25 kg/m²). However, the currently available data do not necessarily indicate *one* clear BMI cut-off point for all Asians for overweight or obesity. The BMI cut-off point for observed risk in different Asian populations varies from 22 kg/m² to 25 kg/m²; for high risk, it varies from 26 kg/m² to 31 kg/m². Therefore, no attempt was made to redefine BMI cut-off points for each population separately. Rather, the Expert Consultation identified potential public health action points along the continuum of BMI (23.0, 27.5, 32.5, and 37.5 kg/m²) and proposed methods by which countries could make decisions about the definitions of increased risk for their populations. It was further agreed that the current WHO BMI cut-off points should be retained as international classifications.

Furthermore, the 1997 WHO Expert Consultation also recommended that waist circumference (WC) be used in addition to BMI as indicative of abdominal fatness associated with an increased risk of metabolic and other complications associated with obesity [3]. However, the Expert Consultation concluded that globally applicable cut-off points for WC or waist–hip ratio (WHR), which is another possible indicator of abdominal fatness, could not be developed at that stage due to the fact that populations differ in the risks associated with a particular WC or WHR. In 2008, WHO organized an Expert Consultation to review the scientific evidence and draw up clear recommendations on the issues related to WC and WHR in adults [11]. Given the limited data available, the Expert Consultation did not recommend actual cut-off points for WC or WHR but provided guidance and steps to be taken to arrive at appropriate WHO recommendations in this critical area.

Trends in obesity in adults

The prevalence of obesity in adults has been increasing in all countries. In 2014, 39% of adults aged 18 years and older (38% of men and 40% of women) were overweight. The worldwide prevalence of obesity nearly doubled between 1980 and 2014 [1] (Fig. 1.2).

In all WHO regions, women are more likely to be obese than men [1] (Fig. 1.3). The prevalence of overweight and obesity generally increases with the income level of countries. The prevalence of obesity in high-income and upper-middle-income countries is more than double that in low-income countries [1] (Fig. 1.4).

Fig. 1.2. Trend in the prevalence of obesity in adults. Red dashed line: data from Stevens et al. (2012) [12]. Blue diamond: latest obesity estimate for adults, from WHO (2014) [1]. The corresponding 95% confidence intervals are shown.

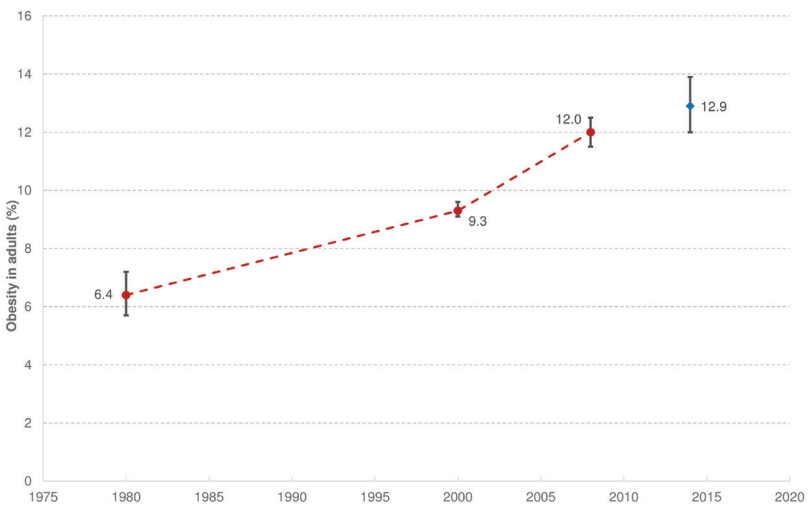
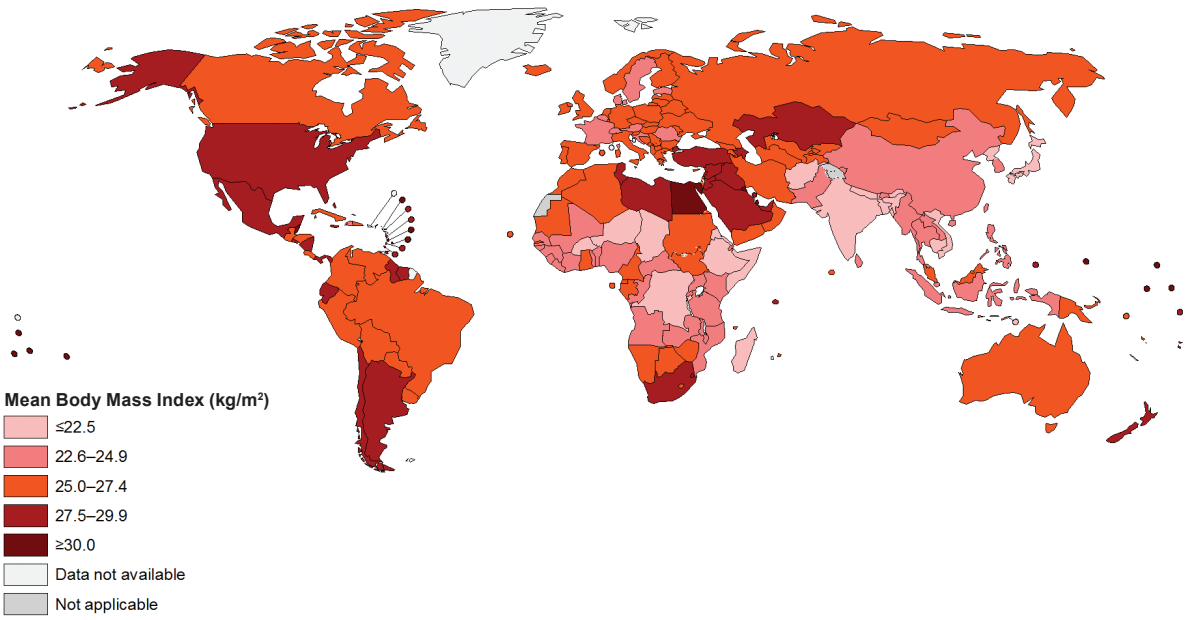


Fig. 1.3. Mean body mass index (kg/m^2), for people aged 18 years and older, in 2014 (age-standardized estimate): (a) women, (b) men. Source: WHO.

a



b

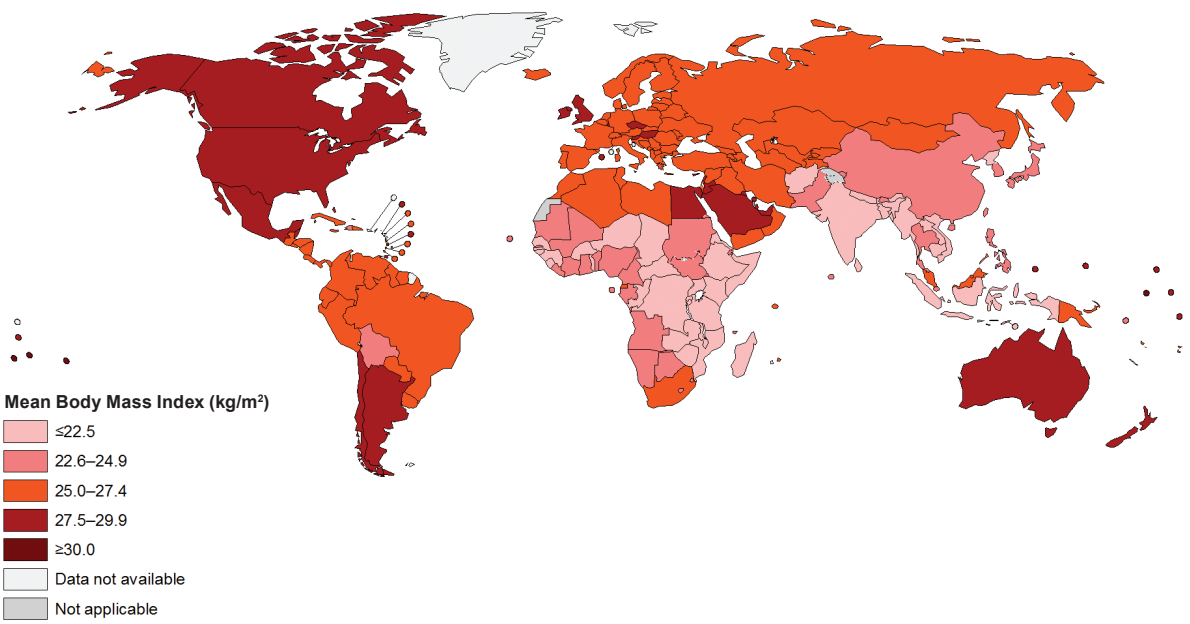
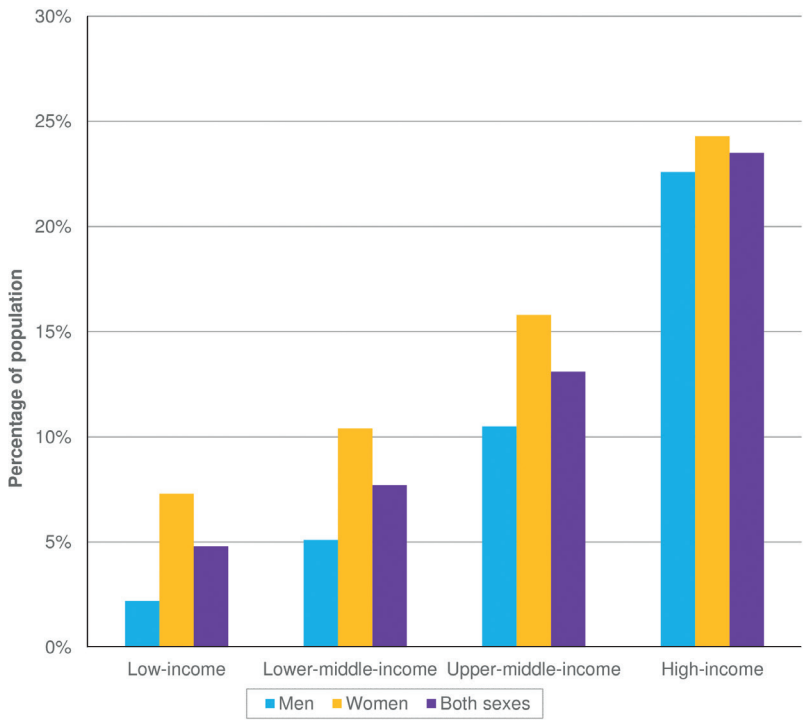


Fig. 1.4. Prevalence of obesity by income level of countries. Source: WHO Global Health Observatory data (http://www.who.int/gho/ncd/risk_factors/overweight/en/index2.html).



Discussion

The prevalence of obesity has been constantly increasing during the past 30 years. An increasing number of countries are affected, and low-income countries are not spared. Obesity has increasingly been considered to be a life-course condition, with its roots being established during pregnancy and with an intergenerational cycle, overlapping with the secular trend.

There is increasing evidence indicating the importance of the early-life environment in mitigating the risk of obesity later in life. Intrauterine life, infancy, and the preschool period have all been considered as critical periods during which the long-term regulation of energy balance may be programmed. Therefore, taking a life-course perspective [13] has great potential for identifying the challenges, as well as the opportunities, for taking action to address the increasing public health problem of overweight and obesity in children, with an emphasis on prevention in children younger than 5 years [14].

In childhood, in some countries, the epidemic of overweight and obesity exists alongside a continuing problem of undernutrition and micronutrient deficiencies, creating a "double burden" of nutrition-related health issues. Therefore, actions to prevent and control childhood overweight and obesity need to go hand in hand with actions to achieve the other global nutrition targets: increasing the rate of exclusive breastfeeding in the first 6 months, reducing the number of children younger than 5 years who are stunted, reducing the prevalence of anaemia in women of reproductive age, reducing the rate of childhood wasting, and reducing the rates of low birth weight.

Countries are expected to take action to incorporate the global nutrition targets and NCD targets and their indicators into their national surveillance system to be able to monitor their progress towards halting the increase in the prevalence of overweight in children and of obesity in adolescents and adults. The data gap on the overweight and obesity status of adolescents needs to be overcome quickly.

Overweight and obesity are complex and multifaceted problems. As a result, coherent and comprehensive strategies are needed to effectively and sustainably prevent and manage these conditions. Although evidence on what works as a package of interventions for obesity prevention is limited, much is known about promotion of healthy diets and physical activity, which are key to attaining the obesity-related global nutrition targets and NCD targets by 2025.

Prevention policies, which affect a country's entire population, are imperative. The European Charter on counteracting obesity [15], adopted at the WHO European Ministerial Conference on Counteracting Obesity, held in November 2006, advocated for a package of essential actions, including the protection, promotion, and support of breastfeeding; changes in the food environment (reduction of marketing pressure, particularly to children; ensuring access to and availability of healthier food, including fruits and vegetables; economic measures that facilitate healthier food choices; reduction of fat, free sugars, and salt in manufactured products; and provision of healthier foods in schools); changes in the physical environment (offers of affordable recreational/exercise facilities, including support for socially disadvantaged groups; promotion of cycling and walking by better urban design and transport policies; creation of opportunities in local environments that motivate people to engage in leisure-time physical activity; and opportunities for daily

physical activity in schools); and the promotion of healthy lifestyles (facilitating and motivating people to adopt better diets and physical activity in the workplace; developing/improving national food-based dietary guidelines and guidelines for physical activity; and individually adapted health behaviour change).

Similar regional initiatives are also being implemented in several WHO regional offices to accelerate action in counteracting the increasing problem of obesity. For example, countries of the Americas took a giant step forward in the fight against the rising epidemic of obesity when they unanimously signed on to the new 5-year Plan of Action for the Prevention of Obesity in Children and Adolescents [16], during the Fifty-third Directing Council of the Pan American Health Organization (PAHO), which was also the Sixty-sixth Session of the WHO Regional Committee for the Americas, held in September–October 2014. Among other measures, the plan calls for fiscal policies and regulation of food marketing and labelling, improvement of school nutrition and physical activity environments, and promotion of breastfeeding and healthy eating. Its goal is to halt the rise of the epidemic so that there is no increase in current country prevalence rates of obesity. To support countries in implementing the plan of action, PAHO is providing evidence-based information to inform the development of policies and regulations, regional nutrition guidelines for preschool and school feeding programmes, and guidelines for foods and beverages sold in schools. In addition, PAHO is supporting the adoption of indicators of obesity, will develop and maintain a database of nationally representative figures on overweight and obesity prevalence, and will monitor activities related to the implementation of policies, laws, and programmes in the Americas.

In October 2014, at the Sixty-fifth Session of the WHO Regional Committee for the Western Pacific, Member States supported the Action Plan to Reduce the Double Burden of Malnutrition in the Western Pacific (2015–2020) [17]. The plan addresses the rising double burden of malnutrition reflected in the unfinished agenda of reducing undernutrition and the rising burden of diet-related NCDs. It recommends actions to achieve five objectives: elevating nutrition in the national development agenda; protecting, promoting, and supporting optimal breastfeeding and complementary feeding practices; strengthening and enforcing legal frameworks that protect, promote, and support healthy diets; improving the accessibility, quality, and implementation of nutrition services across public health programmes and settings; and using financing mechanisms to reinforce healthy diets. The WHO Regional Committee for the Western Pacific is supporting countries in adopting the 2025 global nutrition targets and translating the targets into actions suitable for the country context.

References

1. WHO (2014). Global status report on noncommunicable diseases 2014. Geneva, Switzerland: World Health Organization. Available from: http://apps.who.int/iris/bitstream/10665/148114/1/9789241564854_eng.pdf?ua=1.

2. WHO (2014). WHA global nutrition targets 2025: childhood overweight policy brief. Geneva, Switzerland: World Health Organization. Available from: http://www.who.int/nutrition/topics/globaltargets_overweight_policybrief.pdf.

3. WHO (2000). Obesity: preventing and managing the global epidemic: report of a WHO consultation. Geneva, Switzerland: World Health Organization (WHO Technical Report Series, No. 894). Available from: http://www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/.

4. WHO (2012). Resolution WHA65.6. Comprehensive implementation plan on maternal, infant and young child nutrition. In: Sixty-fifth World Health Assembly, Geneva, 21–26 May 2012. Resolutions and decisions, annexes. Geneva, Switzerland: World Health Organization; pp. 12–13. Available from: http://www.who.int/nutrition/topics/WHA65.6_resolution_en.pdf?ua=1.

5. WHO (2012). Global targets 2025. To improve maternal, infant and young child nutrition. Available from: http://www.who.int/nutrition/global-target-2025/en/.

6. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J (2007). Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ. 85(9):660–7. http://dx.doi.org/10.2471/BLT.07.043497 PMID:18026621

7. WHO Multicentre Growth Reference Study Group (2006). WHO Child Growth Standards based on length/height, weight and age. Acta Paediatr Suppl. 450:76–85. PMID:16817681

8. UNICEF, WHO, and World Bank Group (2015). Levels and trends in child malnutrition: UNICEF – WHO – World Bank Group joint child malnutrition estimates: key findings of the 2015 edition. New York, USA: United Nations Children's Fund; Geneva, Switzerland: World Health Organization; Washington (DC), USA: The World Bank. Available from: http://www.who.int/nutgrowthdb/jme_brochure2015.pdf?ua=1.

9. WHO (1995). Physical status: the use and interpretation of anthropometry: report of a WHO Expert Committee. Geneva, Switzerland: World Health Organization (WHO Technical Report Series, No. 854). Available from: http://www.who.int/childgrowth/publications/physical_status/en/.

10. WHO Expert Consultation (2004). Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 363(9403):157–63. http://dx.doi.org/10.1016/S0140-6736(03)15268-3 PMID:14726171

11. WHO (2011). Waist circumference and waist–hip ratio: report of a WHO Expert Consultation, Geneva, 8–11 December 2008. Geneva, Switzerland: World Health Organization. Available from: http://www.who.int/nutrition/publications/obesity/WHO_report_waistcircumference_and_waisthip_ratio/en/.

12. Stevens GA, Singh GM, Lu Y, Danaei G, Lin JK, Finucane MM, et al.; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Body Mass Index) (2012). National, regional, and global trends in adult overweight and obesity prevalences. Popul Health Metr. 10(1):22. http://dx.doi.org/10.1186/1478-7954-10-22 PMID:23167948

13. Darnton-Hill I, Nishida C, James WP (2004). A life course approach to diet, nutrition and the prevention of chronic diseases. Public Health Nutr. 7(1A):101–21. http://dx.doi.org/10.1079/PHN2003584 PMID:14972056

14. WHO (2003). Diet, nutrition and the prevention of chronic diseases: report of a joint WHO/FAO Expert Consultation. Geneva, Switzerland: World Health Organization (WHO Technical Report Series, No. 916). Available from: http://www.who.int/dietphysicalactivity/publications/trs916/en/.

15. WHO Regional Office for Europe (2006). European Charter on counteracting obesity. WHO European Ministerial Conference on Counteracting Obesity, Istanbul, Turkey, 15–17 November 2006. Copenhagen, Denmark: World Health Organization Regional Office for Europe. Available from: http://www.euro.who.int/__data/assets/pdf_file/0009/87462/E89567.pdf?ua=1.

16. WHO Regional Office for the Americas (2014). Plan of action for the prevention of obesity in children and adolescents. Washington (DC), USA: World Health Organization Regional Office for the Americas. Available from: http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=28890&lang=en&usg=AFQjCNHGJxhuPZbx-7sYGY9JB9AqaaOHQ&cad=rja.

17. WHO Regional Office for the Western Pacific (2014). Action plan to reduce the double burden of malnutrition in the Western Pacific (2015–2020). Manila, Philippines: World Health Organization Regional Office for the Western Pacific. Available from: iris.wpro.who.int/bitstream/handle/10665.1/10892/9789290617037_eng.pdf.

CHAPTER 2.

The double burden of malnutrition in low- and middle-income countries

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The double burden of malnutrition (DBM) (sometimes referred to as "malnutrition in all its forms") is the coexistence of undernutrition (including macronutrient and micronutrient deficiencies) and overnutrition in the same population across the life-course [1]. Undernutrition is the result of insufficient intake, poor absorption, and/or poor biological use of the nutrients. Overnutrition is the result of excess or imbalanced nutrient intakes, which can result in impaired body functions as well as overweight and/or obesity. In most regions, undernutrition and overnutrition coexist in the same country, in the same community, or even in the same household.

There is a complex interplay between early undernutrition (in mothers before and during pregnancy, and in early childhood) and later overnutrition that exacerbates the risk of noncommunicable diseases (NCDs), the prevalence of which is rising rapidly in low- and middle-income countries (LMICs) [2, 3]. Undernutrition during pregnancy, which affects fetal growth, and during the first 2 years of life is a major determinant of the risk of both stunting of linear growth and subsequent obesity and NCDs in adulthood [4]. Fast weight gain and linear growth in children in LMICs are associated with better survival and improved cognitive development but might be associated with an increased risk of obesity and cardiometabolic diseases in later life, particularly for rapid weight gain after age 2 years [5].

Malnutrition affects all countries and one third of people worldwide. Almost 1 billion people continue to be undernourished, with an insufficient intake of calories, protein, and micronutrients [6], and currently about 2 billion people are overweight. Nearly half of all countries face multiple serious burdens of malnutrition, such as poor child growth, micronutrient deficiency, and adult overweight. The cost of treating NCDs, of which nutrition-related NCDs are the major share, is likely to be US$ 30 trillion globally over the next 20 years [7]. Of the top 20 determinants of global deaths, 14 are related to diet and nutrition. Obesity now has the third highest global social burden (US$ 2.0 trillion, or 2.8% of global gross domestic product [GDP]), only marginally less than those of tobacco and armed violence, war, and civil disorder [8].

This chapter summarizes the evidence on the DBM in LMICs in various geographical areas of the world.

Global situation and trends in the DBM

Globally, the prevalence of stunting and wasting (see Box 2.1) in preschool children in LMICs has declined during the past two to three decades, whereas rates of overweight/obesity have been rising at a faster rate than the declines in the rates of stunting and wasting [9–11]. Stevens et al. [10], using nationally representative data for 141 developing countries for the period 1985–2011 from the World Health Organization (WHO) and other sources, showed that in 2011, the average prevalence of moderate and severe stunting (height-for-age < −2 standard deviations from the median) was 29.9%. The number of children with moderate and severe stunting was highest in South Asia, followed by sub-Saharan Africa and South-East Asia, and much lower in Latin America, the Middle East, and North Africa. The differences in the prevalence of stunting among preschool children in LMICs were greater between income groups than between urban and rural areas of residence [4].

Box 2.1. Cut-off points used to classify underweight, wasting, and stunting

Underweight. Moderate and severe: weight-for-age < −2 standard deviations (SD) from the median weight-for-age of the reference population. Severe: weight-for-age < −3 SD from the median weight-for-age of the reference population.

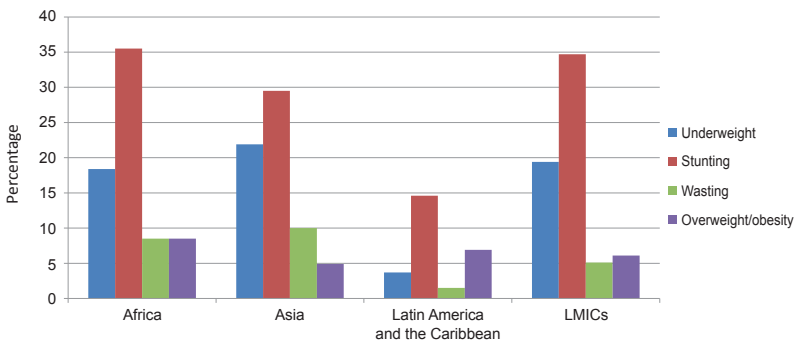
Wasting. Moderate and severe: weight-for-height < −2 SD from the median weight-for-height of the reference population.

Stunting. Moderate and severe: height-for-age < −2 SD from the median height-for-age of the reference population.

The prevalence of obesity varies widely across regions. It is highest in Latin America and the Caribbean, the Middle East, and Oceania. Globally, the prevalence of obesity in preschool children was 6.7%. The average prevalence was 8.5% in Africa (17% in North Africa, but < 6.4–8.7% in other parts of this region) and 6.9% in Latin America. The lowest prevalence (4.9%) was in Asia. However, because of its larger population, Asia is estimated to have the highest number of overweight/obese children [9, 11] (see Fig. 2.1 and Box 2.2).

The causes of obesity have been grouped into four broad cross-cutting themes: the biological/health environment, the economic/food environment, the physical/built environment, and the sociocultural environment. In LMICs, overweight and obesity in adults were recognized much earlier than in children. Between 1980 and 2008, global (including LMICs and high-income countries [HICs]) mean increases in body mass index (BMI) were 0.4 kg/m^2 per decade in men and 0.5 kg/m^2 per decade in women [12]. In men, increases in BMI were observed in almost all regions, but in women the largest increase in BMI was in Oceania and the smallest was in central/eastern Europe and central Asia. Globally, the prevalence of obesity (BMI ≥ 30 kg/m^2) in 2008 was 9.8% in men and 13.8% in women. Overweight accounted for about 37% of the global burden of disease in 2013 [11]. Between 1990 and 2010, the annual increase in the prevalence

Fig. 2.1. Prevalence of underweight, stunting, wasting, and overweight/obesity in children younger than 5 years, by region (LMICs, low- and middle-income countries). Data for underweight, stunting, and wasting from Table 3 in Black et al. (2013) [4]; data for overweight/obesity (weight-for-height > +2 standard deviations from the median) from Table 4 in de Onis et al. (2010) [9].



Box 2.2. The double burden of malnutrition in low- and middle-income countries

Stunting of young children, which reflects both maternal and child undernutrition, affects about one quarter of the world's children. Overweight and obesity affect about one third of adults and about 10% of children worldwide. Whereas the rates of stunting and wasting have declined over the past two decades, the rates of obesity have risen, with the most rapid rates of increase in Latin America and the Caribbean, the Middle East, and Oceania. High rates of stunting persist in many parts of the world, particularly South Asia, where disparities between income groups are greater than those between urban and rural areas of residence.

of overweight (BMI ≥ 25 and < 30 kg/m^2) in women aged 19–49 years in LMICs was highest (0.9% per year) in the Middle East and North Africa, where the prevalence of overweight was 70.6% in 2010, and lowest (0.3% per year) in Latin America and the Caribbean, where the prevalence was 56.7% in 2010 [13]. In contrast, underweight (BMI < 18.5 kg/m^2) still predominated in South Asia, with a prevalence of 30.2%, compared with a prevalence of 16.8% for overweight. In East Asia and the Pacific and in sub-Saharan Africa, the prevalence of overweight (26.5% and 22.2%, respectively) in 2010 was greater than that of underweight (7.9% and 12.1%, respectively). Finally, substantial increases in the prevalence of overweight or obesity were also observed in children and adolescents in developing countries (where the prevalence in 2013 was 12.9% for boys and 13.4% for girls) as well as in developed countries (where the prevalence in 2013 was 23.8% for boys and 22.6% for girls) [11].

Much more limited data are available on the prevalence of overweight and obesity in pregnant and lactating women; most of the nationally representative surveys do not include these vulnerable groups. Overweight/obesity in women of reproductive age before pregnancy was shown to pose potential health risks during pregnancy (gestational diabetes, hypertensive disorders) and, alone or together with high gestational weight gain, resulted in poor birth outcomes (e.g. large for gestational age) [14, 15]. The prevalence and impacts of the DBM before and during pregnancy and the interaction between undernutrition and overnutrition at these critical times have not been thoroughly explored, although a few hospital-based studies have been reported. Poor maternal nutrition has also been linked to poor birth outcomes and an increased risk of NCDs among the offspring in later life. Maternal and child undernutrition in the aggregate has been estimated to be a cause of 3.1 million child deaths annually, or 45% of all child deaths in 2011 [4].

Common micronutrient deficiencies in women and children that are of public health importance in LMICs (and persist in sectors of HICs) include deficiencies of vitamin A, iron, iodine, and recently, also folate, zinc, and vitamin D; many of these deficiencies coexist in the same individuals, suggesting that poor-quality diets, poor sanitation, and inadequate health care are major contributory factors [16, 17]. Anaemia (presumably due to iron deficiency, with a prevalence of 37–46% in women and children) and iodine deficiency disorders separately affect about 2 billion people in both developed and developing countries, and vitamin A deficiency (with a prevalence of 10–12%) is still common in developing countries [18]. Muthayya et al. [19] defined a "hidden hunger index" by combining the national prevalence of and the disability-adjusted life years (DALYs) attributable to stunting, iron-deficiency anaemia, vitamin A deficiency, and iodine deficiency in school-aged children to map the global spread of hidden hunger. Hot spots were found in most countries in sub-Saharan Africa (where the prevalence was highest) and South Asia. Moreover, recent evidence has shown that deficiencies of iron and iodine also exist in overweight and obese women. Metabolic disturbances related to overweight/obesity, in addition to poor diets, have been postulated to affect micronutrient (iron and iodine) metabolism in women and children [20].

Drivers of the DBM

Wherever people live – whether they are rural smallholders, urban poor, or urban better-off – they all use food systems to procure the food they eat. The majority of the global hungry live in rural areas and are smallholder farmers who produce most of the food they eat. Improving nutrition for this sector requires an understanding of the factors that currently constrain their access to sufficient healthy, nutritious food. Increasingly, these rural smallholders are purchasing unhealthy, cheap processed foods. With economic development, there is a shift away from diets based largely on minimally processed staple foods to diets high in meat, vegetable oils, and processed foods [21–23] (see Box 2.3). This unhealthy transition has been accompanied by large numbers of people consuming excess calories, thereby contributing to overweight and obesity in more than 2 billion people in 2013 [11], while micronutrient deficiencies persist because the nutrient quality of these foods is poor.

Three important changes have taken place in the industrialized food system that increasingly dominates: (i) the opening of domestic markets to international food trade and foreign direct investment; (ii) the subsequent increased entry of transnational food companies and their global market, and (iii) global food advertising [24–26]. These changes have made energy-dense,

Box 2.3. Changing food patterns in low- and middle-income countries

Food patterns are changing dramatically in LMICs, away from diets based on minimally processed staple foods to diets that are higher in meats, oils, and ultra-processed foods and beverages high in fat, salt, and added sugar. These changing patterns are driving excess calorie intake and are linked to obesity and NCDs; at the same time, these low-quality diets are not meeting micronutrient needs, and thus these patterns are driving the DBM.

nutrient-poor foods relatively more readily available, affordable, and acceptable than nutritious foods [27]. Ultra-processed foods are now the major sources of sugar, salt, and fats in most diets around the world. Total consumption of processed foods is now positively associated with excess energy intake and obesity, and with rising rates of diabetes and NCDs.

Drivers of increased consumption of ultra-processed foods – particularly in Asia, where the change is most dramatic and is closely linked to rising rates of obesity – include rising household incomes, rapid urbanization, and increasing female economic participation, which may be driving the demand for convenience foods. This demand for ultra-processed foods and beverages is also being driven by national and transnational food companies using aggressive, unregulated marketing of processed foods and beverages. To date, in most LMICs, the marketing of foods and non-alcoholic beverages is unregulated; where regulations are in place, they tend to be voluntary codes and are poorly monitored and enforced. WHO guidance on best practice for such marketing [28] is rarely followed.

In addition, there has been a rapid expansion of supermarkets and fast-food companies. For example, the number of international food franchises in the Asia-Pacific region expanded from 1458 in 1991 to 6775 in 2001 [29]. People in countries with industrial and mixed food systems consume on average 80–90 kg per person per year of energy-dense, ultra-processed foods, with added salt, refined sugars, and low amounts of essential micronutrients. People in countries with emerging and rural food systems consume on average 20–30 kg of ultra-processed foods per person per year. Nonetheless, consumption of packaged food is growing fastest in transitioning, emerging, and rural food systems [30].

Although consumption of processed foods and soft drinks is highest in HICs, growth rates are mostly declining or stagnating in HICs, whereas they are rising rapidly in LMICs. Between 1996 and 2002, sales of processed (packaged) foods grew by 28% in LMICs, compared with only 2.5% in HICs. In Viet Nam, consumption of ultra-processed food increased 3.6-fold, from 10.7 kg per capita in 1999 to 38.7 kg per capita in 2013. Volumes of consumption of soft drinks (sodas, sugar-sweetened beverages) have been increasing in almost all countries. Thailand, Indonesia, and the Philippines have consumption patterns comparable to those of HICs. In Viet Nam, retail sales of frozen processed food, cheese, and chocolate confectionery grew by 24%, 15%, and 13%, respectively, in 2013, and consumption of sugar-sweetened beverages rose by about one third from 2010 to 2014, to 836 million litres.

For many LMICs, government policy does not address the drivers of the DBM. Most governments continue to have polarized policies that focus efforts separately on undernutrition and overnutrition in different target populations. They also tend to focus on individual behaviour change or specific interventions, such as fortification and supplementation, although with an increasing emphasis on reformulation of less healthy foods. Little consideration has been given to the impact of fiscal and regulatory policies on the marketing of unhealthy foods and beverages, particularly to children, or to the impact of agricultural policies on the quality of the diet.

The DBM and NCDs

Despite the abundance of knowledge about the substantial burden of cancer that is attributable to obesity, there is a significant research gap between LMICs and HICs. Most available research has focused on Caucasians in HICs, where the combinations of risk factors and exposures may differ from those in LMICs. The acquisition by people in LMICs of diet and lifestyle habits typical of industrialized countries, particularly among the poorest people, has produced changing patterns of diseases.

In East Asia and the Pacific, the DALYs lost due to high BMI increased by 198% between 1990 and 2010, nearly 2.5 times the global average [31]. Overweight and obesity are key underlying risk factors for the growing burden of NCDs, particularly diabetes, heart disease, and certain cancers. NCDs are already the leading cause of death in 12 Pacific Island countries; importantly, at least one quarter of the deaths from NCDs in Tonga, Samoa, and Vanuatu are premature [32].

Currently, the most frequently diagnosed cancers in LMICs are tumours of the lung, female breast, stomach, liver, colorectum, cervix, and oesophagus [33]. The increase in the burden of NCDs may be explained partly by demographic changes; however, changes in lifestyle factors and globalization related to diet (increased consumption of highly processed foods, red meat, and sugar-sweetened beverages) and increases in sedentary behaviour are also increasingly being recognized as major contributors to the increase in the burden of NCDs, including cancer [34]. Interactions between undernutrition and the immune response remain unresolved and are now further complicated by the rising impact of obesity. A major challenge is to capture life-course exposure and identify windows of susceptibility. The growth patterns of infants and children can be altered by early exposure to poor diet, increased consumption of sugar-sweetened beverages, dietary contaminants (e.g. mycotoxins), physical

inactivity, tobacco smoke, and other environmental exposures, including those from the way foods are produced, and these factors may result in altered metabolism, obesity, and a high risk of chronic diseases in adulthood [14].

Discussion

The rapidly changing dietary patterns unfolding in LMICs provide an important window of opportunity to study the impact of these changes on health outcomes. In particular, research conducted in these dynamic environments can help fill the gaps in our knowledge as to which of these factors can explain the increases in the risk of NCDs, including cancer, observed across different populations. Strengthening the evidence base will support the development of more effective policies and programmes to prevent and ameliorate the growing burden of NCDs in LMICs.

Adopting a food systems approach to the DBM provides the opportunity to explore how a coherent approach to the way food is grown, processed, and sold can address both the quality and the quantity of the food supply. Thus, a coherent approach that focuses on food systems and food security can ensure that those who are currently not getting enough of the right food can improve the quality of their diet, without healthy foods being displaced by the cheap, unhealthy, ultra-processed foods high in fat, salt, and sugar that are driving the rise in rates of obesity and diet-related NCDs. There is the potential for a win–win solution, with all forms of malnutrition being reduced.

Food consumption and dietary choices are culturally structured from birth. In some cultures food is seen merely as a source of energy for the body, whereas in other cultures food is considered to be part of social bonding and an essential feature of cultural or religious experiences. The available global nutrition data are often limited to weight and height, with poor or limited data available on dietary patterns or more detailed aspects of nutritional status, such as body composition or biochemical/metabolic status. There is often not even agreement about how best to measure nutritional status in infants and children and what cut-offs to use for adults from different regions of the world. Limited data are available on the impact of poor nutrition at different stages of the life-course on subsequent longer-term health. The wider socioecological determinants of change in nutrition-related behaviours need to be assessed. Understanding how local, national, and international food systems shape consumption is important to help guide local policy responses. To influence positive change and to protect desirable culinary traditions, it is vital that the link between culture and nutritional choice be acknowledged, understood, and addressed for each specific context.

To date, most of the evidence that supports global nutrition policy comes from HICs, with limited data from surveillance surveys and cross-sectional studies available from LMICs. The lack of data from LMICs is a function of limited support for infrastructure and human capacity to undertake and lead the research and data collection from within countries. Without consideration of how to build and support this capacity, the opportunities that arise to learn from the rapid dietary changes that are occurring will be lost. It will also be difficult to provide reliable surveillance data for key indicators to assess progress on global targets for both NCDs and infant and young child nutrition. Global funders need to consider how to support this capacity within LMICs.

Key points

- Half of all stunted and overweight children in the world live in LMICs, where rates of obesity are rising, particularly in Asia.
- Micronutrient deficiencies persist.
- There are more premature deaths from NCDs in LMICs than in HICs.
- Early undernutrition and later overnutrition exacerbate the risk of NCDs.
- Changing food patterns and food systems are driving the rising rates of overweight, while not addressing micronutrient deficiencies.
- The policy response is polarized and is not addressing the DBM in a coherent way; the drivers of the food systems need to be addressed.
- The capacity and evidence base in LMICs are limited, which is weakening the policy commitment to action.

Research needs

- Study the impact of the nutrition transition on health outcomes in LMICs, to strengthen the evidence base to support the development of more effective policies and programmes to prevent and ameliorate the growing burden of NCDs in LMICs.
- Adopt a food systems approach to the DBM, to explore how a coherent approach to the way food is grown, processed, and sold can address both the quality and the quantity of the food supply (a win–win approach to reduce all forms of malnutrition).
- Assess the wider socioecological determinants of change in nutrition-related behaviours.
- Understand how local, national, and international food systems shape consumption, to help guide local policy responses.
- Assess the link between culture and nutritional choice for each specific context, to influence positive change and to protect desirable culinary traditions.
- Identify and validate key indicators for reliable surveillance to assess progress on global targets for both NCDs and infant and young child nutrition.
- Build and support infrastructure and human capacity to undertake and lead the research and data collection from within LMICs.

References

1. Shrimpton R, Rokx C (2012). Health, Nutrition, and Population (HNP) Discussion Paper: The double burden of malnutrition: a review of global evidence. Washington (DC), USA: The World Bank. Available from: http://documents.worldbank.org/curated/en/905651468339879888/The-double-burden-of-malnutrition-a-review-of-global-evidence.

2. Darnton-Hill I, Nishida C, James WPT (2004). A life course approach to diet, nutrition and the prevention of chronic diseases. Public Health Nutr. 7(1A):101–21. http://dx.doi.org/10.1079/PHN2003584 PMID:14972056

3. James PT, Norum KR, Smitasiri S, Swaminathan MS, Tagwireyi J, Uauy R, et al. (2000). Ending malnutrition by 2020: an agenda for change in the millennium. Geneva, Switzerland: United Nations Standing Committee on Nutrition. Available from: www.unscn.org/layout/modules/resources/files/2020Report_1.pdf.

4. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, de Onis M, et al.; Maternal and Child Nutrition Study Group (2013). Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet. 382(9890):427–51. http://dx.doi.org/10.1016/S0140-6736(13)60937-X PMID:23746772

5. Adair LS, Fall CHD, Osmond C, Stein AD, Martorell R, Ramirez-Zea M, et al.; COHORTS group (2013). Associations of linear growth and relative weight gain during early life with adult health and human capital in countries of low and middle income: findings from five birth cohort studies. Lancet. 382(9891):525–34. http://dx.doi.org/10.1016/S0140-6736(13)60103-8 PMID:23541370

6. FAO, IFAD, and WFP (2014). The state of food insecurity in the world 2014: strengthening the enabling environment for food security and nutrition. Rome, Italy: Food and Agriculture Organization of the United Nations; International Fund for Agricultural Development; World Food Programme. Available from: www.fao.org/3/a-i4030e.pdf.

7. Bloom DE, Cafiero ET, Jané-Llopis E, Abrahams-Gessel S, Bloom LR, Fathima S, et al. (2011). The global economic burden of noncommunicable diseases. Geneva, Switzerland: World Economic Forum.

8. McKinsey Global Institute (2014). Overcoming obesity: an initial economic analysis. London, UK: McKinsey & Company. Available from: http://www.mckinsey.com/~/media/McKinsey/Business Functions/Economic Studies TEMP/Our Insights/How the world could better fight obesity/MGI_Overcoming_obesity_Full_report.ashx.

9. de Onis M, Blössner M, Borghi E (2010). Global prevalence and trends of overweight and obesity among preschool children. Am J Clin Nutr. 92(5):1257–64. http://dx.doi.org/10.3945/ajcn.2010.29786 PMID:20861173

10. Stevens GA, Finucane MM, Paciorek CJ, Flaxman SR, White RA, Donner AJ, et al.; Nutrition Impact Model Study Group (Child Growth) (2012). Trends in mild, moderate, and severe stunting and underweight, and progress towards MDG 1 in 141 developing countries: a systematic analysis of population representative data. Lancet. 380(9840):824–834. http://dx.doi.org/10.1016/S0140-6736(12)60647-3 PMID:22770478

11. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. (2014). Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 384(9945):766–81. http://dx.doi.org/10.1016/S0140-6736(14)60460-8 PMID:24880830

12. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, et al.; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Body Mass Index) (2011). National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet. 377(9765):557–67. http://dx.doi.org/10.1016/S0140-6736(10)62037-5 PMID:21295846

13. Popkin BM, Slining MM (2013). New dynamics in global obesity facing low- and middle-income countries. Obes Rev. 14(Suppl 2):11–20. http://dx.doi.org/10.1111/obr.12102 PMID:24102717

14. Godfrey KM, Gluckman PD, Hanson MA (2010). Developmental origins of metabolic disease: life course and intergenerational perspectives. Trends Endocrinol Metab. 21(4):199–205. http://dx.doi.org/10.1016/j.tem.2009.12.008 PMID:20080045

15. Hanson MA, Gluckman PD (2015). Developmental origins of health and disease – global public health implications. Best Pract Res Clin Obstet Gynaecol. 29(1):24–31. http://dx.doi.org/10.1016/j.bpobgyn.2014.06.007 PMID:25225058

16. Bailey RL, West KP Jr, Black RE (2015). The epidemiology of global micronutrient deficiencies. Ann Nutr Metab. 66(Suppl 2): 22–33. http://dx.doi.org/10.1159/000371618 PMID:26045325

17. Darnton-Hill I, Mkparu UC (2015). Micronutrients in pregnancy in low- and middle-income countries. Nutrients. 7(3):1744–68. http://dx.doi.org/10.3390/nu7031744 PMID:25763532

18. WHO (2009). Global prevalence of vitamin A deficiency in populations at risk 1995–2005: WHO global database on vitamin A deficiency. Geneva, Switzerland: World Health Organization. Available from: http://whqlibdoc.who.int/publications/2009/9789241598019_eng.pdf.

19. Muthayya S, Rah JH, Sugimoto JD, Roos FF, Kraemer K, Black RE (2013). The global hidden hunger indices and maps: an advocacy tool for action. PLoS One. 8(6):e67860. http://dx.doi.org/10.1371/journal.pone.0067860 PMID:23776712

20. Gowachirapant S, Melse-Boonstra A, Winichagoon P, Zimmermann MB (2014). Overweight increases risk of first trimester hypothyroxinaemia in iodine-deficient pregnant women. Matern Child Nutr. 10(1):61–71. http://dx.doi.org/10.1111/mcn.12040 PMID:23937433

21. Baker P, Friel S (2014). Processed foods and the nutrition transition: evidence from Asia. Obes Rev. 15(7):564–77. http://dx.doi.org/10.1111/obr.12174 PMID:24735161

22. Monteiro CA, Levy RB, Claro RM, de Castro IR, Cannon G (2011). Increasing consumption of ultra-processed foods and likely impact on human health: evidence from Brazil. Public Health Nutr. 14(1):5–13. http://dx.doi.org/10.1017/S1368980010003241 PMID:21211100

23. Moubarac JC, Martins AP, Claro RM, Levy RB, Cannon G, Monteiro CA (2013). Consumption of ultra-processed foods and likely impact on human health. Evidence from Canada. Public Health Nutr. 16(12):2240–8. http://dx.doi.org/10.1017/S1368980012005009 PMID:23171687

24. Hawkes C, Murphy S (2010). An overview of global food trade. In: Hawkes C, Blouin C, Henson S, Drager N, Dube L, editors. Trade, food, diet and health: perspectives and policy options. Chichester, UK: John Wiley & Sons.

25. Friel S, Gleeson D, Thow A, Labonte R, Stuckler D, Kay A, et al. (2013). A new generation of trade policy: potential risks to diet-related health from the Trans Pacific Partnership agreement. Global Health. 9:46. http://dx.doi.org/10.1186/1744-8603-9-46 PMID:24131595

26. Friel S, Ford L (2015). Systems, food security and human health. Food Sec. 7(2):437–51. http://dx.doi.org/10.1007/s12571-015-0433-1

27. Hawkes C, Friel S, Lobstein T, Lang T (2012). Linking agricultural policies with obesity and noncommunicable diseases: a new perspective for a globalising world. Food Policy. 37(3):343–53. http://dx.doi.org/10.1016/j.foodpol.2012.02.011

28. WHO (2010). Set of recommendations on the marketing of foods and non-alcoholic beverages to children. Geneva, Switzerland: World Health Organization. Available from: http://whqlibdoc.who.int/publications/2010/9789241500210_eng.pdf.

29. Fast food in the Asia-Pacific. The Establishment Post. 16 January 2015. Available from: http://www.worldfranchiseassociates.com/franchise-news-article.php?nid=2895.

30. IFPRI (2015). Global nutrition report 2015: actions and accountability to advance nutrition and sustainable development. Washington (DC), USA: International Food Policy Research Institute. Available from: http://www.ifpri.org/publication/global-nutrition-report-2015.

31. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. (2012). A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 380(9859):2224–60. http://dx.doi.org/10.1016/S0140-6736(12)61766-8 PMID:23245609

32. Anderson I (2012). The economic costs of noncommunicable diseases in the Pacific Islands. Washington (DC), USA: The World Bank.

33. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. (2015). Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 136(5):E359–86. http://dx.doi.org/10.1002/ijc.29210 PMID:25220842

34. Lachat C, Otchere S, Roberfroid D, Abdulai A, Seret FM, Milesevic J, et al. (2013). Diet and physical activity for the prevention of noncommunicable diseases in low- and middle-income countries: a systematic policy review. PLoS Med. 10(6):e1001465. http://dx.doi.org/10.1371/journal.pmed.1001465 PMID:23776415

CHAPTER 3.

Can energy intake and expenditure (energy balance) be measured accurately in epidemiological studies? Is this important?

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The roles of energy intake and expenditure are extremely important in human health and disease, for many reasons. Thus, the assessment and interpretation of energy intake and expenditure are major issues in epidemiological studies. Overweight and obesity have been recognized to be major risk factors for cancer, cardiovascular disease, diabetes, and many other health conditions. Therefore, the difference between energy intake and expenditure, frequently referred to as energy balance, has become of great interest, because of its direct relationship to long-term gain or loss of adipose tissue.

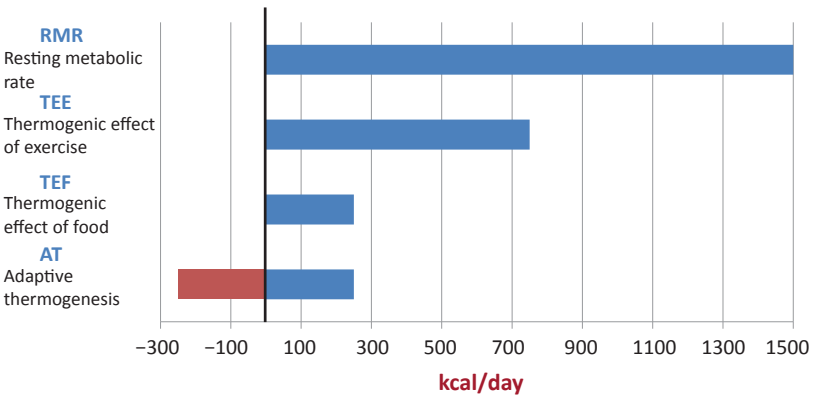
For this reason, questions have arisen about whether energy intake and expenditure can be measured adequately in epidemiological studies, to enable energy balance to be assessed adequately. Some [1–3] have argued that self-reported energy intake has no value and should be abandoned, and have extended this argument to all self-reported information. Others [4–8] have suggested that it is not realistically possible to measure energy intake and expenditure with sufficient precision in epidemiological studies to assess energy balance, but that this is not a serious problem because other means can be used to evaluate the effects (e.g. on disease incidence or mortality) of energy balance as an exposure and to study the determinants (e.g. dietary factors and physical activity) of energy balance as an outcome.

In this chapter, the factors contributing to energy balance and the measurement of these factors are reviewed. Notably, energy intake and expenditure have important roles in human health, and in epidemiological studies, independent of their contribution to energy balance; although these other applications are not the focus of this chapter, they are also mentioned.

Components of total energy expenditure

Total energy expenditure has traditionally been partitioned into several components: resting metabolic rate (RMR), physical activity, thermogenic effect of food, and adaptive thermogenesis (Fig. 3.1) [9]. RMR is quantitatively the most important, making up approximately 60% of total energy expenditure in an individual with moderate physical activity. In a moderately active individual, physical activity accounts for approximately 30% of total energy expenditure. The thermogenic effect of food (i.e. the metabolic cost of

Fig. 3.1. Components of energy expenditure during weight maintenance for a 70 kg man consuming 2500 kcal/day, and the potential modifying effect of adaptive thermogenesis. Adapted with permission from Horton (1983) [9].



absorbing and processing macronutrients) accounts for only about 10% of total energy expenditure. Adaptive thermogenesis (i.e. the compensatory capacity of an individual to conserve or expend energy in response to variable intake of food or temperature extremes) has been estimated to be less than ± 10% of total energy expenditure [9].

In epidemiological studies, the thermogenic effect of food is not likely to vary appreciably, because this becomes important only on extreme diets, and this can generally be assumed to be constant. Adaptive thermogenesis is practically important, because it can account for resistance to weight loss in the face of moderate restriction of energy intake by downregulating metabolic processes to become more energy-efficient. These differences in metabolic efficiency are difficult to measure even under highly controlled conditions as well as in epidemiological studies, so this needs to be recognized as a source of modest unmeasured variation in energy expenditure. RMR is determined mainly by body weight, although this is primarily a function of lean body mass. Because measurement of RMR requires metabolic facilities and is therefore not feasible in epidemiological studies and most clinical investigations, a series of prediction models based on age, weight, and sex have been developed [4]. In principle, height should also be added to the prediction models because, for the same weight, a taller person would be leaner, but height appears to add minimal variability. Because age, weight (or body mass index [BMI] plus height), and sex are routinely covariates in epidemiological studies, RMR is reasonably controlled for in most epidemiological analyses.

After age, weight, and sex have been controlled for, physical activity assumes a relatively large role in determining the variation in energy expenditure among free-living individuals. The true proportion of variation in energy expenditure accounted for by physical activity differs substantially among populations and is likely to be underestimated in most studies because of imperfect measurements of physical activity. Ravussin et al. [10] have demonstrated that even motor activity within the confines of a respiratory chamber ("fidgeting") varies dramatically between individuals and can account for hundreds of kilocalories per day. Such differences in activity would not be detected by typical questionnaires. Thus, physical activity, which includes both fine motor and major muscle movement, is a major determinant of between-person variation in energy expenditure in many populations. Indeed, in most instances total energy intake can be interpreted as a crude measure of physical activity, especially after controlling for body size, age, and sex.

Energy balance and deviations from energy balance

Energy balance exists when weight is constant because energy expenditure equals energy intake. This can happen when no components change or when a change in one component is compensated for by changes in other components.

In adults, deviations from energy balance are a critical concern because these underlie weight gain and ultimately obesity. Of particular concern to public health and epidemiologists are small increments in weight, such as 0.5–1 kg per year, which are typical of many high-income populations [11] and which over a period of 20–30 years lead to large changes in weight and major morbidity and mortality [12]. The deviations from energy balance needed to produce this change in weight are very modest. For example, simply on the basis of the energy content of adipose tissue [4], if an adult man who consumes 2500 kcal/day (10 460 kJ/day) increases his energy intake by only 1% while other factors remain constant, over a 10-year period a theoretical weight gain of 10 kg would result. In reality, the increase in weight will be considerably less, because the additional energy cost of maintaining and moving the added body mass eventually equals the increment in energy intake and a new steady state in weight, i.e. balance, is reached.

By combining data on energy intake and weight gain and on the compensatory effects of added body mass on energy expenditure, Hall et al. [13] estimated that for each 10 kcal/day (42 kJ/day) increase in

energy intake, the new mean steady-state weight will be about 0.5 kg higher (equivalently, each change of 100 kJ/day will lead to a weight change of 1 kg) and that the new steady-state weight will be reached in about 3 years. Their model, based on demographic models and repeated measures of weight, is available interactively at http://bwsimulator.niddk.nih.gov and was recently validated by comparison with repeated dual-energy X-ray absorptiometry (DEXA) measures of body composition and the doubly labelled water (DLW) method [14]. Using a similar approach, Wang et al. [15] estimated that an average increase in energy intake of 110–165 kcal/day (460–690 kJ/day) accounted for the large increase in weight gain among children in the USA between 1990 and 2000. Similarly, Hall et al. [13] estimated that a difference of only 7 kcal/day (30 kJ/day) between energy intake and expenditure could explain the average increase in weight (about 10 kg) in adults in the USA between 1978 and 2005. However, they estimated that the average additional energy intake accumulated over that time was about 220 kcal/day (920 kJ/day); this is the amount by which energy intake would have to be decreased in order to return to the distribution of body weight in 1978.

The important conclusion of these analyses using different approaches is that very small deviations from energy balance, on the order of 1–2% of daily energy intake, can result in large long-term changes in body weight, with major individual and public health implications.

Accuracy and precision of measures of energy intake

Because the calculation of energy balance is based on the difference between energy intake and energy expenditure, and differences of approximately 1% are of great importance, extremely accurate and precise measurements of both intake and expenditure would be needed. Energy intake represents a unique challenge for dietary assessment because, unlike any other nutrient, energy intake is tightly regulated by physiological controls, and thus between-person variation is low after taking into account weight and demographic variables.

A large literature exists on the accuracy of measures of energy intake, specifically comparing mean values obtained by different methods [4, 16]. Progress has been hampered by the lack of a perfect reference method; the closest to that would be the 24-hour whole-body calorimeter, but it artificially constrains physical activity. The DLW method, which measures the relative turnover of hydrogen and oxygen during a period of days or weeks, has become the operational gold standard for assessing energy expenditure, because it is unobtrusive and provides similar mean values to whole-body and respiratory calorimetry. However, the DLW method is extremely expensive, and therefore not practical in epidemiological studies, and is not robust across laboratories, because values have ranged widely in blinded testing [17]. Compared with this standard, most dietary intake assessment methods, including 24-hour dietary recalls, dietary records, and many food frequency questionnaires, underestimate energy intake by 10–20%, although this varies with the population, the details of the specific method, and BMI [4, 18].

Precision is also critical. Precision is difficult to quantify because it is hard to separate true changes in energy intake from measurement errors, although in epidemiological applications, within-person variation due to both sources will have similar implications. A large validation study has recently been completed in which all four methods of dietary assessment were used, which allowed assessment of mean intakes and within-person variation over a 1-year period (see Table 3.1). For all measures of total energy expenditure or intake, the within-person variability, expressed as the within-person coefficient of variation (CV%) and the intraclass correlation coefficient (ICC), is considerable. This includes the DLW method (CV%, 9%; ICC, 0.73) even though its major determinant, weight, has low variability (ICC, 0.98). This degree of variation is similar to what has been seen in other populations; for example, among 111 women the ICC for repeated DLW measurements over 6 months was 0.72 [19]. In another recent evaluation, measurements of energy expenditure using DLW were reproducible over a period of several years, but precision (CV%, ~5%) was still not sufficient for reliably detecting individual changes of 1–2% per year [20]. These analyses of within-person variation underestimate the measurement errors because they assume that each measurement is an unbiased estimate of the true value for individuals, i.e. that there is no systematic within-person error, also described as person-specific bias. This assumption would not apply to food frequency questionnaires, because of their structured nature [16], but is very likely to affect all measurements to some degree, including DLW assessments.

Assessment of energy expenditure due to physical activity in epidemiological studies has been less well developed than assessment of energy intake. Most questionnaires have been focused on discretionary activities or moderate to vigorous activities, assuming that other activities are less important for health or relatively constant in modern lifestyles [21]. Energy expenditure due to physical activity is usually not calculated, in recognition

Table 3.1. Distribution, within-person coefficient of variation (CV%), and intraclass correlation coefficient (ICC) for different measures of energy intake and expenditure in the Women's Lifestyle Validation Study [25] (data provided by 622 female nurses in the USA aged 45–80 years)[a]

Method (*n* = 622)	Time interval	Mean (SD)	Within-person SD	Within-person CV%	ICC
FFQ (kcal/day)	1 year	1901 (480)	286	15	0.70
Dietary records (kcal/day)	~6 months	1745 (334)	226	13	0.63
ASA24 (kcal/day)	Every 3 months	1825 (475)	507	28	0.29
DLW (kcal/day)	6–12 months	2195 (360)	190	9	0.73
Weight (lb)	Every 3 months	157.6 (33.4)	5.1	3	0.98
PAQ (MET-h/day)	1 year	16.5 (6.8)	5.3	32	0.54
Accelerometer (min/day)[b]	~6 months	19.5 (16.6)	8.9	46	0.75
Accelerometer (counts/day)	~6 months	243 056 (94 356)	45 827	19	0.79
PAEE (kcal/day)	6–12 months	708 (239)	166	23	0.53
PAEE (kcal/day)[c]	6–12 months	708 (237)	165	23	0.53
PAEE (kcal/day)[d]	6–12 months	708 (230)	165	23	0.51

ASA24, automated self-administered 24-hour dietary recall; CV, coefficient of variation; DLW, doubly labelled water; FFQ, food frequency questionnaire; ICC, intraclass correlation coefficient; METs, metabolic equivalents; PAEE, physical activity energy expenditure; PAQ, physical activity questionnaire; SD, standard deviation.

[a] ICC and CV% were calculated based on the original value.

[b] Moderate and vigorous activity (min/day), 1-minute bouts.

[c] Measure of activity assessed by DLW with weight regressed out.

[d] Measure of activity assessed by DLW with weight, age, and height regressed out.

of the fact that the data do not capture many activities of daily living and fine motor movements. Physical activity records and 24-hour physical activity recalls, analogous to their corresponding dietary assessment methods, have been minimally used in epidemiological studies thus far. Motion sensors – small devices for monitoring physical activity – are becoming sufficiently inexpensive to be used in epidemiological studies, but the best way to convert movement counts to energy expenditure is still being evaluated. The DLW measure, after subtracting energy expenditure due to RMR, is now often considered to be the gold standard for evaluation of other methods to assess energy expenditure due to physical activity. The variation of these methods over 1 year is also shown in Table 3.1. The most consistent measure appears to be by accelerometer, expressed as counts over 1 day (CV%, 19%; ICC, 0.79), and the DLW measure for physical activity was considerably more variable than that for total energy expenditure (CV%, 23%; ICC, 0.51).

As can be appreciated, the within-person CV% values both for total energy intake and for physical activity assessed by all methods are all far greater than the approximately 1% deviation from energy balance that would be needed to evaluate small but important long-term deviations from energy balance in individuals. Because the deviation would be calculated as the difference between the variables, its within-person error would be even greater because it would include variability from both measures of energy intake and physical activity. Thus, as has been noted earlier [4], it is clear that available methods for measuring energy intake and physical activity in epidemiological studies, as well as methods considered to be the gold standard, are far from adequate for assessing long-term deviations from energy balance in individuals. The relative absence of this approach in the epidemiological literature reflects this understanding. Further, it is unlikely that such methods will become available, because of inherent challenges in obtaining highly precise measurements of long-term behaviours of free-living individuals.

Alternative methods to assess energy balance in epidemiological studies

Fortunately, the study of energy balance does not require measurements of energy intake and expenditure, because attained weight and changes in weight are readily measured with high precision, even by self-report [4]. These measurements of weight provide a simple but precise time-integrated measure of changes in energy balance. Also, weight and

changes in weight directly represent the primary health concern due to deviations from energy balance, which is adiposity. Thus, the inability to evaluate long-term deviations from energy balance in individuals by measuring energy intake and expenditure is not important.

The use of weight in epidemiological analyses, both as an exposure and as an outcome, is an important topic that has been discussed widely [22]. When adjusted for height, often expressed as BMI, weight is widely used as a surrogate for adiposity. Although conceptually imperfect because it does not separate lean mass and fat mass, BMI works remarkably well compared with gold-standard methods [23]. When it is used as an exposure, it is important for the analysis to address confounding by smoking, reverse causation due to underlying disease, and loss of lean mass due to frailty at older ages. When it is used as an outcome to study the effects of diet and activity, the study design needs careful consideration.

In cross-sectional studies, reverse causation can readily occur. In prospective studies with only a baseline measurement, the results can be misleading, because a change in diet or activity will often result in a change in weight for some period of time, and then a new steady-state weight will be reached. For example, if physical activity is increased, weight may decrease initially but does not continue to decrease to zero. If most study participants have already reached a steady-state weight at baseline, an effect of physical activity on weight could be missed. A better design will usually be to examine change in diet or activity in relation to change in weight [24], which more closely approximates the design of a clinical trial. Unlike most studies with disease outcomes, which can require many thousands of participants and many years of follow-up, the effects of changes in diet and activity on change in weight can be investigated with a few hundred subjects and 1 or 2 years of follow-up. Randomized trials should play a large role in addressing the effects of diet on weight, because they better control for confounding by variables that are hard to measure.

Other applications of data on total energy intake and expenditure

Although measurements of energy intake and expenditure will not be useful for assessing energy balance in epidemiological studies, they do play other important roles. For example, population trends in mean energy intake over time using 24-hour dietary recalls can provide useful information, because the effects of within-person variation over time can be dampened with large sample sizes. If the method remains standardized over time, temporal trends can still be valid even if there is some systematic underestimation or overestimation. Unfortunately, standardized methods for physical activity assessment over time do not seem to have been used, so there is less certainty about temporal trends in energy expenditure.

In nutritional epidemiological studies, assessment of energy intake is also important as an adjustment variable for nutrient intakes, because the focus is primarily on the composition of diet rather than on absolute intakes. This is because the composition of diet is what can most realistically be changed by individuals or a population [4]. Multiple aspects of dietary composition have been associated with weight changes [11], probably due to differences in satiety and possible hormonal effects that favour or inhibit accumulation of lean mass versus fat mass. Adjustment for total energy intake also has the benefit of cancelling correlated errors in nutrients, thus reducing measurement errors [4].

Assessment of physical activity, primarily by structured questionnaires, has documented the importance of moderate to vigorous activity in prevention of many diseases. Although these measures of physical activity have error, they have been validated by comparisons with more detailed assessments [21] and can thus provide useful information in prospective studies. The fact that these are based on self-reports rather than an objective measure is not important, because objective measures also have error and are subject to confounding. Even if a good measure of total energy expenditure from physical activity were available, this would not provide the important information on specific types of activity that can be obtained by questionnaires. Small motion sensors are now being incorporated into epidemiological studies; the structure of their measurement errors is now being investigated.

Conclusions

Deviations from energy balance are important in human health and disease. However, these cannot be assessed adequately in epidemiological studies by differences between energy intake and expenditure, because very small long-term deviations in energy intake or expenditure can have major effects on body weight. Neither the available methods nor the foreseeable future methods will be sufficiently precise and accurate to measure these small differences. However, body weight and change in weight provide precise indicators of long-term deviations from energy balance and are widely available for epidemiological studies. These simple and inexpensive measures of energy balance can be used as both exposure and outcome

variables, taking into consideration their other determinants and confounding factors. Although they are not useful for assessing energy balance, which requires extreme accuracy and precision, measures of energy intake and physical activity will continue to play other important roles in epidemiological studies and in monitoring population trends.

Key points

- Very small differences between energy intake and expenditure can, over time, lead to important gains in weight. Measures of both energy intake and expenditure that are sufficiently precise to quantify these differences will not be available in the foreseeable future.
- Weight and changes in weight provide simple and inexpensive measures of deviations from energy balance.
- Measures of physical activity and energy intake are still valuable in epidemiological studies, even if they cannot be used to evaluate energy balance.

Research needs

- Continued work is needed to evaluate and improve the assessment of physical activity, both amount and type, in epidemiological studies.
- Further effort is needed to understand sources of error in measuring energy intake, including errors in the DLW method, the presumed gold standard.

References

1. Schoeller DA, Thomas D, Archer E, Heymsfield SB, Blair SN, Goran MI, et al. (2013). Self-report-based estimates of energy intake offer an inadequate basis for scientific conclusions. Am J Clin Nutr. 97(6):1413–5. http://dx.doi.org/10.3945/ajcn.113.062125 PMID:23689494

2. Archer E, Blair SN (2015). Implausible data, false memories, and the status quo in dietary assessment. Adv Nutr. 6(2):229–30. http://dx.doi.org/10.3945/an.114.007799 PMID:25770263

3. Dhurandhar NV, Schoeller D, Brown AW, Heymsfield SB, Thomas D, Sørensen TIA, et al.; Energy Balance Measurement Working Group (2015). Energy balance measurement: when something is not better than nothing. Int J Obes (Lond). 39(7):1109–13. http://dx.doi.org/10.1038/ijo.2014.199 PMID:25394308

4. Willett WC (2013). Implications of total energy intake for epidemiologic analyses. In: Willett WC, editor. Nutritional epidemiology. 3rd ed. New York (NY), USA: Oxford University Press; pp. 260–86.

5. Satija A, Yu E, Willett WC, Hu FB (2015). Objective measures are complementary to, rather than a replacement for, self-reported methods. Int J Obes (Lond). 39(7):1179. http://dx.doi.org/10.1038/ijo.2015.80 PMID:25924712

6. Freedman LS, Carroll RJ, Neuhouser ML, Prentice RL, Spiegelman D, Subar AF, et al. (2015). Reply to E Archer and SN Blair. Adv Nutr. 6(4):489. http://dx.doi.org/10.3945/an.115.009118 PMID:26178033

7. Hébert JR, Hurley TG, Steck SE, Miller DR, Tabung FK, Kushi LH, et al. (2015). Reply to E Archer and SN Blair. Adv Nutr. 6(2):230–3. http://dx.doi.org/10.3945/an.114.007831 PMID:25770264

8. Subar AF, Freedman LS, Tooze JA, Kirkpatrick SI, Boushey C, Neuhouser ML, et al. (2015). Addressing current criticism regarding the value of self-report dietary data. J Nutr. 145(12):2639–45. http://dx.doi.org/10.3945/jn.115.219634 PMID:26468491

9. Horton ES (1983). Introduction: an overview of the assessment and regulation of energy balance in humans. Am J Clin Nutr. 38(6):972–7. PMID:6650453

10. Ravussin E, Lillioja S, Anderson TE, Christin L, Bogardus C (1986). Determinants of 24-hour energy expenditure in man. Methods and results using a respiratory chamber. J Clin Invest. 78(6):1568–78. http://dx.doi.org/10.1172/JCI112749 PMID:3782471

11. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB (2011). Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med. 364(25):2392–404. http://dx.doi.org/10.1056/NEJMoa1014296 PMID:21696306

12. Willett WC, Dietz WH, Colditz GA (1999). Guidelines for healthy weight. N Engl J Med. 341(6):427–34. http://dx.doi.org/10.1056/NEJM199908053410607 PMID:10432328

13. Hall KD, Sacks G, Chandramohan D, Chow CC, Wang YC, Gortmaker SL, et al. (2011). Quantification of the effect of energy imbalance on bodyweight. Lancet. 378(9793):826–37. http://dx.doi.org/10.1016/S0140-6736(11)60812-X PMID:21872751

14. Sanghvi A, Redman LM, Martin CK, Ravussin E, Hall KD (2015). Validation of an inexpensive and accurate mathematical method to measure long-term changes in free-living energy intake. Am J Clin Nutr. 102(2):353–8. http://dx.doi.org/10.3945/ajcn.115.111070 PMID:26040640

15. Wang YC, Gortmaker SL, Sobol AM, Kuntz KM (2006). Estimating the energy gap among US children: a counterfactual approach. Pediatrics. 118(6):e1721–33. http://dx.doi.org/10.1542/peds.2006-0682 PMID:17142497

16. Willett W, Lenart E (2013). Reproducibility and validity of food-frequency questionnaires. In: Willett W, editor. Nutritional epidemiology. 3rd ed. New York (NY), USA: Oxford University Press; pp. 96–141.

17. Roberts SB, Fuss P, Evans WJ, Heyman MB, Young VR (1993). Energy expenditure, aging and body composition. J Nutr. 123 (2 Suppl): 474–80. PMID:8429407

18. Freedman LS, Commins JM, Moler JE, Willett W, Tinker LF, Subar AF, et al. (2015). Pooled results from 5 validation studies of dietary self-report instruments using recovery biomarkers for potassium and sodium intake. Am J Epidemiol. 181(7):473–87. http://dx.doi.org/10.1093/aje/kwu325 PMID:25787264

19. Neuhouser ML, Tinker L, Shaw PA, Schoeller D, Bingham SA, Horn LV, et al. (2008). Use of recovery biomarkers to calibrate nutrient consumption self-reports in the Women's Health Initiative. Am J Epidemiol. 167(10):1247–59. http://dx.doi.org/10.1093/aje/kwn026 PMID:18344516

20. Wong WW, Roberts SB, Racette SB, Das SK, Redman LM, Rochon J, et al. (2014). The doubly labeled water method produces highly reproducible longitudinal results in nutrition studies. J Nutr. 144(5):777–83. http://dx.doi.org/10.3945/jn.113.187823 PMID:24523488

21. Hu FB (2013). Assessment of physical activity in nutritional epidemiology. In: Willett W, editor. Nutritional epidemiology. 3rd ed. New York (NY), USA: Oxford University Press; pp. 241–59.

22. Manson JE, Stampfer MJ, Hennekens CH, Willett WC (1987). Body weight and longevity. A reassessment. JAMA. 257(3):353–8. http://dx.doi.org/10.1001/jama.1987.03390030083026 PMID:3795418

23. Sun Q, van Dam RM, Spiegelman D, Heymsfield SB, Willett WC, Hu FB (2010). Comparison of dual-energy x-ray absorptiometric and anthropometric measures of adiposity in relation to adiposity-related biologic factors. Am J Epidemiol. 172(12):1442–54. http://dx.doi.org/10.1093/aje/kwq306 PMID:20952596

24. Smith JD, Hou T, Hu FB, Rimm EB, Spiegelman D, Willett WC, et al. (2015). A comparison of different methods for evaluating diet, physical activity, and long-term weight gain in 3 prospective cohort studies. J Nutr. 145(11):2527–34. http://dx.doi.org/10.3945/jn.115.214171 PMID:26377763

25. Yuan C, Spiegelman D, Rimm EB, Rosner BA, Stampfer MJ, Barnett JB, et al. (2017). Validity of a dietary questionnaire assessed by comparison with multiple weighed dietary records or 24-hour recalls. Am J Epidemiol. 185(7):570–84. PMID:28338828

CHAPTER 4.

How are components of dietary intake, dietary composition, foods, and nutrients related to obesity and weight gain?

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Current evidence and recommendations

A report on diet, nutrition, and the prevention of chronic diseases was published after the joint World Health Organization (WHO)/Food and Agriculture Organization of the United Nations (FAO) Expert Consultation held in 2002 [1]. A summary of the risk factors in relation to prevention of excess weight gain and obesity is presented in Table 4.1 [2]. Lifestyle factors listed as obesity-promoting factors (with the strength of evidence) included high intake of energy-dense foods (convincing) and high-sugar drinks (probable). The review found evidence that protective factors against obesity were a high intake of energy-dilute foods (non-starch polysaccharides/fibre) (convincing) and foods of low glycaemic index (GI) (possible). Correspondingly, energy-dense foods (foods high in fat and/or sugar) and sugary drinks were considered to be probable determinants of obesity by the World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) in the second WCRF/AICR expert report, published in 2007 (Table 4.2) [3]. Recent WHO guidelines, from 2015, which focus on reducing the risk of noncommunicable diseases in adults and children, including prevention and control of unhealthy weight gain, strongly recommend reducing the intake of free sugars to less than 10% of total energy intake [4]. Another probable risk factor for weight gain, overweight, and obesity, which did not appear in the WHO/FAO Expert Consultation report but was mentioned in the second WCRF/AICR expert report, referred to fast foods, defined as foods that "are consumed often, in large portions, and are energy-dense" [3]. The only dietary factor that was considered by WCRF/AICR to decrease the risk of weight gain, overweight, and obesity, by promoting appropriate energy intake, was intake of low-energy-dense foods, i.e. wholegrain cereals and cereal products, non-starchy vegetables, and dietary fibre.

Dietary scores and dietary patterns

An analysis of three cohorts in the USA indicated that better diet quality, i.e. higher Alternate Mediterranean Diet (aMED), Alternate Healthy Eating Index-2010 (AHEI-2010), and Dietary

Table 4.1. Factors that might promote or protect against overweight and weight gain

Strength of evidence[a]	Decreases risk	No relationship	Increases risk
Convincing	Regular physical activity High intake of dietary non-starch polysaccharides/fibre		Sedentary lifestyles High intake of energy-dense foods[b]
Probable	Home and school environments that support healthy food choices for children Breastfeeding		Heavy marketing of energy-dense foods[b] and fast-food outlets Adverse social and economic conditions (in developed countries, especially for women) High-sugar drinks
Possible	Foods with low glycaemic index	Protein content of the diet	Large portion sizes High proportion of food prepared outside the home (developed countries) "Rigid restraint/periodic disinhibition" eating patterns
Insufficient	Increased eating frequency		Alcohol consumption

[a] Strength of evidence: The totality of the evidence was taken into account. The World Cancer Research Fund schema was taken as the starting point but was modified in the following manner: randomized controlled trials (RCTs) were given prominence as the highest ranking study design (RCTs not a major source of cancer evidence); associated evidence was also taken into account in relation to environmental determinants (direct trials were usually not available or possible).

[b] Energy-dense foods are high in fat and/or sugar; energy-dilute foods are high in non-starch polysaccharides/fibre and water, such as fruits, legumes, vegetables, and wholegrain cereals.

Source: Reproduced with permission from Swinburn et al. (2004) [2].

Table 4.2. Factors that modify the risk of weight gain, overweight, and obesity

Strength of evidence	Decreases risk	Increases risk
Convincing	Physical activity	Sedentary living[a]
Probable	Low-energy-dense foods[b] Being breastfed[d]	Energy-dense foods[b,c] Sugary drinks[e] Fast foods[f] Television viewing[g]
Limited – suggestive		
Limited – no conclusion	Refined cereals (grains) and their products; starchy roots, tubers, and plantains; fruits; meat; fish; milk and dairy products; fruit juices; coffee; alcoholic drinks; sweeteners	
Substantial effect on risk unlikely	None identified	

[a] Sedentary living comprises both high levels of physical inactivity and low levels of physical activity (in terms of intensity, frequency, and duration).

[b] The direct epidemiological evidence for low-energy-dense foods is from wholegrain cereals (grains) and cereal products, non-starchy vegetables, and dietary fibre. The direct epidemiological evidence for energy-dense foods is from animal fat and fast foods. These are interpreted as markers of the energy density of diets, based on compelling physiological and mechanistic evidence.

[c] Some relatively unprocessed energy-dense foods (which tend to be eaten sparingly), such as nuts, seeds, and some vegetable oils, are valuable sources of nutrients.

[d] The evidence relates principally to obesity in childhood, but overweight and obesity in children tend to track into adult life: overweight children are liable to become overweight and obese adults.

[e] The evidence relates to all drinks containing added caloric sweeteners, notably sucrose and high-fructose corn syrup. Fruit juices are also sugary drinks and could have similar effects, but the evidence is currently limited.

[f] Fast foods characteristically are consumed often, in large portions, and are energy-dense.

[g] Television viewing is here identified as a sedentary activity. It is also associated with consumption of energy-dense foods. The evidence relates specifically to childhood and adolescence, and is taken also to apply to adults.

Source: Reproduced with permission from WCRF/AICR (2007) [3].

Approaches to Stop Hypertension (DASH) scores, was associated with less weight gain during adult life [5]. This finding was in agreement with the results obtained from European cohorts using similar indices [6, 7]. A systematic review found that 13 of 21 epidemiological studies reported a negative association between adherence to the Mediterranean diet and overweight/obesity or weight gain [8]. In turn, increased frequency of consumption of fast-food products was linearly associated with lower Mediterranean Diet and Healthy Eating Index scores [9]. In today's environment, both the increased availability of and the portion sizes of fast-food products may contribute to rising obesity rates [10, 11].

Dietary patterns derived a posteriori by using dimension-reduction techniques such as factor or cluster analysis also showed that adherence

to a healthy dietary pattern (high intake of whole grains, fruits and vegetables, and reduced-fat dairy products) was associated with smaller gains in body mass index (BMI) and waist circumference (WC), whereas adoption of a dietary pattern typical of developed countries (also called the meat–sweet diet) may lead to weight gain [12–17]. A diet characterized by higher intakes of vegetables and wholemeal cereal products resulted in a lower risk of becoming overweight or obese (odds ratio [OR], 0.69; 95% confidence interval [CI], 0.54–0.88) in children followed up for 2 years [18]. The first study to prospectively investigate the association between dietary patterns at the nutrient level and weight change corroborated the previous findings that a healthy dietary pattern is associated with less weight gain and also highlighted combinations of nutrients that may be responsible for such associations at the food level [19].

The nutrition transition

The nutrition transition in developing countries leads to dietary intakes of micronutrient-poor, energy-dense foods, which may be important determinants of overweight/obesity and important for child development [20]. In low- and middle-income countries (LMICs), consumption of fruits and vegetables was observed to be lower in groups with low socioeconomic status compared with those with high socioeconomic status; this may be due to a lack of knowledge of the health benefits of fruits and vegetables, their high cost, and limited access to fresh-food markets in groups with lower socioeconomic status [21]. In addition, groups with high socioeconomic status were observed to have a higher intake of protein (due to increased intake of animal foods accompanying the nutrition transition), a lower intake of carbohydrates and fibre (attributable to a higher intake of processed foods replacing traditional, carbohydrate-rich foods), and a higher intake of fat (associated with increased prosperity and supermarket expansion) [21]. Nutrient-dense foods are often more expensive than the energy-dense alternatives [22].

Foods

One of the most consistent results with regard to obesogenic dietary factors pertains to the high energy density of some foods, i.e. an energy content of more than about 225–275 kcal per 100 g (941–1151 kJ per 100 g). *Energy-dense foods* have been rated as probable [3], convincing [1], or suggestive [23] obesity-promoting factors by three comprehensive reports and reviews on nutrition and obesity/weight gain. A study based on a prospective cohort from five European countries indicated an increase in WC of 0.09 cm/year (95% CI, 0.01–0.18 cm/year) per 1 kcal/g (4.2 kJ/g) dietary energy density, but did not observe a significant association of energy density with weight gain [24].

Fast foods are energy-dense, micronutrient-poor foods that are often high in saturated and trans-fatty acids, processed starches, and added sugars [25]. Several observational studies have indicated an increased risk of being obese, greater weight gain, higher BMI, and higher rates of overweight/obesity in those consuming fast-food products compared with non-consumers, in both developed regions [9, 26–28] and developing regions [29–31]. Consumption of a fast-food product (including hamburgers, cheeseburgers, and French fries) more than once per week by adults in Spain increased the risk of being obese by 129%, compared with non-consumers, after controlling for energy intake and several lifestyle factors [9]. In a cohort of participants aged 18–30 years in the USA, more frequent consumers (more than twice per week) gained an extra 4.5 kg of body weight over a 15-year period compared with less frequent consumers (less than once per week) of fast-food products [26]. Also, an increase of 5 BMI units (kg/m^2) was observed in children and adolescents in China who consumed processed foods frequently [29]. A recent analysis of the European Prospective Investigation into Cancer and Nutrition (EPIC) study using biomarkers of dietary exposure to industrially processed foods reported that a high blood level of industrial trans-fatty acids may increase the risk of weight gain, particularly in women [32].

In contrast, the evidence is not straightforward for beverages that may be a significant source of additional energy intake, including sugary drinks and alcoholic drinks.

Both the WHO/FAO report and the WCRF/AICR report indicated the probable role of *sugary drinks* (also called sodas, soft drinks, high-sugar drinks, or sugar-sweetened beverages) in obesity development [1, 3]. Some [33–37] but not all later meta-analyses and reviews [38–42] concluded that there is a significant positive association between intake of this food group and risk of obesity. Several factors are likely to contribute to these discrepant findings, including methodological differences between studies (different outcomes [overweight, weight gain, obesity]; varying exposure [types of beverages]; types of studies included [interventional and/or observational]; adjusted or not for energy intake and physical activity; different populations considered [age groups, sex, geographical regions that may vary in the composition of sugary drinks and the level of intake]), reporting and publication bias, and conflict of interest with the food industry [43]. Nevertheless, evidence supporting the obesogenic effect of sugary drinks of poor nutritional quality is growing, with increasing relevance

in children, especially in low-income socioeconomic groups [44] and in LMICs [45]. A meta-analysis of 22 cohort studies showed that each increment of one sugary drink per day was associated with an increase of 0.05–0.06 BMI units (kg/m^2) in children per year and an additional weight gain of 0.12–0.22 kg in adults per year [34]. A meta-analysis of five cohort studies indicated a 55% (95% CI, 32–82%) higher risk of being overweight in children who consume sugary drinks daily [46].

In the above-mentioned studies, the main methodological difference that may cause the discrepancies may be related to adjustment for energy intake. Because sugary drinks are believed to be an additional non-compensated energy source, an ad libitum strategy (energy intake not controlled or adjusted for) was proposed to be a better measure of the association of the intake of sugary drinks with obesity and/or weight gain. Indeed, an ad libitum strategy resulted in significant positive associations in meta-analyses of both experimental and observational studies [33]. Other authors claim that adjustment for energy intake should be taken into consideration; these studies generally observed no significant association [37]. Moreover, more pronounced genetic predisposition to obesity was observed with higher consumption of sugary drinks [47].

Discrepant results have been found also for *alcoholic drinks*. A recent review summarizing the metabolic effect of intake of energy-containing beverages concluded that observational studies have shown a positive association, a negative association, or no relationship between intake of alcohol or sugary drinks and body weight [48]. For alcohol intake, both the WHO/FAO report and the WCRF/AICR report ranked the evidence as insufficient to draw any conclusion in relation to body weight gain or obesity. Longer intervention studies and more detailed assessment of energy balance and other possible confounding lifestyle factors are still warranted to ascertain the obesogenic effect of these beverages. Also, better exposure assessment, with the possible use of validated biomarkers of intake (discussed later in this chapter), would be a valuable asset in judging the evidence, especially from existing well-powered epidemiological studies.

Sweets and desserts is another food group that may be characterized by high sugar content and high energy density. Suggestive evidence was found that high intake of sweets and desserts is a risk factor for weight gain [23]. In an analysis in the EPIC-Potsdam cohort, each increment of 100 g per day in intake of sweets was shown to be associated with the likelihood of a short-term weight gain in men (OR, 1.48; 95% CI, 1.03–2.13) [49]. Also in cohorts in the USA, each portion of sweets and desserts was significantly associated with an increase of 0.19 kg (95% CI, 0.07–0.30 kg) in weight per 4-year period [50].

Intake of *meat in general*, which is a significant dietary source of high-quality protein and specific fatty acids, was ranked by Fogelholm et al. as a probable risk factor for weight gain [23]. Higher intake of *red and processed meat* was positively associated with both BMI (mean difference between groups with high and low intake, 1.37 kg/m^2 [95% CI, 0.90–1.84 kg/m^2] for red meat and 1.32 kg/m^2 [95% CI, 0.64–2.00 kg/m^2] for processed meat) and WC (mean difference between groups with high and low intake, 2.79 cm [95% CI, 1.86–3.70 cm] for red meat and 2.77 cm [95% CI, 1.87–2.66 cm] for processed meat), based on a meta-analysis of 18 observational studies [51]. However, as stated in the WCRF/AICR report, the energy density of meat depends on the amount of fat it contains and how it is cooked, whereas the fatty acid composition of meat depends on its origin, processing, and animal feed. The quality of meat may differ according to the socioeconomic status of the consumer [52].

Sufficient evidence does not exist for establishing an association between body weight and intake of *fish*, a major source of omega-3 polyunsaturated fatty acids [3, 23]. No significant association was observed between fish intake and 5-year change in body weight in the EPIC study [53]. Additional evidence from a recent meta-analysis of randomized controlled trials (RCTs) that studied the effect of *fish or fish oils* on body composition found that participants in supplemented groups lost 0.59 kg more body weight, 0.49% more body fat, and 0.24 kg/m^2 more BMI compared with the control group and that their WC decreased by 0.81 cm more than the control group [54].

Results from two independent meta-analyses of RCTs suggested a potential beneficial effect of intake of *total dairy products* on weight loss (mean difference between groups with high and low intake, −0.61 kg [95% CI, −1.29 to 0.07 kg] [55] and −0.14 kg [95% CI, −0.66 to 0.38 kg] [56]) and improved body composition. However, this effect was significant only when dairy products were used as components of energy-restricted weight-loss diets or short-term interventions [56]. A systematic review of prospective cohort studies concluded that the protective effect of consumption of dairy products on the risk of overweight and obesity is suggestive but not consistent [57]. Subsequent findings from the Framingham Heart Study indicated a 0.10 ± 0.04 kg smaller annual weight gain in participants who consumed dairy products more frequently, probably attributable to yogurt intake [58]. Three prospective cohorts in the USA indicated a 0.82 lb (~0.37 kg) lower 4-year weight associated with yogurt consumption [50].

Legumes (i.e. beans, chickpeas, lentils, lupins, soybeans) could be

consumed as a plant-based alternative to animal protein. They have a lower energy density than animal protein and are good sources of fibre and microelements. Replacing energy-dense foods with legumes has been shown to have a favourable effect on obesity prevention [59] and short-term weight loss [60–62] in adults. Longer-term interventions with specific legume sources did not confirm these findings [63, 64]. The effect of legume consumption on weight control in children remains to be evaluated.

For *refined cereal products*, most reviews state that insufficient evidence exists for an association between intake and obesity [3, 35, 36], with a suggestion of an adverse effect by Fogelholm et al. [23]. *Wholegrain cereals and foods*, due to their low energy density and high fibre content, were indicated by several reports as having a protective effect against obesity and weight gain [3, 23, 35, 36]. A meta-analysis of prospective cohorts indicated a reduction of weight gain in those who consumed whole grains more frequently by 0.4–1.5 kg during 8–13 years of follow-up [65], whereas RCTs found only a small effect of wholegrain intake on the percentage of body fat (weighted difference, −0.48%; 95% CI, −0.95% to −0.01%, per g/day) [65a].

The group of *non-starchy vegetables* has similar characteristics in terms of fibre content and energy density. High-fibre/low-energy-density foods as a group were evaluated by WCRF/AICR as a probable obesity-preventive factor [3]. A meta-analysis of eight RCTs indicated that the change in body weight was 0.68 kg lower in the group with high intake of *fruits and vegetables* compared with the group with low intake [66]; however, not all studies [67] supported this inverse association, particularly in children [68]. When fruits and vegetables were considered separately, a meta-analysis of prospective cohort studies indicated that intake of fruits and intake of vegetables were each associated with a 17% reduced risk of adiposity, whereas intake of combined fruits and vegetables was associated with a 9% reduced risk of adiposity (OR, 0.91; 95% CI, 0.84–0.99), but only intake of fruits was inversely associated with weight change [69]. A negative association with long-term weight change was also observed for higher consumption of *nuts* in three prospective cohorts (−0.26 kg 4-year weight change per one-serving increment per day in the intake of nuts) [70]. A protective effect of nuts against weight gain has been also supported by several intervention studies [71].

In a meta-analysis of three prospective cohorts, a 4-year weight loss was observed for consumption of vegetables (−0.22 lb, or −0.10 kg), whole grains (−0.37 lb, or −0.17 kg), fruits (−0.49 lb, or −0.22 kg), and nuts (−0.57 lb, or −0.26 kg) [50]. However, it should be kept in mind that GI differs for different types of fruits and vegetables. For example, potatoes – similarly to refined carbohydrates characterized by high GI – could be positively associated with higher weight; however, sufficient evidence is still lacking [3, 23] to discourage intake of starchy vegetables in relation to obesity prevention. Nevertheless, the above-mentioned meta-analysis of cohorts in the USA [50], as well as an observational study from Denmark [72], indicated a 4-year weight gain of 1.28 lb (0.58 kg) and a 5-year increase in WC in women of 0.1 cm (per 60 kcal/day, or 250 kJ/day) in relation to higher intake of potatoes. These results require confirmation based on well-established cohorts.

Macronutrients

Fat is characterized by the highest energy density of all macronutrients (37 kJ/g, or 8.8 kcal/g). However, at the macronutrient level, according to the WHO/FAO report and a systematic review [1, 23], no sufficient or consistent evidence exists for fat or specific fatty acids and their ratios to be listed as determinants of obesity [73]. Long-term supplementation of the Mediterranean diet with unsaturated fat from olive oil or nuts improved cardiovascular health and was associated with a lower risk of obesity, as shown in the Prevención con Dieta Mediterránea (PREDIMED) trial [74, 75]. A recent systematic review evaluated four RCTs and two meta-analyses that investigated intake of fat and fatty acids in relation to body weight and composition [76]. The study concluded that there was probable evidence for a moderate positive association between total fat intake and body weight. A subsequent comprehensive meta-analysis of RCTs with a follow-up of 6–96 months showed that reduction of dietary fat intake (≤ 30% of energy from fat) led to greater weight loss (−1.5 kg; 95% CI, −2.0 to −1.1 kg) and reductions in BMI (–0.5 kg/m^2; 95% CI, −0.7 to −0.3 kg/m^2) and WC (−0.3 cm; 95% CI, −0.6 to −0.02 cm) than in the control group with usual fat intake [77], but no significant association between total fat intake and measures of body fatness was found based on the evidence from 25 cohort studies [77]. This meta-analysis included only RCTs that compared a lower fat intake versus usual or moderate fat intake in subjects from the general population without any intention to reduce body weight. However, another meta-analysis based on 53 studies that compared the long-term effect (≥ 1 year) of low-fat and higher-fat dietary interventions on weight loss found no effect of lowering fat intake on long-term weight loss [78].

Nevertheless, at the level of the overall dietary composition, interaction of macronutrients is more likely to have an impact on obesity control. In their meta-analysis of 23 RCTs, Hu et al. [79] compared the effects of low-fat diets (≤ 30% of energy from

fat) versus low-carbohydrate diets (≤ 45% of energy from carbohydrates) and found that the two types of diets resulted in comparable reduction in weight and WC. However, compared with participants following low-fat diets, those following low-carbohydrate diets experienced a slightly but statistically significantly lower reduction in total cholesterol and low-density lipoprotein cholesterol but a greater increase in high-density lipoprotein cholesterol and a greater decrease in triglycerides. Following a *low-carbohydrate* diet for at least 6 months reduced body weight by 2.1–14.3 kg and WC by 2.2–9.5 cm and led to similar or greater abdominal fat loss compared with an isoenergetic low-fat intervention [80].

With respect to the type of carbohydrate, increased intake of dietary *sugars* may be associated with an increase in body weight by 0.75 kg (95% CI, 0.30–1.19 kg) and decreased intake with a comparable weight decrease, by 0.80 kg (95% CI, 0.39–1.21 kg), as suggested by a meta-analysis of 30 trials of adults with ad libitum diets. Isoenergetic exchange of free sugars (from a diet high in fructose or sucrose) with other carbohydrates (i.e. starch or fibre) did not result in a change in body weight, suggesting that energy intake rather than the type of carbohydrate is a determinant of weight change [46]. On the basis of these outcomes, WHO concluded that the strength of evidence is moderate for the association between added sugar (including in the form of sugary drinks) and body weight gain/obesity, and suggested that longer trials (> 8 weeks) with increasing or decreasing intake of sugars should be conducted in free-living individuals to confirm this association and set the threshold of intake [4]. Special attention should be paid to fructose and fructose-containing sugars, for which mechanistic data suggest their potential effect on increased energy intake and reduced energy expenditure (failure to stimulate leptin production) and their effect on lipid and carbohydrate metabolism (stimulation of de novo lipogenesis) [81], but also on inducing signalling and inflammatory pathways [82].

A probable obesity-protective effect of *fibre* (in both adults and children) and of low GI (in women only) has been advocated by two reviews [23, 35]. The WHO/FAO report also suggested a possible anti-obesogenic effect of *low-GI foods* [1]. As shown by a European trial, lowering the GI of a diet and increasing its protein content in an ad libitum setting led to a weight regain that was 0.95 kg lower (95% CI, 0.33–1.57 kg) compared with a high-GI diet in obese individuals after the loss of more than 8% of their initial weight. That study found an additive effect of a high-protein and low-GI diet on body weight maintenance during the 6 months after the weight loss [83, 84]. In a meta-analysis of six RCTs, a greater decrease in fat mass and BMI was observed in participants assigned to a low-GI diet compared with controls [85]. A recently published study investigated the effect of changes in intake of protein foods and glycaemic load on long-term weight gain [86]. The study, based on three prospective cohorts in the USA, showed that protein foods were not interchanged with each other but rather replaced with carbohydrate-rich foods and that an interaction between changes in intake of protein foods and glycaemic load and long-term weight gain was present. The study found that an increase in intake of protein foods that were positively associated with weight gain (i.e. unprocessed red meat and processed meat) together with a concomitant increase in glycaemic load augmented the weight gain, whereas a higher intake of protein foods associated with weight loss (i.e. nuts, seafood, and plain yogurt) generally reduced the amount of weight loss when there was a concurrent increase in glycaemic load and increased the amount of weight loss when there was a concurrent decrease in glycaemic load.

However, the existing epidemiological evidence in relation to *protein* intake in terms of obesity prevention is not clear. In 2004, WHO concluded that there is no relationship between obesity and the protein content of the diet [1]. Later studies suggested an inverse association between protein intake and BMI (−4.54 kg/m^2 per g/kg body weight) and WC (−2.45 cm per g/kg body weight) [87] or no association for total protein intake, increased body weight for animal protein intake, and decreased body weight for plant protein intake (per ~38 g/day) [88]. This was confirmed by Freisling et al., who investigated nutrient patterns based on the EPIC cohort [19]. The study indicated that a pattern characterized by higher intakes of plant food sources (characterized by higher intakes of folate, vitamin C, and β-carotene) was negatively associated with weight gain (−22 g/year for men and −18 g/year for women), whereas a pattern characterized by higher intakes of total protein, vitamin B_2, phosphorus, and calcium was associated with a weight gain of +41 g/year (95% CI, +2 to +80 g/year) in men and +88 g/year (95% CI, +36 to +140 g/year) in women. However, another study based on the EPIC cohort concluded that a diet with the highest consumption of protein (> 22% of energy from protein) was associated with a 23–24% higher risk of overweight or obesity in models adjusted for energy intake, and that isoenergetic replacement of 5% of energy from carbohydrate (especially fibre) or fat by 5% of energy from protein was positively associated with weight gain after 5 years, regardless of the type of protein (animal protein or plant protein) [89].

Given the possible mechanisms of the effect of proteins on body weight related to satiety control, studies in an ad libitum setting are more likely

to observe their potential anti-obesity effect. Proteins, similarly to fibre, are believed to induce greater satiety signals by affecting gastric kinetics and release of gut hormones [90, 91]. However, this effect may depend on the type (casein vs whey) and form (liquid or solid) of macronutrient ingested, and it still needs to be elucidated whether this effect is maintained in the long term [92]. More consensus exists in the literature for the effect of protein intake on weight loss and/or maintenance. Based on two meta-analyses of experimental studies, high-protein diets resulted in greater reduction of weight/WC/fat mass and preservation of lean body mass compared with low-protein diets with similar dietary fat content [93, 94]. This effect, in turn, is believed to be attributable to greater diet-induced thermogenesis, affecting energy balance and alterations in protein turnover. Adverse health outcomes may be observed with excessive protein intakes [95].

Biomarkers of exposure

Despite the fact that the field of metabolomics is growing, to date few validated biomarkers of dietary exposure have been used to validate dietary intakes. Some examples are urinary nitrogen (biomarker of protein intake), urinary sucrose and fructose (intake of sugars), fatty acid profiles of plasma phospholipids, erythrocytes, and adipose tissue (intake of dietary fats/fatty acids), plasma vitamins (surrogate of intake of fruits and vegetables), plasma alkylresorcinols (intake of whole grains), urine methylhistidine (meat intake), trimethylamine *N*-oxide (fish intake), and urine polyphenols (intakes of red wine, citrus, tea, soy, and olive oil), which are discussed in reviews [96–99]. More recently, the application of stable carbon isotope (^{13}C) analysis of alanine in red blood cells was suggested as a validation marker of intake of sugary drinks and sugars [100], and a specific plasma fatty acid (elaidic acid) was suggested as a biomarker of industrial trans-fatty acids [101].

Conclusions

Taken together, the evidence indicates that adherence to a healthy diet characterized by increased intake of low-GI foods and/or fibre (wholegrain products, non-starchy vegetables, and nuts) and avoidance of energy-dense foods (fast foods, sweets, and desserts), simple carbohydrates (including sugary drinks), low-quality processed meats, and refined cereal products should be implemented for obesity prevention. More studies are required to ascertain the effect of intake of legumes, fish, different types of dairy products, and specific fatty acids on weight and in relation to obesity prevention. To ensure better estimation of true dietary intakes, the use of exposure biomarkers is warranted.

Key points

- Energy intake as part of energy balance plays a major role in weight gain and obesity management.
- In an ad libitum free-living setting, specific macronutrients may reduce energy intake by affecting satiety signalling.
- As part of a healthy diet, foods that are micronutrient-dense, are high in fibre, have a low GI, and/or have a low energy density (fruits and non-starchy vegetables, wholegrain products, nuts, and seeds) help to maintain a healthy body weight.
- The following may be obesity-promoting factors: energy-dense, micronutrient-poor fast foods that are high in saturated and industrial fatty acids and/or refined starches and sugars, low-quality processed meats, sweets and desserts, and sugary drinks.

Research needs

- Well-designed longer observational and intervention studies, especially in children and adolescents, are needed to establish the link between intake of fish, different types of dairy products, fruits, vegetables, legumes, specific fatty acids, energy density, and interaction between nutrients as a part of diet and obesity and weight gain.
- Detailed, appropriate, and standardized assessment of potential confounders (including baseline BMI, weight gain during follow-up, energy intake from different dietary sources, and socioeconomic status) and outcomes (obesity and adiposity measures) should be considered.
- Measurement of validated biomarkers of dietary exposure should be used in order to better control for measurement error and reporting bias in dietary intake assessment.

References

1. WHO (2003). Diet, nutrition and the prevention of chronic diseases: report of a joint WHO/FAO Expert Consultation. Geneva, Switzerland: World Health Organization (WHO Technical Report Series, No. 916). Available from: http://www.who.int/dietphysicalactivity/publications/trs916/en/.

2. Swinburn BA, Caterson I, Seidell JC, James WP (2004). Diet, nutrition and the prevention of excess weight gain and obesity. Public Health Nutr. 7(1A):123–46. PMID:14972057

3. WCRF/AICR (2007). Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington (DC), USA: World Cancer Research Fund/American Institute for Cancer Research. Available from: www.aicr.org/assets/docs/pdf/reports/Second_Expert_Report.pdf.

4. WHO (2015). Guideline: sugars intake for adults and children. Geneva, Switzerland: World Health Organization. Available from: apps.who.int/iris/bitstream/10665/149782/1/9789241549028_eng.pdf?ua=1.

5. Fung TT, Pan A, Hou T, Chiuve SE, Tobias DK, Mozaffarian D, et al. (2015). Long-term change in diet quality is associated with body weight change in men and women. J Nutr. 145(8):1850–6. http://dx.doi.org/10.3945/jn.114.208785 PMID:26084363

6. Romaguera D, Norat T, Vergnaud A-C, Mouw T, May AM, Agudo A, et al. (2010). Mediterranean dietary patterns and prospective weight change in participants of the EPIC-PANACEA project. Am J Clin Nutr. 92(4):912–21. http://dx.doi.org/10.3945/ajcn.2010.29482 PMID:20810975

7. Funtikova AN, Benítez-Arciniega AA, Gomez SF, Fitó M, Elosua R, Schröder H (2014). Mediterranean diet impact on changes in abdominal fat and 10-year incidence of abdominal obesity in a Spanish population. Br J Nutr. 111(8):1481–7. http://dx.doi.org/10.1017/S0007114513003966 PMID:24382017

8. Buckland G, Bach A, Serra-Majem L (2008). Obesity and the Mediterranean diet: a systematic review of observational and intervention studies. Obes Rev. 9(6):582–93. http://dx.doi.org/10.1111/j.1467-789X.2008.00503.x PMID:18547378

9. Schröder H, Fïto M, Covas MI; REGICOR investigators (2007). Association of fast food consumption with energy intake, diet quality, body mass index and the risk of obesity in a representative Mediterranean population. Br J Nutr. 98(6):1274–80. http://dx.doi.org/10.1017/S0007114507781436 PMID:17625027

10. Vandevijvere S, Chow CC, Hall KD, Umali E, Swinburn BA (2015). Increased food energy supply as a major driver of the obesity epidemic: a global analysis. Bull World Health Organ. 93(7):446–56. http://dx.doi.org/10.2471/BLT.14.150565 PMID:26170502

11. Piernas C, Popkin BM (2011). Increased portion sizes from energy-dense foods affect total energy intake at eating occasions in US children and adolescents: patterns and trends by age group and sociodemographic characteristics, 1977-2006. Am J Clin Nutr. 94(5):1324–32. http://dx.doi.org/10.3945/ajcn.110.008466 PMID:21918222

12. Newby PK, Muller D, Hallfrisch J, Qiao N, Andres R, Tucker KL (2003). Dietary patterns and changes in body mass index and waist circumference in adults. Am J Clin Nutr. 77(6):1417–25. PMID:12791618

13. Schulz M, Nöthlings U, Hoffmann K, Bergmann MM, Boeing H (2005). Identification of a food pattern characterized by high-fiber and low-fat food choices associated with low prospective weight change in the EPIC-Potsdam cohort. J Nutr. 135(5):1183–9. PMID:15867301

14. Newby PK, Muller D, Hallfrisch J, Andres R, Tucker KL (2004). Food patterns measured by factor analysis and anthropometric changes in adults. Am J Clin Nutr. 80(2):504–13. PMID:15277177

15. Schulze MB, Fung TT, Manson JE, Willett WC, Hu FB (2006). Dietary patterns and changes in body weight in women. Obesity (Silver Spring). 14(8):1444–53. http://dx.doi.org/10.1038/oby.2006.164 PMID:16988088

16. Shi Z, Yuan B, Hu G, Dai Y, Zuo H, Holmboe-Ottesen G (2011). Dietary pattern and weight change in a 5-year follow-up among Chinese adults: results from the Jiangsu Nutrition Study. Br J Nutr. 105(7):1047–54. http://dx.doi.org/10.1017/S0007114510004630 PMID:21106132

17. Yu C, Shi Z, Lv J, Du H, Qi L, Guo Y, et al. (2015). Major dietary patterns in relation to general and central obesity among Chinese adults. Nutrients. 7(7):5834–49. http://dx.doi.org/10.3390/nu7075253 PMID:26184308

18. Pala V, Lissner L, Hebestreit A, Lanfer A, Sieri S, Siani A, et al. (2013). Dietary patterns and longitudinal change in body mass in European children: a follow-up study on the IDEFICS multicenter cohort. Eur J Clin Nutr. 67(10):1042–9. http://dx.doi.org/10.1038/ejcn.2013.145 PMID:23942180

19. Freisling H, Pisa PT, Ferrari P, Byrnes G, Moskal A, Dahm CC, et al. (2016). Main nutrient patterns are associated with prospective weight change in adults from 10 European countries. Eur J Nutr. 55(6):2093–104. http://dx.doi.org/10.1007/s00394-015-1023-x PMID:26303194

20. Troesch B, Biesalski HK, Bos R, Buskens E, Calder PC, Saris WH, et al. (2015). Increased intake of foods with high nutrient density can help to break the intergenerational cycle of malnutrition and obesity. Nutrients. 7(7):6016–37. http://dx.doi.org/10.3390/nu7075266 PMID:26197337

21. Mayén AL, Marques-Vidal P, Paccaud F, Bovet P, Stringhini S (2014). Socioeconomic determinants of dietary patterns in low- and middle-income countries: a systematic review. Am J Clin Nutr. 100(6):1520–31. http://dx.doi.org/10.3945/ajcn.114.089029 PMID:25411287

22. Rao M, Afshin A, Singh G, Mozaffarian D (2013). Do healthier foods and diet patterns cost more than less healthy options? A systematic review and meta-analysis. BMJ Open. 3(12):e004277. http://dx.doi.org/10.1136/bmjopen-2013-004277 PMID:24309174

23. Fogelholm M, Anderssen S, Gunnarsdottir I, Lahti-Koski M (2012). Dietary macronutrients and food consumption as determinants of long-term weight change in adult populations: a systematic literature review. Food Nutr Res. 56:19103. http://dx.doi.org/10.3402/fnr.v56i0.19103 PMID:22893781

24. Du H, van der A DL, Ginder V, Jebb SA, Forouhi NG, Wareham NJ, et al. (2009). Dietary energy density in relation to subsequent changes of weight and waist circumference in European men and women. PLoS One. 4(4):e5339. http://dx.doi.org/10.1371/journal.pone.0005339 PMID:19396357

25. Jaworowska A, Blackham T, Davies IG, Stevenson L (2013). Nutritional challenges and health implications of takeaway and fast food. Nutr Rev. 71(5):310–8. http://dx.doi.org/10.1111/nure.12031 PMID:23590707

26. Pereira MA, Kartashov AI, Ebbeling CB, Van Horn L, Slattery ML, Jacobs DR Jr, et al. (2005). Fast-food habits, weight gain, and insulin resistance (the CARDIA study): 15-year prospective analysis. Lancet. 365 (9453):36–42. http://dx.doi.org/10.1016/S0140-6736(04)17663-0 PMID:15639678

27. Alkerwi A, Crichton GE, Hébert JR (2014). Consumption of ready-made meals and increased risk of obesity: findings from the Observation of Cardiovascular Risk Factors in Luxembourg (ORISCAV-LUX) study. Br J Nutr. 9:1–8. PMID:25488071

28. Kant AK, Whitley MI, Graubard BI (2015). Away from home meals: associations with biomarkers of chronic disease and dietary intake in American adults, NHANES 2005-2010. Int J Obes (Lond). 39(5):820–7. http://dx.doi.org/10.1038/ijo.2014.183 PMID:25319744

29. Zhou Y, Du S, Su C, Zhang B, Wang H, Popkin BM (2015). The food retail revolution in China and its association with diet and health. Food Policy. 55:92–100. http://dx.doi.org/10.1016/j.foodpol.2015.07.001 PMID:26217068

30. Rouhani MH, Mirseifinezhad M, Omrani N, Esmaillzadeh A, Azadbakht L (2012). Fast food consumption, quality of diet, and obesity among Isfahanian adolescent girls. J Obes. 2012: 597924. http://dx.doi.org/10.1155/2012/597924 PMID:22619703

31. ALFaris NA, Al-Tamimi JZ, Al-Jobair MO, Al-Shwaiyat NM (2015). Trends of fast food consumption among adolescent and young adult Saudi girls living in Riyadh. Food Nutr Res. 59:26488. http://dx.doi.org/10.3402/fnr.v59.26488 PMID:25792229

32. Chajès V, Biessy C, Ferrari P, Romieu I, Freisling H, Huybrechts I, et al. (2015). Plasma elaidic acid level as biomarker of industrial trans fatty acids and risk of weight change: report from the EPIC study. PLoS One. 10(2):e0118206. http://dx.doi.org/10.1371/journal.pone.0118206 PMID:25675445

33. Hu FB, Malik VS (2010). Sugar-sweetened beverages and risk of obesity and type 2 diabetes: epidemiologic evidence. Physiol Behav. 100(1):47–54. http://dx.doi.org/10.1016/j.physbeh.2010.01.036 PMID:20138901

34. Malik VS, Pan A, Willett WC, Hu FB (2013). Sugar-sweetened beverages and weight gain in children and adults: a systematic review and meta-analysis. Am J Clin Nutr. 98(4):1084–102. http://dx.doi.org/10.3945/ajcn.113.058362 PMID:23966427

35. Hauner H, Bechthold A, Boeing H, Brönstrup A, Buyken A, Leschik-Bonnet E, et al.; German Nutrition Society (2012). Evidence-based guideline of the German Nutrition Society: carbohydrate intake and prevention of nutrition-related diseases. Ann Nutr Metab. 60(Suppl 1):1–58. http://dx.doi.org/10.1159/000335326 PMID:22286913

36. Fardet A, Boirie Y (2014). Associations between food and beverage groups and major diet-related chronic diseases: an exhaustive review of pooled/meta-analyses and systematic reviews. Nutr Rev. 72(12):741–62. http://dx.doi.org/10.1111/nure.12153 PMID:25406801

37. Trumbo PR, Rivers CR (2014). Systematic review of the evidence for an association between sugar-sweetened beverage consumption and risk of obesity. Nutr Rev. 72(9):566–74. http://dx.doi.org/10.1111/nure.12128 PMID:25091794

38. Kaiser KA, Shikany JM, Keating KD, Allison DB (2013). Will reducing sugar-sweetened beverage consumption reduce obesity? Evidence supporting conjecture is strong, but evidence when testing effect is weak. Obes Rev. 14(8):620–33. http://dx.doi.org/10.1111/obr.12048 PMID:23742715

39. Keller A, Bucher Della Torre S (2015). Sugar-sweetened beverages and obesity among children and adolescents: a review of systematic literature reviews. Child Obes. 11(4):338–46. http://dx.doi.org/10.1089/chi.2014.0117 PMID:26258560

40. van Baak MA, Astrup A (2009). Consumption of sugars and body weight. Obes Rev. 10(Suppl 1):9–23. http://dx.doi.org/10.1111/j.1467-789X.2008.00561.x PMID:19207532

41. Forshee RA, Anderson PA, Storey ML (2008). Sugar-sweetened beverages and body mass index in children and adolescents: a meta-analysis. Am J Clin Nutr. 87(6):1662–71. PMID:18541554

42. Gibson S (2008). Sugar-sweetened soft drinks and obesity: a systematic review of the evidence from observational studies and interventions. Nutr Res Rev. 21(2):134–47. http://dx.doi.org/10.1017/S0954422408110976 PMID:19087367

43. Bes-Rastrollo M, Schulze MB, Ruiz-Canela M, Martinez-Gonzalez MA (2013). Financial conflicts of interest and reporting bias regarding the association between sugar-sweetened beverages and weight gain: a systematic review of systematic reviews. PLoS Med. 10(12):e1001578. http://dx.doi.org/10.1371/journal.pmed.1001578 PMID:24391479

44. Han E, Powell LM (2013). Consumption patterns of sugar-sweetened beverages in the United States. J Acad Nutr Diet. 113(1):43–53. http://dx.doi.org/10.1016/j.jand.2012.09.016 PMID:23260723

45. Basu S, McKee M, Galea G, Stuckler D (2013). Relationship of soft drink consumption to global overweight, obesity, and diabetes: a cross-national analysis of 75 countries. Am J Public Health. 103(11):2071–7. http://dx.doi.org/10.2105/AJPH.2012.300974 PMID:23488503

46. Te Morenga L, Mallard S, Mann J (2012). Dietary sugars and body weight: systematic review and meta-analyses of randomised controlled trials and cohort studies. BMJ. 346:e7492. http://dx.doi.org/10.1136/bmj.e7492 PMID:23321486

47. Qi Q, Chu AY, Kang JH, Jensen MK, Curhan GC, Pasquale LR, et al. (2012). Sugar-sweetened beverages and genetic risk of obesity. N Engl J Med. 367(15):1387–96. http://dx.doi.org/10.1056/NEJMoa1203039 PMID:22998338

48. Poppitt SD (2015). Beverage consumption: are alcoholic and sugary drinks tipping the balance towards overweight and obesity? Nutrients. 7(8):6700–18. http://dx.doi.org/10.3390/nu7085304 PMID:26270675

49. Schulz M, Kroke A, Liese AD, Hoffmann K, Bergmann MM, Boeing H (2002). Food groups as predictors for short-term weight changes in men and women of the EPIC-Potsdam cohort. J Nutr. 132(6):1335–40. PMID:12042455

50. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB (2011). Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med. 364(25):2392–404. http://dx.doi.org/10.1056/NEJMoa1014296 PMID:21696306

51. Rouhani MH, Salehi-Abargouei A, Surkan PJ, Azadbakht L (2014). Is there a relationship between red or processed meat intake and obesity? A systematic review and meta-analysis of observational studies. Obes Rev. 15(9): 740–8. http://dx.doi.org/10.1111/obr.12172 PMID:24815945

52. Webb EC, O'Neill HA (2008). The animal fat paradox and meat quality. Meat Sci. 80(1):28–36. http://dx.doi.org/10.1016/j.meatsci.2008.05.029 PMID:22063167

53. Jakobsen MU, Dethlefsen C, Due KM, May AM, Romaguera D, Vergnaud A-C, et al. (2013). Fish consumption and subsequent change in body weight in European women and men. Br J Nutr. 109(2):353–62. http://dx.doi.org/10.1017/S0007114512001079 PMID:22716915

54. Bender N, Portmann M, Heg Z, Hofmann K, Zwahlen M, Egger M (2014). Fish or n3-PUFA intake and body composition: a systematic review and meta-analysis. Obes Rev. 15(8):657–65. http://dx.doi.org/10.1111/obr.12189 PMID:24891155

55. Abargouei AS, Janghorbani M, Salehi-Marzijarani M, Esmaillzadeh A (2012). Effect of dairy consumption on weight and body composition in adults: a systematic review and meta-analysis of randomized controlled clinical trials. Int J Obes (Lond). 36(12):1485–93. http://dx.doi.org/10.1038/ijo.2011.269 PMID:22249225

56. Chen M, Pan A, Malik VS, Hu FB (2012). Effects of dairy intake on body weight and fat: a meta-analysis of randomized controlled trials. Am J Clin Nutr. 96(4):735–47. http://dx.doi.org/10.3945/ajcn.112.037119 PMID:22932282

57. Louie JC, Flood VM, Hector DJ, Rangan AM, Gill TP (2011). Dairy consumption and overweight and obesity: a systematic review of prospective cohort studies. Obes Rev. 12(7):e582–92. http://dx.doi.org/10.1111/j.1467-789X.2011.00881.x PMID:21521450

58. Wang H, Troy LM, Rogers GT, Fox CS, McKeown NM, Meigs JB, et al. (2014). Longitudinal association between dairy consumption and changes of body weight and waist circumference: the Framingham Heart Study. Int J Obes (Lond). 38(2):299–305. http://dx.doi.org/10.1038/ijo.2013.78 PMID:23736371

59. Rebello CJ, Greenway FL, Finley JW (2014). A review of the nutritional value of legumes and their effects on obesity and its related co-morbidities. Obes Rev. 15(5):392–407. http://dx.doi.org/10.1111/obr.12144 PMID:24433379

60. Papanikolaou Y, Fulgoni VL 3rd (2008). Bean consumption is associated with greater nutrient intake, reduced systolic blood pressure, lower body weight, and a smaller waist circumference in adults: results from the National Health and Nutrition Examination Survey 1999-2002. J Am Coll Nutr. 27(5):569–76. http://dx.doi.org/10.1080/07315724.2008.10719740 PMID:18845707

61. Abete I, Parra D, Martinez JA (2009). Legume-, fish-, or high-protein-based hypocaloric diets: effects on weight loss and mitochondrial oxidation in obese men. J Med Food. 12(1):100–8. http://dx.doi.org/10.1089/jmf.2007.0700 PMID:19298202

62. Hermsdorff HH, Zulet MÁ, Abete I, Martínez JA (2011). A legume-based hypocaloric diet reduces proinflammatory status and improves metabolic features in overweight/obese subjects. Eur J Nutr. 50(1):61–9. http://dx.doi.org/10.1007/s00394-010-0115-x PMID:20499072

63. Belski R, Mori TA, Puddey IB, Sipsas S, Woodman RJ, Ackland TR, et al. (2011). Effects of lupin-enriched foods on body composition and cardiovascular disease risk factors: a 12-month randomized controlled weight loss trial. Int J Obes (Lond). 35(6):810–9. http://dx.doi.org/10.1038/ijo.2010.213 PMID:20938438

64. Hodgson JM, Lee YP, Puddey IB, Sipsas S, Ackland TR, Beilin LJ, et al. (2010). Effects of increasing dietary protein and fibre intake with lupin on body weight and composition and blood lipids in overweight men and women. Int J Obes (Lond). 34(6):1086–94. http://dx.doi.org/10.1038/ijo.2010.26 PMID:20157326

65. Ye EQ, Chacko SA, Chou EL, Kugizaki M, Liu S (2012). Greater whole-grain intake is associated with lower risk of type 2 diabetes, cardiovascular disease, and weight gain. J Nutr. 142(7):1304–13. http://dx.doi.org/10.3945/jn.111.155325 PMID:22649266

65a. Pol K, Christensen R, Bartels EM, Raben A, Tetens I, Kristensen M (2013). Whole grain and body weight changes in apparently healthy adults: a systematic review and meta-analysis of randomized controlled studies. Am J Clin Nutr. 98(4):872–84. http://dx.doi.org/10.3945/ajcn.113.064659 PMID:23945718

66. Mytton OT, Nnoaham K, Eyles H, Scarborough P, Ni Mhurchu C (2014). Systematic review and meta-analysis of the effect of increased vegetable and fruit consumption on body weight and energy intake. BMC Public Health. 14(1):886. http://dx.doi.org/10.1186/1471-2458-14-886 PMID:25168465

67. Kaiser KA, Brown AW, Bohan Brown MM, Shikany JM, Mattes RD, Allison DB (2014). Increased fruit and vegetable intake has no discernible effect on weight loss: a systematic review and meta-analysis. Am J Clin Nutr. 100(2):567–76. http://dx.doi.org/10.3945/ajcn.114.090548 PMID:24965308

68. Ledoux TA, Hingle MD, Baranowski T (2011). Relationship of fruit and vegetable intake with adiposity: a systematic review. Obes Rev. 12(5):e143–50. http://dx.doi.org/10.1111/j.1467-789X.2010.00786.x PMID:20633234

69. Schwingshackl L, Hoffmann G, Kalle-Uhlmann T, Arregui M, Buijsse B, Boeing H (2015). Fruit and vegetable consumption and changes in anthropometric variables in adult populations: a systematic review and meta-analysis of prospective cohort studies. PLoS One. 10(10):e0140846. http://dx.doi.org/10.1371/journal.pone.0140846 PMID:26474158

70. Jackson CL, Hu FB (2014). Long-term associations of nut consumption with body weight and obesity. Am J Clin Nutr. 100 (Suppl 1): 408S–11S. http://dx.doi.org/10.3945/ajcn.113.071332 PMID:24898229

71. Vadivel V, Kunyanga CN, Biesalski HK (2012). Health benefits of nut consumption with special reference to body weight control. Nutrition. 28(11–12):1089–97. http://dx.doi.org/10.1016/j.nut.2012.01.004 PMID:23044160

72. Halkjaer J, Tjønneland A, Overvad K, Sørensen TIA (2009). Dietary predictors of 5-year changes in waist circumference. J Am Diet Assoc. 109(8):1356–66. http://dx.doi.org/10.1016/j.jada.2009.05.015 PMID:19631041

73. van Baak MA (2013). Nutrition as a link between obesity and cardiovascular disease: how can we stop the obesity epidemic? Thromb Haemost. 110(4):689–96. http://dx.doi.org/10.1160/TH13-01-0045 PMID:23945609

74. Martínez-González MA, Salas-Salvadó J, Estruch R, Corella D, Fitó M, Ros E; PREDIMED INVESTIGATORS (2015). Benefits of the Mediterranean diet: insights from the PREDIMED study. Prog Cardiovasc Dis. 58(1):50–60. http://dx.doi.org/10.1016/j.pcad.2015.04.003 PMID:25940230

75. Ibarrola-Jurado N, Bulló M, Guasch-Ferré M, Ros E, Martínez-González MA, Corella D, et al.; PREDIMED Study Investigators (2013). Cross-sectional assessment of nut consumption and obesity, metabolic syndrome and other cardiometabolic risk factors: the PREDIMED study. PLoS One. 8(2):e57367. http://dx.doi.org/10.1371/journal.pone.0057367 PMID:23460844

76. Schwab U, Lauritzen L, Tholstrup T, Haldorssoni T, Riserus U, Uusitupa M, et al. (2014). Effect of the amount and type of dietary fat on cardiometabolic risk factors and risk of developing type 2 diabetes, cardiovascular diseases, and cancer: a systematic review. Food Nutr Res. 58:25145. http://dx.doi.org/10.3402/fnr.v58.25145 PMID:25045347

77. Hooper L, Abdelhamid A, Bunn D, Brown T, Summerbell CD, Skeaff CM (2015). Effects of total fat intake on body weight. Cochrane Database Syst Rev. 8:CD011834. PMID:26250104

78. Tobias DK, Chen M, Manson JE, Ludwig DS, Willett W, Hu FB (2015). Effect of low-fat diet interventions versus other diet interventions on long-term weight change in adults: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 3(12):968–79. http://dx.doi.org/10.1016/S2213-8587(15)00367-8 PMID:26527511

79. Hu T, Mills KT, Yao L, Demanelis K, Eloustaz M, Yancy WS Jr, et al. (2012). Effects of low-carbohydrate diets versus low-fat diets on metabolic risk factors: a meta-analysis of randomized controlled clinical trials. Am J Epidemiol. 176(Suppl 7):S44–54. http://dx.doi.org/10.1093/aje/kws264 PMID:23035144

80. Hu T, Bazzano LA (2014). The low-carbohydrate diet and cardiovascular risk factors: evidence from epidemiologic studies. Nutr Metab Cardiovasc Dis. 24(4):337–43. http://dx.doi.org/10.1016/j.numecd.2013.12.008 PMID:24613757

81. Stanhope KL, Schwarz JM, Havel PJ (2013). Adverse metabolic effects of dietary fructose: results from the recent epidemiological, clinical, and mechanistic studies. Curr Opin Lipidol. 24(3):198–206. http://dx.doi.org/10.1097/MOL.0b013e3283613bca PMID:23594708

82. Sanders FW, Griffin JL (2016). De novo lipogenesis in the liver in health and disease: more than just a shunting yard for glucose. Biol Rev Camb Philos Soc. 91(2):452–68. http://dx.doi.org/10.1111/brv.12178 PMID:25740151

83. Larsen TM, Dalskov S-M, van Baak M, Jebb SA, Papadaki A, Pfeiffer AFH, et al.; Diet, Obesity, and Genes (Diogenes) Project (2010). Diets with high or low protein content and glycemic index for weight-loss maintenance. N Engl J Med. 363(22):2102–13. http://dx.doi.org/10.1056/NEJMoa1007137 PMID:21105792

84. Astrup A, Raben A, Geiker N (2015). The role of higher protein diets in weight control and obesity-related comorbidities. Int J Obes (Lond). 39(5):721–6. http://dx.doi.org/10.1038/ijo.2014.216 PMID:25540980

85. Thomas DE, Elliott EJ, Baur L (2007). Low glycaemic index or low glycaemic load diets for overweight and obesity. Cochrane Database Syst Rev. (3):CD005105. PMID:17636786

86. Smith JD, Hou T, Ludwig DS, Rimm EB, Willett W, Hu FB, et al. (2015). Changes in intake of protein foods, carbohydrate amount and quality, and long-term weight change: results from 3 prospective cohorts. Am J Clin Nutr. 101(6):1216–24. http://dx.doi.org/10.3945/ajcn.114.100867 PMID:25854882

87. Pasiakos SM, Lieberman HR, Fulgoni VL 3rd (2015). Higher-protein diets are associated with higher HDL cholesterol and lower BMI and waist circumference in US adults. J Nutr. 145(3):605–14. http://dx.doi.org/10.3945/jn.114.205203 PMID:25733478

88. Halkjær J, Olsen A, Overvad K, Jakobsen MU, Boeing H, Buijsse B, et al. (2011). Intake of total, animal and plant protein and subsequent changes in weight or waist circumference in European men and women: the Diogenes project. Int J Obes (Lond). 35(8):1104–13. http://dx.doi.org/10.1038/ijo.2010.254 PMID:21139559

89. Vergnaud AC, Norat T, Mouw T, Romaguera D, May AM, Bueno-de-Mesquita HB, et al. (2013). Macronutrient composition of the diet and prospective weight change in participants of the EPIC-PANACEA study. PLoS One. 8(3):e57300. http://dx.doi.org/10.1371/journal.pone.0057300 PMID:23472080

90. Rebello C, Greenway FL, Dhurandhar NV (2014). Functional foods to promote weight loss and satiety. Curr Opin Clin Nutr Metab Care. 17(6):596–604. http://dx.doi.org/10.1097/MCO.0000000000000110 PMID:25159561

91. Chambers L, McCrickerd K, Yeomans MR (2015). Optimising foods for satiety. Trends Food Sci Technol. 41(2):149–60. http://dx.doi.org/10.1016/j.tifs.2014.10.007

92. Bendtsen LQ, Lorenzen JK, Bendsen NT, Rasmussen C, Astrup A (2013). Effect of dairy proteins on appetite, energy expenditure, body weight, and composition: a review of the evidence from controlled clinical trials. Adv Nutr. 4(4):418–38. http://dx.doi.org/10.3945/an.113.003723 PMID:23858091

93. Santesso N, Akl EA, Bianchi M, Mente A, Mustafa R, Heels-Ansdell D, et al. (2012). Effects of higher- versus lower-protein diets on health outcomes: a systematic review and meta-analysis. Eur J Clin Nutr. 66(7):780–8. http://dx.doi.org/10.1038/ejcn.2012.37 PMID:22510792

94. Wycherley TP, Moran LJ, Clifton PM, Noakes M, Brinkworth GD (2012). Effects of energy-restricted high-protein, low-fat compared with standard-protein, low-fat diets: a meta-analysis of randomized controlled trials. Am J Clin Nutr. 96(6):1281–98. http://dx.doi.org/10.3945/ajcn.112.044321 PMID:23097268

95. Pesta DH, Samuel VT (2014). A high-protein diet for reducing body fat: mechanisms and possible caveats. Nutr Metab (Lond). 11(1):53. http://dx.doi.org/10.1186/1743-7075-11-53 PMID:25489333

96. Jenab M, Slimani N, Bictash M, Ferrari P, Bingham SA (2009). Biomarkers in nutritional epidemiology: applications, needs and new horizons. Hum Genet. 125(5–6):507–25. http://dx.doi.org/10.1007/s00439-009-0662-5 PMID:19357868

97. Pérez-Jiménez J, Hubert J, Hooper L, Cassidy A, Manach C, Williamson G, et al. (2010). Urinary metabolites as biomarkers of polyphenol intake in humans: a systematic review. Am J Clin Nutr. 92(4):801–9. http://dx.doi.org/10.3945/ajcn.2010.29924 PMID:20810980

98. Hedrick VE, Dietrich AM, Estabrooks PA, Savla J, Serrano E, Davy BM (2012). Dietary biomarkers: advances, limitations and future directions. Nutr J. 11(1):109. http://dx.doi.org/10.1186/1475-2891-11-109 PMID:23237668

99. Scalbert A, Brennan L, Manach C, Andres-Lacueva C, Dragsted LO, Draper J, et al. (2014). The food metabolome: a window over dietary exposure. Am J Clin Nutr. 99(6):1286–308. http://dx.doi.org/10.3945/ajcn.113.076133 PMID:24760973

100. Nash SH, Kristal AR, Bersamin A, Choy K, Hopkins SE, Stanhope KL, et al. (2014). Isotopic estimates of sugar intake are related to chronic disease risk factors but not obesity in an Alaska native (Yup'ik) study population. Eur J Clin Nutr. 68(1):91–6. http://dx.doi.org/10.1038/ejcn.2013.230 PMID:24219893

101. Chajès V, Biessy C, Byrnes G, Deharveng G, Saadatian-Elahi M, Jenab M, et al. (2011). Ecological-level associations between highly processed food intakes and plasma phospholipid elaidic acid concentrations: results from a cross-sectional study within the European Prospective Investigation into Cancer and Nutrition (EPIC). Nutr Cancer. 63(8):1235–50. http://dx.doi.org/10.1080/01635581.2011.617530 PMID:22043987

CHAPTER 5.

How are overall energy intake and expenditure related to obesity?

Klaas R. Westerterp

Food intake is a function of energy requirements as determined by body size and physical activity. Adult humans maintain a balance between their energy intake and energy expenditure, as shown by the constancy of body weight and body composition [1]. Energy balance is achieved by control of energy intake, energy expenditure, or both. Humans, however, do not balance energy intake and energy expenditure on a daily basis, as smaller animals do. They can afford to rely on their body reserves, whereas smaller species show signs of energy shortage sooner, as expressed in a lowered body temperature and reduced physical activity. Smaller species have a higher energy expenditure per kilogram of body mass as well as a relatively smaller body energy reserve [2]. Thus, a mouse cannot survive 3 days without food, whereas a normal adult human can survive more than 30 days without food.

Of course, humans can maintain a perfect energy balance in the long term, as shown by a constant body weight in adult life [1]. An average person has an energy expenditure of 10–15 MJ/day, or 3650–5475 MJ/year. Even a weight change of 1 kg, equivalent to 30 MJ, denotes a discrepancy between intake and expenditure of only 0.6–0.8% on an annual basis. Energy intake strongly correlates with energy expenditure on a weekly basis. Discrepancies on a daily basis between intake and expenditure are especially large when days with high energy expenditure are alternated with quieter intervals. For example, military cadets did not show an increase in energy intake on days with a higher energy expenditure when they joined a drill competition. The corresponding increase in energy intake occurred about 2 days later [3].

Despite the capacity to maintain energy balance [1], there is currently a worldwide increase in the prevalence of obesity. It has been suggested that modern inactive lifestyles are the predominant factor in the increasing prevalence of overweight and obesity [4]. An analysis of measurements of daily energy expenditure by the doubly labelled water (DLW) method, as available over the past decades, suggests that physical activity levels have not declined over the period during which obesity rates have increased [5]. The data analysis included hundreds of subjects in Europe, North America, and developing countries, extending back to the 1980s. The relationship between daily energy expenditure and body mass suggests that increases in body mass are driven by increased energy intake [6].

This chapter reviews the available evidence on overall energy intake and expenditure in relation to obesity. The following questions are addressed: how to assess whether

energy and macronutrient intake are different between subjects, and how overweight and obesity affect energy expenditure. Subsequently, interventions to control the obesity epidemic are reviewed, with a focus on dietary and exercise interventions.

Dietary intake and obesity

Since the application of the DLW technique for measuring energy requirements in free-living humans, it is known that reported dietary intake is generally lower than habitual dietary intake. Previously, overweight and obesity as derived from reported dietary intake were associated with a reduced energy requirement. A typical example is shown in Fig. 5.1. In women, reported energy intake is independent of body weight, whereas in men, reported intake is significantly lower in heavier subjects. For the same subjects and in both sexes, the difference between measured expenditure and reported intake is significantly higher in heavier subjects than in leaner ones. Heavier subjects tend to show more underreporting of dietary intake compared with leaner ones [10], leading to erroneous conclusions from intake as reported.

Underreporting of food intake seems to be more of a concern for specific food items, which are generally considered to be “bad for health”. An example is the inverse relationship between fat intake and obesity, called the American paradox [11]. In the adult population, the prevalence of overweight has increased while at the same time reported energy intake and percentage of energy derived from fat appear to have decreased. This is very likely to be due to selective underreporting. For example, a DLW study in obese subjects showed a negative correlation between the reported percentage of energy from fat in the diet and the amount of underreporting [9]. In the case of no underreporting, the percentage of energy from fat would be 46% ± 5%. Food supply data showed an increase in fat availability over the past 40 years [12]. Therefore, the observed decrease in reported fat intake seems to be doubtful.

Recognition of underreporting is ideally based on simultaneous DLW assessment of energy requirements. However, the cost of the DLW method limits its application in large-scale studies. A more practical alternative, which is often used to recognize underreporting, is the application of the ratio of reported energy intake to basal metabolic rate (BMR), by analogy with the ratio of daily energy expenditure to BMR known as the physical activity level (PAL). A cut-off limit for the ratio of reported energy intake to BMR is set at a minimum value, often 1.3 [13]. However, cut-off limits do not take variation in individual PAL values into account, although more recently this has become the practice in the analysis of epidemiological studies [14]. A subject with a reported intake of 10 MJ/day and a PAL value of 1.4 could be a correct reporter, whereas the energy expenditure, and thus the intake, of the same subject should be more than 14 MJ/day when the PAL value is 2.0. Therefore, to validate reported energy intake, one should use a combination of BMR and physical activity. BMR can be measured or estimated with an equation from the literature, based on the height, weight, age, and sex of the subject [15]. Physical activity can be estimated with a DLW-validated accelerometer to record body movement [16].

In conclusion, before data on reported intake are interpreted, misreporters should be identified. This will result in the exclusion of much, if not most, of the data, especially for studies in overweight and obese subjects. Therefore, it was recently advised that the scientific and medical communities should discontinue reliance on self-reported energy intake as a measure of energy intake [17].

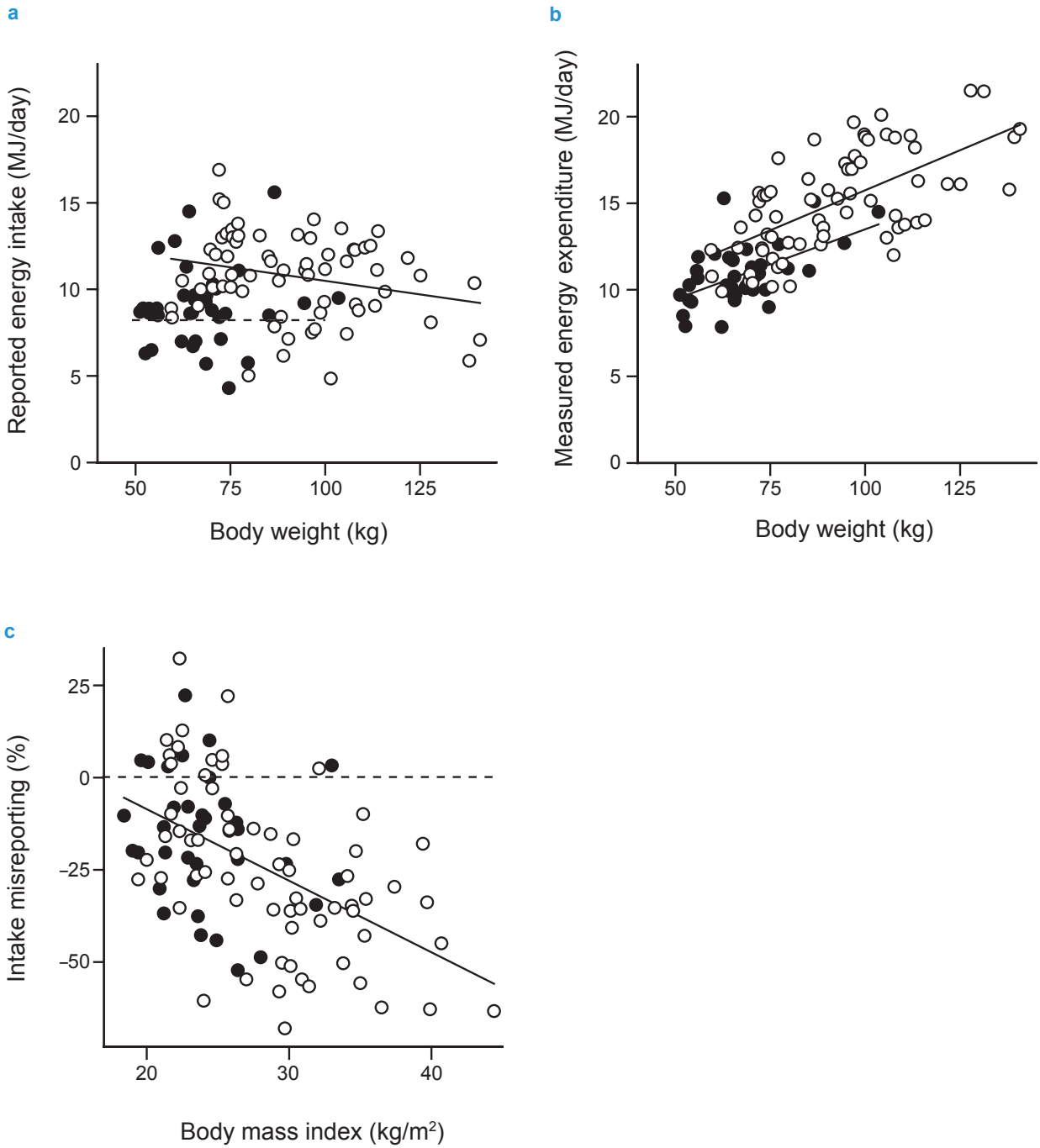
Energy expenditure and obesity

The main determinants of total energy expenditure, and thus of energy requirement, are body size and physical activity. Body size and body composition determine maintenance metabolism (BMR), which is the largest of the three components, making up 50–70% of total energy expenditure. Body movement or physical activity determines activity-induced energy expenditure, the most variable component of total daily energy expenditure. The third component, diet-induced energy expenditure, is generally assumed to be 10% of total daily energy expenditure in subjects who consume the average mixed diet and are in energy balance [18].

Maintenance metabolism is determined mainly by fat-free body mass. Overweight and obese subjects typically have a larger fat mass but also a larger fat-free mass compared with lean subjects [19]. Excess energy during weight gain in adult subjects is stored as fat mass and fat-free mass in an energy ratio of 95:5 or in a mass ratio of 75:25 [20]. The larger fat-free body mass in overweight and obese subjects implies a higher maintenance metabolism. Maintenance metabolism in morbidly obese subjects is generally higher than total daily energy expenditure in lean subjects, possibly limiting activity-induced energy expenditure and resulting in a lower PAL [21].

Activity-induced energy expenditure is determined by body movement and body mass. In the same environment, body movement as measured with an accelerometer is higher in lean subjects than in overweight subjects. A study of adolescents attending the same school showed similar activity-induced energy expenditure for lean subjects and obese subjects, whereas body movement was lower in obese subjects than in lean subjects (Fig. 5.2). Overweight

Fig. 5.1. Reported energy intake as measured with a 7-day food record (a) and measured energy expenditure as measured simultaneously with the doubly labelled water method (b) in the same subjects, plotted as a function of body weight for women (filled dots) and men (open dots), with the linear regression lines shown when there was a significant relationship. (c) Intake misreporting, calculated as (reported energy intake – measured energy expenditure)/measured energy expenditure, is plotted as a function of body mass index. Data from Meijer et al. (1992) [7], Westerterp et al. (1996) [8], and Goris et al. (2000) [9]. Republished with permission of John Wiley & Sons, Inc., from Lovegrove JA, Hodson L, Sharma S, Lanham-New SA, editors (2015). Nutrition research methodologies. Permission conveyed through Copyright Clearance Center, Inc.



implies less physical activity, i.e. less body movement, but because of the larger body weight, the decreased body movement still results in similar or even higher activity-induced energy expenditure.

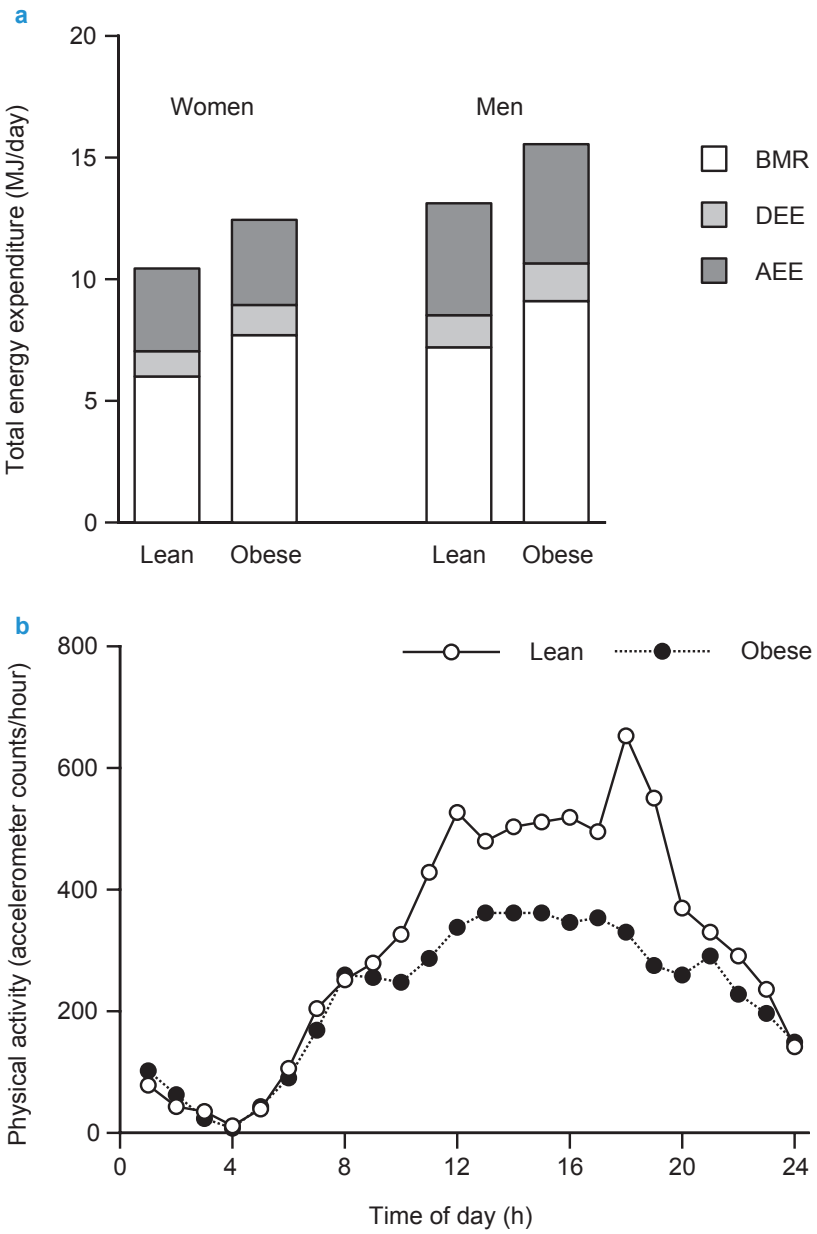
In conclusion, due to a larger body size, overweight induces a higher maintenance requirement, and obese subjects are less physically active than normal-weight subjects, although activity-induced energy expenditure is not necessarily lower.

Dietary and exercise interventions to control the obesity epidemic

Interventions to induce weight loss in overweight and obese subjects include a reduction of energy intake, an increase in energy expenditure through exercise, or both, aiming for a negative energy balance. Whatever the intervention, the success rate for long-term weight loss is low [23, 24]. First, compliance with an energy-restricted diet is low, resulting in less weight loss than expected. Second, compensatory mechanisms reduce the discrepancy between energy intake and energy expenditure required to induce weight loss [25].

Energy restriction induces a reduction in all three components of daily energy expenditure: maintenance metabolism, diet-induced energy expenditure, and activity-induced energy expenditure. The reduction in maintenance metabolism is larger than that expected from the loss of fat-free mass and fat mass and is positively related to the amount of weight lost [26]. The reduction in diet-induced energy expenditure is a direct consequence of the reduction in the amount of food consumed. The reduction in activity-induced energy expenditure is not only through a reduction of body weight but also through an energy restriction-induced reduction of body movement as measured with an accelerometer [27].

Fig. 5.2. (a) The three components of total energy expenditure – basal metabolic rate (BMR), diet-induced energy expenditure (DEE), and activity-induced energy expenditure (AEE) – and (b) physical activity, measured with an accelerometer and averaged hourly, as observed in lean and obese adolescents from the same school. BMR and DEE are higher in obese subjects than in sex-matched lean subjects ($P < 0.001$), whereas AEE is similar in lean and obese subjects, and physical activity is lower in obese subjects. Data from Ekelund et al. (2002) [22].



The potential of exercise programmes to induce weight loss is limited by several factors. Overweight and obesity reduce the exercise capacity of the body. In addition, it is difficult to comply with an exercise programme without compensating for an exercise-induced increase in energy expenditure by increasing energy intake [28]. Finally, exercise-induced

energy expenditure is compensated for by a reduction in non-exercise activity thermogenesis, especially when subjects are in a negative energy balance [29, 30].

In conclusion, adaptive responses limit the effect of energy restriction and exercise on energy balance in overweight and obese subjects. Therefore, weight loss is lower than expected, and very few people are successful in maintaining weight loss to achieve a healthier weight.

Key points

- Before data on reported intake are interpreted, misreporters should be identified.
- Overweight and obese subjects have a higher energy requirement than lean subjects, because of a higher maintenance requirement.
- Obese subjects move less than normal-weight subjects, although activity-induced energy expenditure is not necessarily lower.
- Adaptive responses limit the effect of energy restriction and exercise on energy balance in overweight and obese subjects.
- Eating less is the most effective method for preventing weight gain.

Research needs

- Studies are needed on determinants of energy intake, to develop strategies for successful long-term weight maintenance by limiting energy intake, in an environment where food availability stimulates the majority of the population to overeat.

References

1. James WPT (1985). Appetite control and other mechanisms of weight homeostasis. In: Blaxter K, Waterlow JC, editors. Nutritional adaptations. London, UK: John Libbey; pp. 141–154.

2. Schmidt-Nielsen K (1972). Animal physiology: adaptation and environment. London, UK: Cambridge University Press.

3. Edholm OG, Fletcher JG, Widdowson EM, McCance RA (1955). The energy expenditure and food intake of individual men. Br J Nutr. 9(3):286–300. http://dx.doi.org/10.1079/BJN19550040 PMID:13250128

4. Prentice AM, Jebb SA (1995). Obesity in Britain: gluttony or sloth? BMJ. 311(7002):437–9. http://dx.doi.org/10.1136/bmj.311.7002.437 PMID:7640595

5. Westerterp KR, Speakman JR (2008). Physical activity energy expenditure has not declined since the 1980s and matches energy expenditures of wild mammals. Int J Obes (Lond). 32(8): 1256–63. http://dx.doi.org/10.1038/ijo.2008.74 PMID:18504442

6. Swinburn BA, Sacks G, Lo SK, Westerterp KR, Rush EC, Rosenbaum M, et al. (2009). Estimating the changes in energy flux that characterize the rise in obesity prevalence. Am J Clin Nutr. 89(6):1723–8. http://dx.doi.org/10.3945/ajcn.2008.27061 PMID:19369382

7. Meijer GAL, Westerterp KR, van Hulsel AMP, ten Hoor F (1992). Physical activity and energy expenditure in lean and obese adult human subjects. Eur J Appl Physiol Occup Physiol. 65(6):525–8. http://dx.doi.org/10.1007/BF00602359 PMID:1483440

8. Westerterp KR, Verboeket-van de Venne WPHG, Bouten CVC, De Graaf C, Van het Hof KH, Weststrate JA (1996). Energy expenditure and physical activity in subjects consuming full- or reduced-fat products as part of their normal diet. Br J Nutr. 76:785–95. http://dx.doi.org/10.1079/BJN19960086 PMID:9014648

9. Goris AHC, Westerterp-Plantenga MS, Westerterp KR (2000). Undereating and underrecording of habitual food intake in obese men: selective underreporting of fat intake. Am J Clin Nutr. 71(1):130–4. PMID:10617957

10. Westerterp KR, Goris AHC (2002). Validity of the assessment of dietary intake: problems of misreporting. Curr Opin Clin Nutr Metab Care. 5(5):489–93. http://dx.doi.org/10.1097/00075197-200209000-00006 PMID:12172471

11. Heini AF, Weinsier RL (1997). Divergent trends in obesity and fat intake patterns: the American paradox. Am J Med. 102(3):259–64. http://dx.doi.org/10.1016/S0002-9343(96)00456-1 PMID:9217594

12. Balanza R, García-Lorda P, Pérez-Rodrigo C, Aranceta J, Bonet MB, Salas-Salvadó J (2007). Trends in food availability determined by the Food and Agriculture Organization's food balance sheets in Mediterranean Europe in comparison with other European areas. Public Health Nutr. 10(2):168–76. http://dx.doi.org/10.1017/S1368980007246592 PMID:17261226

13. Goldberg GR, Black AE, Jebb SA, Cole TJ, Murgatroyd PR, Coward WA, et al. (1991). Critical evaluation of energy intake data using fundamental principles of energy physiology: 1. Derivation of cut-off limits to identify under-recording. Eur J Clin Nutr. 45(12):569–81. PMID:1810719

14. Black AE (2000). Critical evaluation of energy intake using the Goldberg cut-off for energy intake:basal metabolic rate. A practical guide to its calculation, use and limitations. Int J Obes Relat Metab Disord. 24(9):1119–30. http://dx.doi.org/10.1038/sj.ijo.0801376 PMID:11033980

15. Sabounchi NS, Rahmandad H, Ammerman A (2013). Best-fitting prediction equations for basal metabolic rate: informing obesity interventions in diverse populations. Int J Obes (Lond). 37(10):1364–70. http://dx.doi.org/10.1038/ijo.2012.218 PMID:23318720

16. Goris AH, Meijer EP, Kester A, Westerterp KR (2001). Use of a triaxial accelerometer to validate reported food intakes. Am J Clin Nutr. 73(3):549–53. PMID:11237930

17. Dhurandhar NV, Schoeller D, Brown AW, Heymsfield SB, Thomas D, Sørensen TI, et al.; Energy Balance Measurement Working Group (2015). Energy balance measurement: when something is not better than nothing. Int J Obes (Lond). 39(7):1109–13. http://dx.doi.org/10.1038/ijo.2014.199 PMID:25394308

18. Westerterp KR (2004). Diet induced thermogenesis. Nutr Metab (Lond). 1(1):5. http://dx.doi.org/10.1186/1743-7075-1-5 PMID:15507147

19. Westerterp KR, Donkers JH, Fredrix EW, Boekhoudt P (1995). Energy intake, physical activity and body weight: a simulation model. Br J Nutr. 73(3):337–47. http://dx.doi.org/10.1079/BJN19950037 PMID:7766558

20. Schutz Y, Kyle UU, Pichard C (2002). Fat-free mass index and fat mass index percentiles in Caucasians aged 18–98 y. Int J Obes Relat Metab Disord. 26(7):953–60. PMID:12080449

21. Prentice AM, Black AE, Coward WA, Cole TJ (1996). Energy expenditure in overweight and obese adults in affluent societies: an analysis of 319 doubly-labelled water measurements. Eur J Clin Nutr. 50(2):93–7. PMID:8641251

22. Ekelund U, Aman J, Yngve A, Renman C, Westerterp K, Sjöström M (2002). Physical activity but not energy expenditure is reduced in obese adolescents: a case-control study. Am J Clin Nutr. 76(5):935–41. PMID:12399263

23. Franz MJ, VanWormer JJ, Crain AL, Boucher JL, Histon T, Caplan W, et al. (2007). Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. J Am Diet Assoc. 107(10):1755–67. http://dx.doi.org/10.1016/j.jada.2007.07.017 PMID:17904936

24. Anderson JW, Konz EC, Frederich RC, Wood CL (2001). Long-term weight-loss maintenance: a meta-analysis of US studies. Am J Clin Nutr. 74(5):579–84. PMID:11684524

25. Anastasiou CA, Karfopoulou E, Yannakoulia M (2015). Weight regaining: from statistics and behaviors to physiology and metabolism. Metabolism. 64(11):1395–407. http://dx.doi.org/10.1016/j.metabol.2015.08.006 PMID:26362728

26. Camps SG, Verhoef SP, Westerterp KR (2013). Weight loss, weight maintenance, and adaptive thermogenesis. Am J Clin Nutr. 97(5):990–4. http://dx.doi.org/10.3945/ajcn.112.050310 PMID:23535105

27. Camps SG, Verhoef SP, Westerterp KR (2013). Weight loss-induced reduction in physical activity recovers during weight maintenance. Am J Clin Nutr. 98(4):917–23. http://dx.doi.org/10.3945/ajcn.113.062935 PMID:23985804

28. Thomas DM, Bouchard C, Church T, Slentz C, Kraus WE, Redman LM, et al. (2012). Why do individuals not lose more weight from an exercise intervention at a defined dose? An energy balance analysis. Obes Rev. 13(10):835–47. http://dx.doi.org/10.1111/j.1467-789X.2012.01012.x PMID:22681398

29. Pontzer H (2015). Constrained total energy expenditure and the evolutionary biology of energy balance. Exerc Sport Sci Rev. 43(3):110–6. http://dx.doi.org/10.1249/JES.0000000000000048 PMID:25906426

30. Melanson EL, Keadle SK, Donnelly JE, Braun B, King NA (2013). Resistance to exercise-induced weight loss: compensatory behavioral adaptations. Med Sci Sports Exerc. 45(8):1600–9. http://dx.doi.org/10.1249/MSS.0b013e31828ba942 PMID:23470300

CHAPTER 6.

Physical activity, sedentary behaviour, and obesity

Michael Leitzmann

Insufficient levels of daily physical activity play a potentially major role in contributing to the obesity epidemic that currently affects both developed and developing countries. Therefore, physical activity has become a vital part of public health strategies for prevention of weight gain, for weight loss, and for prevention of weight regain after weight loss. In fact, virtually all public health agencies and scientific organizations recommend physical activity as part of weight management, including but not limited to the World Health Organization (WHO), the United States Centers for Disease Control and Prevention (CDC), the National Heart, Lung, and Blood Institute, the American Heart Association, the American College of Sports Medicine (ACSM), and the World Obesity Federation, as well as several national and regional guidelines.

In 2001, the ACSM issued guidelines recommending at least 150 minutes per week of moderate-intensity physical activity for overweight or obese adults to improve their health, and 200–300 minutes per week for long-term weight loss [1]. Moderate-intensity activities are those that require 3–6 times as much energy as sitting quietly. In 2002, the Institute of Medicine of the National Academies recommended 60 minutes per day of moderate-intensity physical activity for prevention of unhealthful weight gain [2]. In 2003, the International Association for the Study of Obesity advocated 40–50 minutes per day of moderate-intensity physical activity for prevention of obesity, and 60–90 minutes per day for prevention of weight regain in formerly obese individuals [3].

Setting definitions for clinically significant weight loss has been challenging, in part because health gains related to weight maintenance or weight loss probably operate under a continuum and are not based on a particular threshold. Despite this issue, some have operationalized the definition of weight maintenance as a change of ≤ 5 lb (≤ 2.3 kg) [4] or < 3% of body weight [5], with a weight change of > 5% considered to be clinically significant [5].

This chapter discusses whether physical activity is effective for prevention of weight gain, for weight loss, and for prevention of weight regain after weight loss. This chapter focuses primarily on adults.

Physical activity and prevention of weight gain

Primary prevention of obesity begins with weight maintenance, not weight reduction. Long-term observational studies of physical activity in relation to weight maintenance fairly consistently show a relationship between the two. For example, the prospective Harvard cohorts showed that women and men who reported

increasing their recreational activity levels by 23.2 metabolic equivalent (MET)-hours per week (top quintile) gained 1.76 lb less (0.8 kg less) within the next 4 years of follow-up than those who decreased their activity levels by 16.3 MET-hours per week (bottom quintile) [6]. One MET is defined as the ratio of the energy consumed during a specific activity to the energy consumed while sitting quietly (3.5 mL O_2 kg^{-1} min^{-1}). Similarly, the 15-year Coronary Artery Risk Development in Young Adults (CARDIA) Study reported that each 0.5 hour per day of walking, the most popular type of recreational activity among adults, was associated with 0.15 kg/year less weight gain in men and 0.29 kg/year less weight gain in women, with stronger associations noted among those with a larger baseline weight [7]. Taken together, these long-term epidemiological investigations indicate that moderate-intensity physical activity is associated with prevention of weight gain. A 2009 position paper from the ACSM stated that 150–250 minutes per week of moderate-intensity physical activity is effective to prevent weight gain [8].

Physical activity and weight loss

A negative energy balance brought about by physical activity will lead to weight loss, with a greater negative energy balance resulting in a more pronounced weight loss. Directed research on the long-term effect of physical activity on weight loss has been sparse. A 12-month randomized controlled trial found a cumulative weight loss of 1.8 kg in men and 1.4 kg in women for those engaging in moderate to vigorous activity for 60 minutes per day, 6 days per week [9]. By comparison, sedentary controls gained 0.1 kg (men) and 0.7 kg (women) during that period. A recent systematic review and meta-analysis examined the available evidence on the effect of isolated physical activity on weight loss among overweight and obese individuals from randomized clinical trials and reported that 120–240 minutes per week of aerobic exercise at intensities of 40–85% of maximum heart rate were related to weighted mean differences in weight of −1.6 kg (95% confidence interval [CI], −1.64 to −1.56 kg) for 6-month programmes and −1.7 kg (95% CI,−2.29 to −1.11 kg) for 12-month programmes. The authors concluded that isolated aerobic exercise is not an effective weight-loss therapy but may be effective in conjunction with diets [10].

Most recommendations from public health organizations and government agencies use both physical activity and dietary energy restriction for weight loss. Weight-loss programmes vary considerably with respect to the amount of physical activity used and the level of energy restriction imposed, with a greater energy deficit yielding a more pronounced weight loss. Evidence suggests that dietary energy restriction combined with physical activity results in greater weight loss than dietary energy restriction alone. For example, a Cochrane review involving 1049 subjects from 14 trials with follow-up of 3–12 months compared exercise plus diet versus diet alone and reported a weight loss of −1.1 kg (95% CI, −1.5 to −0.6 kg) in the exercise-plus-diet group versus the diet-only group [11]. Similarly, pooling the data from 452 subjects from five trials yielded a reduction in body mass index (BMI) of −0.4 kg/m^2 (95% CI, −0.7 to −0.1 kg/m^2) in the exercise-plus-diet group versus the diet-only group [11]. Physical activity and dietary energy restriction yield comparable weight loss if they offer similar amounts of negative energy balance. Importantly, energy restriction combined with exercise training is more effective than energy restriction alone for increasing loss of fat mass and preserving lean body mass, and therefore it leads to a more desirable effect on overall body composition [12].

Moreover, physical activity of high intensity leads to more pronounced weight loss than physical activity of lower intensity. This is indicated by pooled data on a comparison of high-intensity versus low-intensity exercise without changes in diet during 3.5–12-month periods in 317 subjects from four trials, in which the high-intensity-exercise group showed a reduction in weight of −1.5 kg (95% CI, −2.3 to −0.7 kg) compared with the low-intensity-exercise group [11].

According to the 2009 ACSM position paper, physical activity demonstrates a dose–response relationship with weight loss, such that < 150 minutes per week of moderate-intensity physical activity yields minimal weight loss, > 150 minutes per week of moderate-intensity physical activity results in weight loss of 2–3 kg, and 225–420 minutes per week of moderate-intensity physical activity leads to weight loss of 5–7.5 kg [8]. In addition to the effect of physical activity on weight loss, regular exercise yields numerous health benefits independent of weight loss, such as improvements in insulin action, blood lipids, endothelial function, haemostatic factors, and blood pressure [13].

Physical activity and prevention of weight regain after weight loss

Most people are able to lose weight but have considerable difficulty maintaining weight loss. Physical activity is widely endorsed as being indispensable for long-term weight maintenance [1] and is frequently referred to as a stable predictor of weight maintenance after weight loss [14]. The evidence for maintenance of weight loss is far less abundant than that for initiation of weight loss.

A recent systematic review and meta-analysis of randomized controlled trials on long-term maintenance of weight loss reported that the combination of physical activity and dietary energy restriction resulted in a difference of −1.56 kg (95% CI, −2.27 to −0.86 kg) in weight regain compared with controls at 12 months [15]. There was no evidence of effectiveness for interventions involving physical activity only. An earlier systematic review that also included observational studies reported that individuals who engaged in physical activity experienced less weight regain than their sedentary counterparts, but confounding by a healthy lifestyle or reverse causation by better exercise adherence among those with less weight regain could not be ruled out [16]. Taken together, findings from observational studies and controlled trials show inconsistent results, and the volume of physical activity needed to prevent weight regain after weight loss remains poorly defined. Despite these uncertainties, the 2009 ACSM position paper suggested that weight maintenance after weight loss is improved with > 250 minutes of physical activity per week [8].

Resistance training

Resistance training has not been considered a major contributor to weight loss, because the energy expenditure associated with weight training is generally less than that associated with a typical aerobic exercise session of the same duration. In addition, resistance exercise increases fat-free mass, potentially leading to a net gain in body weight. However, resistance exercise is associated with acute stimulation of metabolic rate and fat oxidation, and it enhances total energy expenditure because of increased muscle mass; this provides some rationale for examining its relationship to weight loss [17].

Intervention studies have consistently found no effect of resistance exercise on reducing body weight [8] or visceral adipose tissue [18]. The combination of resistance and aerobic exercise may enhance loss of fat mass compared with resistance exercise alone. A recent meta-analysis of 15 trials with 741 participants compared the effect of 2.5–6 months of aerobic training and resistance training on weight loss in overweight and obese subjects and reported that compared with resistance training, aerobic training produced greater decreases in body weight (mean difference [MD], −1.15 kg; 95% CI, −2.23 to −0.07 kg), waist circumference (MD, −1.10 cm; 95% CI, −1.85 to −0.36 cm), and fat mass (MD, −1.14 kg; 95% CI, −1.83 to −1.45 kg) [19]. However, resistance training was more effective than aerobic training in increasing lean body mass (MD, 1.26 kg; 95% CI, 0.71 to 1.81 kg). Moreover, compared with resistance training alone, the combination of aerobic and resistance training yielded more pronounced reductions in body weight (MD, −2.03 kg; 95% CI, −2.94 to −1.12 kg), waist circumference (MD, −1.57 cm; 95% CI, −2.38 to −0.75 cm), and fat mass (MD, −1.88 kg; 95% CI, −2.67 to −1.08 kg), whereas the combination of aerobic and resistance training generated a greater increase in lean body mass (MD, 0.90 kg; 95% CI, 0.31 to 1.48 kg) than aerobic training alone [19]. These pooled findings on the combination of aerobic and resistance training need to be interpreted with caution, because the total volume of exercise prescribed in some of the combination training groups was greater than the respective volumes in the aerobic training and resistance training groups. Notwithstanding the potential confounding effects of training volume, these data suggest that the combination of aerobic and resistance training may be the most efficacious exercise training modality for weight loss.

Few studies have examined the effects of resistance exercise on prevention of weight gain. One randomized trial assessed the efficacy of a 2-year strength programme in 164 overweight and obese premenopausal women and reported decreased percentage of body fat (2-year change of −3.68% ± 0.99% vs −0.14% ± 1.04% in controls) and attenuated intra-abdominal fat (2-year change of 7.05% ± 5.07% vs 21.36% ± 5.34% in controls) [20]. These results are relevant to obesity prevention programmes because most weight gain in adults is assumed to be fat, including abdominal fat.

Data about the influence of resistance training on prevention of weight regain after weight loss are also sparse. One trial assigned 90 middle-aged, obese, physically inactive men to a 2-month very-low-energy diet followed by randomization into 6 months of resistance training, walking, or no exercise [21]. The results showed that resistance training initially attenuated the regain of fat mass during the exercise programme. However, there were no differences in weight regain between the groups after 23 months of follow-up, which was explained by poor long-term adherence to the prescribed exercise programme [21].

Sedentary behaviour

In recent years, physical activity research has expanded its focus to include the potentially detrimental effects of sedentary behaviour on energy balance. The prevalence of sedentary behaviour has increased markedly in recent years, with objectively assessed measures showing that adults spend 50–60% of their day sedentary [22]. Sedentary behaviour occurs in various domains of life, including television or video viewing, computer use, reading, or sitting at a desk, at a counter, or in

a bus, car, or train. Prolonged time spent sedentary decreases energy expenditure and displaces light-intensity physical activities, potentially leading to weight gain over time. Although sedentary behaviour shows an inverse relationship with light-intensity physical activity, it can be conceptualized as a lifestyle factor that can coexist with moderate to vigorous physical activity [23]. Current public health programmes to reduce obesity have focused largely on decreasing dietary energy intake and increasing physical activity but have paid little attention to decreasing time spent sedentary.

The Nurses' Health Study examined the association between sedentary behaviours, in particular television viewing, and risk of obesity [24]. The findings showed that time spent watching television was positively related to risk of obesity. Specifically, each increment of 2 hours per day in television watching was associated with a 23% (95% CI, 17–30%) increase in obesity after adjusting for age, smoking, diet, and physical activity. Also, each increment of 2 hours per day in sitting at work was associated with a statistically non-significant 5% (95% CI, 0–10%) increase in obesity. These results highlight the potential value of decreasing prolonged television watching and other sedentary behaviours for preventing obesity in adults.

Computer gaming and use of social media are additional important sources of time spent sedentary, particularly among young adults. A prospective cohort study of 2593 young adults aged 20–24 years in Sweden examined the association between leisure-time computer use for gaming/emailing/chatting and overweight development during 5 years of follow-up [25]. Compared with those who reported no computer gaming, women with a high volume of computer gaming (> 2 hours per day) had an odds ratio of developing overweight of 3.0 (95% CI, 1.29–6.83) after adjustment for age, occupation, social support, physical activity, sleep, and total computer use. No statistically significant association was noted among men (odds ratio, 1.4; 95% CI, 0.77–2.66). In addition, no statistically significant relationships emerged between leisure-time emailing/chatting and overweight in either women or men. The findings from this small cohort study suggest that sedentary behaviour that occurs during computer gaming is a potential risk factor for overweight, but further research is needed.

Sedentary behaviour is also an independent risk factor for obesity in children and adolescents. In fact, preventing childhood obesity has been described as the most favourable approach to reversing the global obesity epidemic. A recent meta-analysis of 25 studies compared three types of interventions with regard to their potential of reducing BMI in children: (i) interventions aimed at decreasing sedentary behaviours, (ii) interventions aimed at decreasing sedentary behaviours in combination with promoting physical activity, and (iii) interventions aimed at decreasing sedentary behaviours in combination with promoting physical activity and improving dietary habits [26]. The results indicated that interventions aimed at decreasing sedentary behaviours had a significant effect on reducing BMI, and that effect sizes of multicomponent interventions did not differ significantly from those of the single-component interventions.

Physical activity and appetite regulation

At habitually high levels of energy expenditure, energy intake appears to be matched to energy expenditure, resulting in maintenance of energy balance. However, at low levels of energy expenditure, homeostatic regulation of appetite control is lost and fails to restrain appetite to the low levels required to maintain energy balance. There is evidence that enhanced appetite control with high levels of energy expenditure operates through a mechanism involving augmented insulin and leptin sensitivity brought about by decreased fat mass [27].

Conclusions

Moderate-intensity physical activity performed for 150–250 minutes per week appears to prevent weight gain and may produce modest weight loss in adults. Greater amounts of moderate-intensity physical activity (> 250 minutes per week) are required for weight maintenance after weight loss. Resistance exercise does not appear to decrease body weight or body fat, but it promotes gain of lean body mass, and the combination of resistance exercise and aerobic exercise seems to be optimal for weight loss. Increased physical activity decreases levels of risk factors for chronic diseases, independent of its impact on regulating body weight. Moreover, sedentary behaviour is an independent risk factor for the development of overweight and obesity.

Key points

- Insufficient physical activity is a potentially relevant determinant of the global obesity epidemic.
- Moderate-intensity physical activity performed for 150–250 minutes per week appears to prevent weight gain and may produce modest weight loss in adults.
- Greater volumes of moderate-intensity physical activity (> 250 minutes per week) are required for weight maintenance after weight loss.
- Resistance exercise alone has little effect on reducing body weight or adipose tissue.
- The combination of resistance exercise and aerobic exercise appears to be optimal for weight loss.
- Physical activity has important health benefits independent of its effects on regulating body weight.
- Time spent sedentary is a potentially significant risk factor for obesity.

Research needs

- There is a need for observational research using objectively assessed energy intake and energy expenditure in relation to long-term prevention of weight gain in free-living populations.
- Intervention studies on the long-term effect of physical activity on weight loss are needed.
- Research is needed on the amounts and intensities of physical activity required for prevention of weight regain after weight loss.
- The efficacy of combined aerobic and resistance physical activity modalities for weight control should be examined.
- The potential of decreased time spent sedentary for preventing obesity should be evaluated.
- The combined effects of physical activity and body composition on appetite regulation should be investigated.

References

1. Jakicic JM, Clark K, Coleman E, Donnelly JE, Foreyt J, Melanson E, et al.; American College of Sports Medicine (2001). American College of Sports Medicine position stand. Appropriate intervention strategies for weight loss and prevention of weight regain for adults. Med Sci Sports Exerc. 33(12):2145–56. http://dx.doi.org/10.1097/00005768-200112000-00026 PMID:11740312

2. Panel on Macronutrients, Panel on the Definition of Dietary Fiber, Subcommittee on Upper Reference Levels of Nutrients, Subcommittee on Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board (2002). Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. Washington (DC), USA: National Academies Press. Available from: https://www.nap.edu/catalog/10490/dietary-reference-intakes-for-energy-carbohydrate-fiber-fat-fatty-acids-cholesterol-protein-and-amino-acids-macronutrients.

3. Saris WH, Blair SN, van Baak MA, Eaton SB, Davies PS, Di Pietro L, et al. (2003). How much physical activity is enough to prevent unhealthy weight gain? Outcome of the IASO 1st Stock Conference and consensus statement. Obes Rev. 4(2):101–14. http://dx.doi.org/10.1046/j.1467-789X.2003.00101.x PMID:12760445

4. St Jeor ST, Brunner RL, Harrington ME, Scott BJ, Daugherty SA, Cutter GR, et al. (1997). A classification system to evaluate weight maintainers, gainers, and losers. J Am Diet Assoc. 97(5):481–8. http://dx.doi.org/10.1016/S0002-8223(97)00126-0 PMID:9145085

5. Stevens J, Truesdale KP, McClain JE, Cai J (2006). The definition of weight maintenance. Int J Obes (Lond). 30(3):391–9. http://dx.doi.org/10.1038/sj.ijo.0803175 PMID:16302013

6. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB (2011). Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med. 364(25):2392–404. http://dx.doi.org/10.1056/NEJMoa1014296 PMID:21696306

7. Gordon-Larsen P, Hou N, Sidney S, Sternfeld B, Lewis CE, Jacobs DR Jr, et al. (2009). Fifteen-year longitudinal trends in walking patterns and their impact on weight change. Am J Clin Nutr. 89(1):19–26. http://dx.doi.org/10.3945/ajcn.2008.26147 PMID:19056560

8. Donnelly JE, Blair SN, Jakicic JM, Manore MM, Rankin JW, Smith BK; American College of Sports Medicine (2009). American College of Sports Medicine Position Stand. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. Med Sci Sports Exerc. 41(2):459–71. http://dx.doi.org/10.1249/MSS.0b013e3181949333 PMID:19127177

9. McTiernan A, Sorensen B, Irwin ML, Morgan A, Yasui Y, Rudolph RE, et al. (2007). Exercise effect on weight and body fat in men and women. Obesity (Silver Spring). 15(6):1496–512. http://dx.doi.org/10.1038/oby.2007.178 PMID:17557987

10. Thorogood A, Mottillo S, Shimony A, Filion KB, Joseph L, Genest J, et al. (2011). Isolated aerobic exercise and weight loss: a systematic review and meta-analysis of randomized controlled trials. Am J Med. 124(8):747–55. http://dx.doi.org/10.1016/j.amjmed.2011.02.037 PMID:21787904

11. Shaw K, Gennat H, O'Rourke P, Del Mar C (2006). Exercise for overweight or obesity. Cochrane Database Syst Rev. (4):CD003817. PMID:17054187

12. Miller CT, Fraser SF, Levinger I, Straznicky NE, Dixon JB, Reynolds J, et al. (2013). The effects of exercise training in addition to energy restriction on functional capacities and body composition in obese adults during weight loss: a systematic review. PLoS One. 8(11):e81692. http://dx.doi.org/10.1371/journal.pone.0081692 PMID:24409219

13. Gaesser GA, Angadi SS, Sawyer BJ (2011). Exercise and diet, independent of weight loss, improve cardiometabolic risk profile in overweight and obese individuals. Phys Sportsmed. 39(2):87–97. http://dx.doi.org/10.3810/psm.2011.05.1898 PMID:21673488

14. Tate DF, Jeffery RW, Sherwood NE, Wing RR (2007). Long-term weight losses associated with prescription of higher physical activity goals. Are higher levels of physical activity protective against weight regain? Am J Clin Nutr. 85(4):954–9. PMID:17413092

15. Dombrowski SU, Knittle K, Avenell A, Araújo-Soares V, Sniehotta FF (2014). Long term maintenance of weight loss with non-surgical interventions in obese adults: systematic review and meta-analyses of randomised controlled trials. BMJ. 348:g2646. http://dx.doi.org/10.1136/bmj.g2646 PMID:25134100

16. Fogelholm M, Kukkonen-Harjula K (2000). Does physical activity prevent weight gain–a systematic review. Obes Rev. 1(2):95–111. http://dx.doi.org/10.1046/j.1467-789x.2000.00016.x PMID:12119991

17. Strasser B, Arvandi M, Siebert U (2012). Resistance training, visceral obesity and inflammatory response: a review of the evidence. Obes Rev. 13(7):578–91. http://dx.doi.org/10.1111/j.1467-789X.2012.00988.x PMID:22385646

18. Ismail I, Keating SE, Baker MK, Johnson NA (2012). A systematic review and meta-analysis of the effect of aerobic vs. resistance exercise training on visceral fat. Obes Rev. 13(1):68–91. http://dx.doi.org/10.1111/j.1467-789X.2011.00931.x PMID:21951360

19. Schwingshackl L, Dias S, Strasser B, Hoffmann G (2013). Impact of different training modalities on anthropometric and metabolic characteristics in overweight/obese subjects: a systematic review and network meta-analysis. PLoS One. 8(12):e82853. http://dx.doi.org/10.1371/journal.pone.0082853 PMID:24358230

20. Schmitz KH, Hannan PJ, Stovitz SD, Bryan CJ, Warren M, Jensen MD (2007). Strength training and adiposity in premenopausal women: strong, healthy, and empowered study. Am J Clin Nutr. 86(3):566–72. PMID:17823418

21. Borg P, Kukkonen-Harjula K, Fogelholm M, Pasanen M (2002). Effects of walking or resistance training on weight loss maintenance in obese, middle-aged men: a randomized trial. Int J Obes Relat Metab Disord. 26(5):676–83. http://dx.doi.org/10.1038/sj.ijo.0801962 PMID:12032753

22. Matthews CE, Chen KY, Freedson PS, Buchowski MS, Beech BM, Pate RR, et al. (2008). Amount of time spent in sedentary behaviors in the United States, 2003–2004. Am J Epidemiol. 167(7):875–81. http://dx.doi.org/10.1093/aje/kwm390 PMID:18303006

23. Healy GN, Wijndaele K, Dunstan DW, Shaw JE, Salmon J, Zimmet PZ, et al. (2008). Objectively measured sedentary time, physical activity, and metabolic risk: the Australian Diabetes, Obesity and Lifestyle Study (AusDiab). Diabetes Care. 31(2):369–71. http://dx.doi.org/10.2337/dc07-1795 PMID:18000181

24. Hu FB, Li TY, Colditz GA, Willett WC, Manson JE (2003). Television watching and other sedentary behaviors in relation to risk of obesity and type 2 diabetes mellitus in women. JAMA. 289(14):1785–91. http://dx.doi.org/10.1001/jama.289.14.1785 PMID:12684356

25. Thomée S, Lissner L, Hagberg M, Grimby-Ekman A (2015). Leisure time computer use and overweight development in young adults – a prospective study. BMC Public Health. 15(1):839. http://dx.doi.org/10.1186/s12889-015-2131-5 PMID:26329006

26. Liao Y, Liao J, Durand CP, Dunton GF (2014). Which type of sedentary behaviour intervention is more effective at reducing body mass index in children? A meta-analytic review. Obes Rev. 15(3):159–68. http://dx.doi.org/10.1111/obr.12112 PMID:24588966

27. Blundell JE, Gibbons C, Caudwell P, Finlayson G, Hopkins M (2015). Appetite control and energy balance: impact of exercise. Obes Rev. 16(Suppl 1):67–76. http://dx.doi.org/10.1111/obr.12257 PMID:25614205

CHAPTER 7.

What existing epidemiological data could serve to better understand the relationship of energy intake and expenditure to obesity and the obesity epidemic?

Martin Wiseman and Isabelle Romieu

Understanding the relationship between energy balance and obesity is a challenge, particularly in low- and middle-income countries (LMICs), where data are limited. Most of the studies have been conducted in high-income countries, and the results may not be generalizable to other settings because of differences in population characteristics.

This chapter provides an overview of studies focusing on determinants of obesity (adiposity) relating to dietary intake (energy intake) and physical activity (energy expenditure) and proposes study designs that could be implemented in LMICs to improve the understanding of the main drivers of obesity in these countries.

Determinants of obesity

Obesity is defined as a state of excess adiposity that presents a risk to health, for example increased risk of chronic diseases [1], and is the consequence of sustained positive energy balance over time.

Factors that influence energy balance can be considered as relating to the host (i.e. people), the environment (i.e. the set of external factors to which people are exposed), and the vector (i.e. foods and drinks). These factors interact in a complex way to influence eating and drinking patterns as well as activity behaviours. Although these factors are experienced at the individual level as the acceptability, availability, and affordability of foods, drinks, and activity behaviours, their roots lie in policies and actions that determine the environment, which may be local, national, or international [2].

Apart from non-modifiable factors, other characteristics may influence energy balance – in particular, the amount of energy expended in physical activity. Increasing energy expenditure might be expected not to influence energy balance, because of appetite control mechanisms that feed back and tend to maintain balance. However, there is evidence that at the low levels of activity characteristic of many high-income countries and increasingly of LMICs, this feedback operates imperfectly and does not suppress appetite to the low levels necessary to maintain energy balance [3]. Many factors relating to the foods and drinks consumed have been shown to influence the amount consumed or energy balance over the short to medium term, such as energy density and portion size [4, 5].

Measurement of adiposity

Several measures for overweight and obesity have been used in epidemiological studies. However, it is important to be aware that such measures are imperfect markers of the internal physiological processes

that are the actual drivers of cancer development.

Body mass index (BMI) is defined as the quotient between weight in kilograms and height in metres squared (kg/m^2); overweight and obesity are conventionally defined in relation to cut-offs of 25 kg/m^2 and 30 kg/m^2, respectively [6]. BMI is the most commonly used marker of body composition in epidemiological studies, because of the simplicity of assessment and the high precision and accuracy. However, it does not differentiate between lean and adipose tissue or take into account fat distribution, which varies across individuals, among ethnicities, and throughout the lifespan. Nevertheless, BMI at a population level is a useful marker of or proxy for adiposity.

Waist circumference (WC) and waist–hip ratio (WHR) are useful tools to identify abdominal obesity, commonly defined as WHR ≥ 0.90 for men and ≥ 0.85 for women, with WC cut-offs varying according to sex and ethnicity [7]. However, these measures cannot clearly differentiate between visceral and subcutaneous fat compartments [8]. Skinfold thickness can be used to predict body fat and its distribution, but it is particularly prone to measurement error and is generally unfeasible for use in large studies. Bioelectrical impedance analysis estimates lean and fat mass based on the principle that resistance to an electrical current is greater in adipose tissue than in lean tissue. Bioelectrical impedance analysis is an accurate and reproducible measure of body composition [9], but the body composition estimates from this method do not appear to yield stronger correlations with biomarkers of chronic disease risk than BMI does [10].

More direct measures of body composition are available, such as air displacement plethysmography, underwater weighing (hydrodensitometry), dual-energy X-ray absorptiometry (DEXA), ultrasonography, computed tomography, and magnetic resonance imaging [11, 12]. These methods show excellent reproducibility and validity [13] and are increasingly being used to measure body composition at the tissue or organ level, particularly in small-scale studies that require a high level of accuracy. However, because of high costs and lack of portability, their use in large-scale epidemiological studies tends to be as reference methods [14].

Understanding nutritional determinants of obesity

Experimental data

Prevention of weight gain and/or maintenance of weight loss

Short- to medium-term experimental data in humans can illuminate the possible physiological and other mechanisms underpinning how foods, drinks, and nutrients might promote energy overconsumption and positive energy balance.

In such studies, factors relating to the host include genetic variants that are associated with higher risk of obesity; these variants tend to be related to appetite regulation rather than to energy metabolism at a whole-body or cellular level [15]. Such studies may also include the impact of early-life events, so that child growth trajectories can predict later risk of obesity. Thus, children tend to maintain their BMI ranking within their population throughout childhood, particularly after the age of 11 years [16]. Also, the timing of the rebound in BMI in childhood (the so-called adiposity rebound) predicts later obesity, with an earlier rebound indicating a higher risk of obesity [17]. However, such factors are not modifiable in later life, although the effects might be mitigated.

There is evidence that people who are more physically active, and those who spend less time sedentary, are less likely to gain excess weight in adulthood. Results from intervention trials have been inconsistent, but based on observational studies conducted among Caucasian adults, an increase in energy expenditure through physical activity of approximately 6300–8400 kJ/week (1500–2000 kcal/week) was associated with improved weight maintenance [18].

These host factors may also interact with other factors related to the vector (foods and drinks). For example, in studies of young men eating ad libitum diets of different energy density for up to 3 weeks, Stubbs et al. found that the higher the level of activity, the more likely people were to avoid positive energy balance [19]. At high levels of energy density (60% of energy as fat), only the most active people remained in energy balance, whereas the least active were able to maintain energy balance only at low levels of energy density (20% of energy as fat). However, this trial was conducted among a small number of participants and for a short duration (2 weeks).

Long-term (> 1 year) experimental data are also available. In the long-term Prevención con Dieta Mediterránea (PREDIMED) study, with a follow-up of 4 years, the impact of a non-calorie-restricted traditional Mediterranean diet enriched with nuts and olive oil (two high-energy foods) was compared with that of a control diet consisting of advice on a low-fat diet. No substantial weight gain was observed in the group eating the enriched Mediterranean diet [20]. In the European Prospective Investigation into Cancer and Nutrition (EPIC), among participants with baseline BMI < 25 kg/m^2, dietary energy density was weakly associated with weight change, whereas among participants with

BMI > 25 kg/m^2, greater energy density was inversely associated with weight change [21]. The long-term impact of different macronutrient proportions, of the food sources of those macronutrients, and of energy density on adiposity and the development of obesity remains to be more precisely clarified.

There is also evidence that specific foods, drinks, or food components can have an impact on energy homeostasis. A recent systematic review of randomized controlled trials (RCTs) and prospective cohort data on dietary sugar and body weight concluded that among free-living people eating ad libitum diets, intake of free sugars or sugar-sweetened beverages is a determinant of body weight. The change in body fatness that occurs when intake is modified appears to be mediated via changes in energy intakes, because isoenergetic exchange of sugars with other carbohydrates was not associated with weight change [22]. In addition, in a small experimental study that compared isoenergetic meals with low and high glycaemic index (GI), plasma glucose (2-hour area under the curve) after the high-GI meal was 2.4 times that after the low-GI meal. Thereafter, compared with the low-GI meal, the high-GI meal decreased plasma glucose, increased hunger, and selectively stimulated brain regions associated with reward and craving in the late postprandial period. This suggests that reduced consumption of high-GI carbohydrates (specifically, highly processed grain products, potatoes, and concentrated sugar) may ameliorate overeating and facilitate maintenance of a healthy weight in overweight and obese individuals [23].

Evidence from RCTs conducted in *children and adolescents* indicates that consumption of sugar-sweetened beverages, compared with non-calorically sweetened beverages, results in greater weight gain and larger increases in BMI; however, the evidence is limited to a small number of studies. The findings of these trials suggest that there is inadequate energy compensation (degree of reduction in intake of other foods and drinks) for energy delivered as sugar [24]. However, a recent RCT showed a similar effect of a low-fat diet and a low-glycaemic-load diet on BMI over 24 months among Hispanic children [25]. There is inconsistent evidence that dietary fibre has an impact on energy balance but some evidence that wholegrain foods may help maintain energy balance [24].

For prevention of weight gain, few reported interventions have continued for more than 12 months; therefore, extrapolation to lifelong effectiveness should be done with caution. A review of diet and nutrition factors in relation to prevention of weight gain found evidence that protective factors against obesity were regular physical activity (convincing), a high intake of dietary non-starch polysaccharides/fibre (convincing), home and school environments that support healthy food choices for children (probable), and breastfeeding (probable). Risk factors for obesity were sedentary lifestyles (convincing), a high intake of energy-dense, micronutrient-poor foods (convincing), heavy marketing of energy-dense foods and fast-food outlets (probable), sugar-sweetened soft drinks and fruit juices (probable), and adverse social and economic conditions (in developed countries, especially for women) (probable) [26].

Understanding weight loss

There is copious evidence relating to various strategies for promoting weight loss through negative energy balance among overweight and obese people, although there is less evidence relating specifically to maintaining energy balance (or preventing weight gain and obesity). In addition, long-term data from RCTs for obesity prevention are more difficult to obtain than those from trials for weight loss.

For weight loss, there is widespread but not universal agreement that limiting the proportion of dietary energy from fat (or energy density) helps to reduce ad libitum energy intake [27]. More recently, evidence has accrued for the effects of intermittent partial fasting for 2 days per week [28]. Avoiding calorific beverages, especially sugar-sweetened beverages, aids weight control [29], because consumption of these beverages is not followed by adequate compensation in subsequent intake. Simple calorie counting appears to be relatively ineffective. A recent meta-analysis of RCTs comparing the long-term effect (≥ 1 year) of dietary interventions on weight loss showed that low-carbohydrate interventions led to significantly greater weight loss than did low-fat interventions (18 studies), and that low-fat interventions did not lead to differences in weight change compared with other, higher-fat interventions (19 studies) [30]. In a 2-year trial, obese subjects were randomly assigned to one of three diets: low-fat, restricted-calorie; Mediterranean, restricted-calorie; or low-carbohydrate, restricted-calorie. For the Mediterranean-diet group and the low-carbohydrate group, weight loss was similar and significantly higher than that for the low-fat group. Among the subjects with diabetes, the Mediterranean diet led to larger changes in plasma glucose and insulin levels compared with the low-fat diet [31].

The addition of a physical activity component improves the efficacy of a dietary intervention, but physical activity alone has not been shown to lead to weight loss (possibly because in obese people it is difficult to achieve a sufficient volume of activity). Physical activity is helpful

in weight maintenance after weight loss [18].

A review of workplace and community interventions found some evidence for the effectiveness of these interventions in changing diet and physical activity behaviours but limited evidence for their effectiveness in changing BMI [32]. However, many interventions are of relatively short duration, whereas changes in BMI are more distal outcomes.

Most of these studies were conducted in high-income countries. This emphasizes the importance of conducting studies in LMICs, in particular long-term dietary intervention trials focusing on alternative dietary patterns with foods readily available in these countries to propose viable changes in nutritional behaviours.

Epidemiological data

Population surveys, etiological and population intervention studies, and implementation research are all important to develop the evidence base to tackle the rise in the prevalence of obesity associated with changing dietary and physical activity patterns.

Population surveys in representative samples combining the evaluation of diet, physical activity, and anthropometry and chronic outcomes enable the capture of baseline information and provide an indicator of the health status of the population [33]. Repeated surveys would enable the evaluation of trends and changes over time at the population level. Although cross-sectional analysis of these data limits interpretations on causality, it can provide good indications of the major determinants of obesity in that population. For example, Aburto et al. compared overweight and obese children with non-overweight children and observed a strong association between dietary energy density and body mass status [34]. An analysis of data from the National Health and Nutrition Examination Survey (NHANES) showed that among children and adolescents, replacement of sugar-sweetened beverages with water was associated with reductions in total energy intake for all groups studied, a reduction not negated by compensatory increases in intake of other foods or beverages [35]. Other analyses using population surveys can also be implemented, for example to determine the adequacy of the diet with respect to national recommendations.

The scientific value of *prospective epidemiological cohorts* has been solidly established for evaluating exogenous and endogenous exposures in relation to change in weight and obesity. Their primary advantage is the ability to measure exposures before the onset of obesity. Cohorts are also instrumental in spurring mechanistic and translational research. One example is the investigation by Mozaffarian et al. of the relationship between changes in lifestyle factors and weight change at 4-year intervals over a 20-year period in a large cohort of men and women in the USA. The study identified food items and lifestyle factors that were highly associated with weight change within each 4-year period; 4-year weight gain was most strongly associated with the intake of potato chips, potatoes, sugar-sweetened beverages, unprocessed red meats, and processed meats, and was inversely associated with the intake of vegetables, whole grains, fruits, nuts, and yogurt. Physical activity was independently associated with weight loss, whereas alcohol consumption, sleep duration (> 8 hours), and television watching were associated with weight gain [36]. A further analysis of the relationship between change of diet quality indexes and concurrent weight change showed that improvement of diet quality was associated with less weight gain [37].

Several cohort studies in high-income countries have shown an impact of healthy dietary patterns on obesity [38] (see Chapter 14). In a 4-year follow-up to an RCT for weight loss, subjects assigned to the Mediterranean diet during the RCT were more likely to maintain weight loss (during the 2-year trial) compared with subjects assigned to the low-fat diet or the low-carbohydrate diet. This finding suggests that compliance with the Mediterranean diet may be easier in the long term [39]. A recent analysis of the EPIC study using biomarkers of highly processed foods, which are increasingly consumed worldwide, reported that increasing blood levels of industrial trans-fatty acids were associated with an increased risk of weight gain and a decreased likelihood of weight loss, particularly among women; this might be particularly relevant in the context of LMICs [40].

Cohort studies conducted in LMICs would be valuable resources for understanding the impact of the nutrition and lifestyle transition on obesity. Some longitudinal studies have already been initiated in LMICs, for instance those included in the Consortium of Health-Orientated Research in Transitioning Societies (COHORTS) [41] and the Mexican Teachers' Cohort (MTC) [42]. Building on these continuing initiatives may prove informative and cost-efficient. Data from the MTC showed that women with a dietary pattern characterized by high intakes of carbohydrates, sweet drinks, and refined foods had a higher risk of having a larger body shape silhouette and higher BMI, whereas women with a dietary pattern characterized by high intakes of fruits, vegetables, grains, and nuts had a lower risk [43]. This finding emphasizes the need for public health interventions that improve access to

healthy diets, healthy food choices in the workplace, and ways of limiting consumption of beverages with a high sugar content and of highly processed foods, particularly those rich in refined starches.

Research suggests that obesity and chronic diseases in adulthood may be traced back to exposures that occurred during fetal development, childhood, and adolescence. Therefore, cohort *studies covering the whole life-course*, focusing on critical windows of exposure and the time course of exposure to disease (birth cohorts, adolescent cohorts, and young adult cohorts), should be considered. Of particular interest are multicentre cohorts and intergenerational cohorts, which would create resources to enable research on the interplay between genetics, lifestyle, and the environment. For example, in the Avon Longitudinal Study of Parents and Children (ALSPAC), increased intake of energy-dense, nutrient-poor foods during childhood (mainly due to a rise in free [added] sugars) was associated with obesity development, and diets with higher energy density were associated with increased fat mass [44]. Most relevant to LMICs is the observation that children who were stunted in infancy are more likely to be relatively fat at puberty at the same BMI, compared with children who were not stunted in infancy [45]. Poor maternal prenatal dietary intakes of energy, protein, and micronutrients have been shown to be associated with an increased risk of adult obesity in the offspring, and a high-protein diet during the first 2 years of life was also associated with increased obesity later in life, whereas exclusive breastfeeding was associated with a lower risk of later obesity [46]. Results from a cohort study conducted in Mexico showed that children exclusively or predominantly breastfed for 3 months or longer had lower adiposity at age 4 years [47].

Conclusions

Obesity is a state of excess adiposity and is a consequence of sustained positive energy balance over time. Measurements of energy intake, expenditure, and balance are difficult. Measurements of anthropometric indices such as BMI or WC, although imperfect, are useful markers of or proxies for adiposity or visceral adiposity. Establishing repeated population-based measurements of such anthropometric measures, together with estimates of the macronutrient composition of diets, food consumption patterns, and estimates of physical activity and time spent sedentary (preferably with objective measures, such as accelerometers, used in subsamples) will help track changes in the population levels of overweight and obesity, and point to the key nutritional drivers.

Most research has tended to focus on Caucasians, but these findings may not be generalizable to other populations because of differences in age structure, genotype, body composition, lifestyle, culture, religion, and socioeconomic status. Detailed analyses that consider differences in genetic and environmental factors and gene–environment interactions between populations, and take account of the whole life-course, are required to elucidate these complex relationships. Importantly, measures of obesity prevention and control in LMICs will benefit if they are evaluated in the context within which they will be implemented.

Key points

- Obesity is a state of excess adiposity and is a consequence of sustained positive energy balance over time.
- Short-term experimental studies show that among men eating ad libitum diets of different energy density, the higher the level of activity, the less likely was positive energy balance, and at any level of activity, higher energy density led to more positive energy balance.
- In long-term experiments, intake of free sugars or sugar-sweetened beverages was a determinant of body weight. The change in body fatness when intake is modified appears to be mediated via changes in energy intakes.
- Studies in children and adolescents show that consumption of sugar-sweetened beverages results in increases in BMI, mainly by inadequate energy compensation (degree of reduction in intake of other foods and drinks).
- In weight-loss trials, low-carbohydrate interventions led to significantly greater weight loss than did low-fat interventions. Little attention has been paid to the effects of different types of carbohydrate.
- Cohort studies with repeated measurements have identified unhealthy dietary patterns and lifestyle factors associated with weight gain over time, and healthy dietary patterns have been shown to decrease the risk of obesity.
- Exposures during fetal life and early childhood may affect the risk of obesity.

Research needs

- Data from LMICs are limited, and further research is needed in these countries.
- Population surveys, etiological and population intervention studies, and implementation research are all important to develop the evidence base to tackle the rise in the prevalence of obesity associated with changing dietary and physical activity patterns.
- Research needs to take account of differences in age structure, genotype, body composition, lifestyle, culture, religion, and socioeconomic status. In this context, measurements of anthropometric indices such as BMI or WC are useful markers of or proxies for adiposity.
- Measures of obesity prevention and control in LMICs will benefit if they are evaluated in the context within which they will be implemented.

References

1. Anderson AS, Key TJ, Norat T, Scoccianti C, Cecchini M, Berrino F, et al. (2015). European Code against Cancer 4th Edition: obesity, body fatness and cancer. Cancer Epidemiol. 39(Suppl 1):S34–45. http://dx.doi.org/10.1016/j.canep.2015.01.017 PMID:26205840

2. World Cancer Research Fund/American Institute for Cancer Research (2009). Policy and action for cancer prevention: food, nutrition, physical activity: a global perspective. Washington (DC), USA: American Institute for Cancer Research. Available from: www.wcrf-hk.org/sites/default/files/Policy_Report.pdf.

3. Blundell JE, Gibbons C, Caudwell P, Finlayson G, Hopkins M (2015). Appetite control and energy balance: impact of exercise. Obes Rev. 16(Suppl 1):67–76. http://dx.doi.org/10.1111/obr.12257 PMID:25614205

4. Ello-Martin JA, Ledikwe JH, Rolls BJ (2005). The influence of food portion size and energy density on energy intake: implications for weight management. Am J Clin Nutr. 82(1 Suppl):236S–41S. PMID:16002828

5. Prentice AM (1998). Manipulation of dietary fat and energy density and subsequent effects on substrate flux and food intake. Am J Clin Nutr. 67(3 Suppl):535S–41S. PMID:9497166

6. WHO (2000). Obesity: preventing and managing the global epidemic: report of a WHO consultation. Geneva, Switzerland: World Health Organization (WHO Technical Report Series, No. 894). Available from: http://www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/.

7. WHO (2011). Waist circumference and waist–hip ratio: report of a WHO Expert Consultation, Geneva, 8–11 December 2008. Geneva, Switzerland: World Health Organization. Available from: http://www.who.int/nutrition/publications/obesity/WHO_report_waistcircumference_and_waisthip_ratio/en/.

8. van der Kooy K, Leenen R, Seidell JC, Deurenberg P, Droop A, Bakker CJ (1993). Waist-hip ratio is a poor predictor of changes in visceral fat. Am J Clin Nutr. 57(3):327–33. PMID:8438766

9. Segal KR, Van Loan M, Fitzgerald PI, Hodgdon JA, Van Itallie TB (1988). Lean body mass estimation by bioelectrical impedance analysis: a four-site cross-validation study. Am J Clin Nutr. 47(1):7–14. PMID:3337041

10. Willett K, Jiang R, Lenart E, Spiegelman D, Willett W (2006). Comparison of bioelectrical impedance and BMI in predicting obesity-related medical conditions. Obesity (Silver Spring). 14(3):480–90. http://dx.doi.org/10.1038/oby.2006.63 PMID:16648620

11. Heymsfield SB, Lohman TG, Wang Z, Going SB, editors (2005). Human body composition. 2nd ed. Champaign (IL), USA: Human Kinetics.

12. McCrory MA, Gomez TD, Bernauer EM, Molé PA (1995). Evaluation of a new air displacement plethysmograph for measuring human body composition. Med Sci Sports Exerc. 27(12):1686–91. http://dx.doi.org/10.1249/00005768-199512000-00016 PMID:8614326

13. Glickman SG, Marn CS, Supiano MA, Dengel DR (2004). Validity and reliability of dual-energy X-ray absorptiometry for the assessment of abdominal adiposity. J Appl Physiol (1985). 97(2):509–14. http://dx.doi.org/10.1152/japplphysiol.01234.2003 PMID:15075304

14. Bandera EV, Maskarinec G, Romieu I, John EM (2015). Racial and ethnic disparities in the impact of obesity on breast cancer risk and survival: a global perspective. Adv Nutr. 6(6):803–19. http://dx.doi.org/10.3945/an.115.009647 PMID:26567202

15. Karra E, O'Daly OG, Choudhury AI, Yousseif A, Millership S, Neary MT, et al. (2013). A link between FTO, ghrelin, and impaired brain food-cue responsivity. J Clin Invest. 123(8):3539–51. http://dx.doi.org/10.1172/JCI44403 PMID:23867619

16. Guo SS, Chumlea WC (1999). Tracking of body mass index in children in relation to overweight in adulthood. Am J Clin Nutr. 70(1):145S–8S.

17. Brisbois TD, Farmer AP, McCargar LJ (2012). Early markers of adult obesity: a review. Obes Rev. 13(4):347–67. http://dx.doi.org/10.1111/j.1467-789X.2011.00965.x PMID:22171945

18. Fogelholm M, Kukkonen-Harjula K (2000). Does physical activity prevent weight gain – a systematic review. Obes Rev. 1(2):95–111. http://dx.doi.org/10.1046/j.1467-789x.2000.00016.x PMID:12119991

19. Stubbs RJ, Harbron CG, Murgatroyd PR, Prentice AM (1995). Covert manipulation of dietary fat and energy density: effect on substrate flux and food intake in men eating ad libitum. Am J Clin Nutr. 62(2):316–29. PMID:7625338

20. Salas-Salvadó J, Bulló M, Babio N, Martínez-González MA, Ibarrola-Jurado N, Basora J, et al.; PREDIMED Study Investigators (2011). Reduction in the incidence of type 2 diabetes with the Mediterranean diet: results of the PREDIMED-Reus nutrition intervention randomized trial. Diabetes Care. 34(1):14–9. http://dx.doi.org/10.2337/dc10-1288 PMID:20929998

21. Du H, van der A DL, Ginder V, Jebb SA, Forouhi NG, Wareham NJ, et al. (2009). Dietary energy density in relation to subsequent changes of weight and waist circumference in European men and women. PLoS One. 4(4):e5339. http://dx.doi.org/10.1371/journal.pone.0005339 PMID:19396357

22. Te Morenga L, Mallard S, Mann J (2013). Dietary sugars and body weight: systematic review and meta-analyses of randomised controlled trials and cohort studies. BMJ. 346:e7492. http://dx.doi.org/10.1136/bmj.e7492 PMID:23321486

23. Lennerz BS, Alsop DC, Holsen LM, Stern E, Rojas R, Ebbeling CB, et al. (2013). Effects of dietary glycemic index on brain regions related to reward and craving in men. Am J Clin Nutr. 98(3):641–7. http://dx.doi.org/10.3945/ajcn.113.064113 PMID:23803881

24. United Kingdom Scientific Advisory Committee on Nutrition (2015). Carbohydrates and health. London, UK: The Stationery Office. Available from: https://www.gov.uk/government/publications/sacn-carbohydrates-and-health-report.

25. Mirza NM, Palmer MG, Sinclair KB, McCarter R, He J, Ebbeling CB, et al. (2013). Effects of a low glycemic load or a low-fat dietary intervention on body weight in obese Hispanic American children and adolescents: a randomized controlled trial. Am J Clin Nutr. 97(2):276–85. http://dx.doi.org/10.3945/ajcn.112.042630 PMID:23255569

26. Swinburn BA, Caterson I, Seidell JC, James WP (2004). Diet, nutrition and the prevention of excess weight gain and obesity. Public Health Nutr. 7(1A):123–46. PMID:14972057

27. Astrup A, Grunwald GK, Melanson EL, Saris WH, Hill JO (2000). The role of low-fat diets in body weight control: a meta-analysis of ad libitum dietary intervention studies. Int J Obes Relat Metab Disord. 24(12):1545–52. http://dx.doi.org/10.1038/sj.ijo.0801453 PMID:11126204

28. Harvie MN, Pegington M, Mattson MP, Frystyk J, Dillon B, Evans G, et al. (2011). The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized trial in young overweight women. Int J Obes (Lond). 35(5):714–27. http://dx.doi.org/10.1038/ijo.2010.171 PMID:20921964

29. Chen L, Appel LJ, Loria C, Lin PH, Champagne CM, Elmer PJ, et al. (2009). Reduction in consumption of sugar-sweetened beverages is associated with weight loss: the PREMIER trial. Am J Clin Nutr. 89(5):1299–306. http://dx.doi.org/10.3945/ajcn.2008.27240 PMID:19339405

30. Tobias DK, Chen M, Manson JE, Ludwig DS, Willett W, Hu FB (2015). Effect of low-fat diet interventions versus other diet interventions on long-term weight change in adults: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 3(12):968–79. http://dx.doi.org/10.1016/S2213-8587(15)00367-8 PMID:26527511

31. Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I, et al.; Dietary Intervention Randomized Controlled Trial (DIRECT) Group (2008). Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med. 359(3):229–41. http://dx.doi.org/10.1056/NEJMoa0708681 PMID:18635428

32. Allison KR, Dwyer JJM, MacGillivray A, Hawrychuk S; Ontario Agency for Health Protection and Promotion (2011). A review of workplace and community interventions for adults: effects of physical activity, eating behaviours and BMI – risk factors for diabetes. Toronto, Canada: Queen's Printer for Ontario. Available from: https://www.publichealthontario.ca/en/eRepository/A Review of Workplace and Community Interventions for Adults Effects on physical activity, eating behaviours, and BMI.pdf.

33. Romero-Martínez M, Shamah-Levy T, Franco-Núñez A, Villalpando S, Cuevas-Nasu L, Gutiérrez JP, et al. (2013). National Health and Nutrition Survey 2012: design and coverage [in Spanish]. Salud Publica Mex. 55(Suppl 2):S332–40. PMID:24626712

34. Aburto TC, Cantoral A, Hernández-Barrera L, Carriquiry AL, Rivera JA (2015). Usual dietary energy density distribution is positively associated with excess body weight in Mexican children. J Nutr. 145(7):1524–30. http://dx.doi.org/10.3945/jn.114.206359 PMID:25926409

35. Wang YC, Ludwig DS, Sonneville K, Gortmaker SL (2009). Impact of change in sweetened caloric beverage consumption on energy intake among children and adolescents. Arch Pediatr Adolesc Med. 163(4):336–43. http://dx.doi.org/10.1001/archpediatrics.2009.23 PMID:19349562

36. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB (2011). Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med. 364(25):2392–404. http://dx.doi.org/10.1056/NEJMoa1014296 PMID:21696306

37. Fung TT, Pan A, Hou T, Chiuve SE, Tobias DK, Mozaffarian D, et al. (2015). Long-term change in diet quality is associated with body weight change in men and women. J Nutr. 145(8):1850–6. http://dx.doi.org/10.3945/jn.114.208785 PMID:26084363

38. United States Department of Agriculture (2015). Scientific report of the 2015 Dietary Guidelines Advisory Committee. Washington (DC), USA: Department of Agriculture and Department of Health and Human Services. Available from: https://health.gov/dietaryguidelines/2015-scientific-report/.

39. Schwarzfuchs D, Golan R, Shai I (2012). Four-year follow-up after two-year dietary interventions. N Engl J Med. 367(14):1373–4. http://dx.doi.org/10.1056/NEJMc1204792 PMID:23034044

40. Chajès V, Biessy C, Ferrari P, Romieu I, Freisling H, Huybrechts I, et al. (2015). Plasma elaidic acid level as biomarker of industrial trans fatty acids and risk of weight change: report from the EPIC study. PLoS One. 10(2):e0118206. http://dx.doi.org/10.1371/journal.pone.0118206 PMID:25675445

41. Richter LM, Victora CG, Hallal PC, Adair LS, Bhargava SK, Fall CH, et al.; COHORTS Group (2012). Cohort Profile: the Consortium of Health-Orientated Research in Transitioning Societies. Int J Epidemiol. 41(3):621–6. http://dx.doi.org/10.1093/ije/dyq251 PMID:21224276

42. Lajous M, Ortiz-Panozo E, Monge A, Santoyo-Vistrain R, García-Anaya A, Yunes-Díaz E, et al. (2017). Cohort Profile: the Mexican Teachers' Cohort (MTC). Int J Epidemiol. 46(2):e10. http://dx.doi.org/10.1093/ije/dyv123 PMID:26337903

43. Romieu I, Escamilla-Núñez MC, Sánchez-Zamorano LM, Lopez-Ridaura R, Torres-Mejía G, Yunes EM, et al. (2012). The association between body shape silhouette and dietary pattern among Mexican women. Public Health Nutr. 15(1):116–25. http://dx.doi.org/10.1017/S1368980011001182 PMID:21875454

44. Emmett PM, Jones LR (2015). Diet, growth, and obesity development throughout childhood in the Avon Longitudinal Study of Parents and Children. Nutr Rev. 73(Suppl 3):175–206. http://dx.doi.org/10.1093/nutrit/nuv054 PMID:26395342

45. Victora CG, Adair L, Fall C, Hallal PC, Martorell R, Richter L, et al.; Maternal and Child Undernutrition Study Group (2008). Maternal and child undernutrition: consequences for adult health and human capital. Lancet. 371(9609):340–57. http://dx.doi.org/10.1016/S0140-6736(07)61692-4 PMID:18206223

46. Yang Z, Huffman SL (2013). Nutrition in pregnancy and early childhood and associations with obesity in developing countries. Matern Child Nutr. 9(Suppl 1):105–19. http://dx.doi.org/10.1111/mcn.12010 PMID:23167588

47. Ramirez-Silva I, Rivera JA, Trejo-Valdivia B, Martorell R, Stein AD, Romieu I, et al. (2015). Breastfeeding status at age 3 months is associated with adiposity and cardiometabolic markers at age 4 years in Mexican children. J Nutr. 145(6):1295–302. http://dx.doi.org/10.3945/jn.114.198366 PMID:25926414

CHAPTER 8.

Cultural determinants of obesity in low- and middle-income countries in the Eastern Mediterranean Region

Nahla Hwalla, Lara Nasreddine, and Sibelle El Labban

Increasing prevalence of obesity

In the Eastern Mediterranean Region (EMR), there is a high burden of obesity and an increasing trend in the prevalence across all age groups. Differences have been noted between countries and between sexes. In adults, the prevalence of obesity is higher among women than among men, whereas in children, the prevalence of obesity is higher among boys than among girls in most countries in the region.

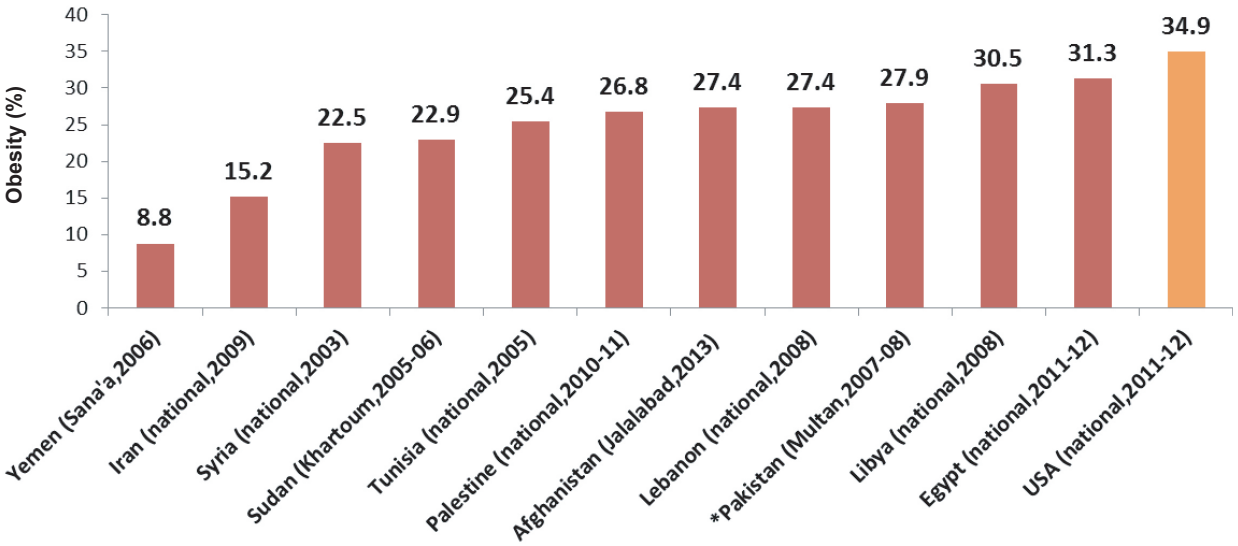
This increasing prevalence of obesity is potentially linked to an obesogenic environment, which includes cultural and social issues such as urbanization, increased wealth, and lower levels of physical activity, coupled with high consumption of energy-dense foods. Addressing these issues in a holistic manner could curb the escalating prevalence of obesity in these countries and relieve the health cost of management of noncommunicable diseases.

The prevalence of obesity among adults in selected low- and middle-income countries (LMICs) in the EMR ranges from 8.8% to 31.3% and approaches the prevalence of 34.9% observed in the USA (Fig. 8.1) [1–12]. Of greater concern is the increasing secular trend in the prevalence of obesity among adults in several countries in the region, with annual secular increases of +1.7 to +16% [5, 13–17].

In adolescents, the prevalence of obesity in LMICs in the EMR ranges between 1% and 8.9% (according to the 2007 World Health Organization [WHO] criteria), which is lower than the prevalence of 20.5% observed in the USA (according to the 2000 Centers for Disease Control and Prevention [CDC] criteria) [12, 17–32]. However, data on secular trends in the region are limited. In some countries where data at different time points were available, the average annual increase in the prevalence of obesity ranged from +2% to +13.5% [14, 26, 28, 33–38].

In children younger than 5 years, rates of overweight and obesity in selected LMICs in the EMR range from 2% to 22.4%; the lower figures are comparable to the estimates from developing countries (6.1%), and the highest figures are double the estimates from developed countries (11.7%) [17, 39–51]. Of greater concern is the increasing trend in the prevalence of overweight and obesity among children younger than 5 years in many countries in the EMR; the annual secular increases of +1.9 to +10.4% are extremely alarming. In contrast, a decrease in the prevalence of overweight and obesity among children younger than 5 years was reported in a few countries in the EMR, with annual decreases ranging from −1.1% to −7.7% [16–17, 39–40, 42, 44–59].

Fig. 8.1. Prevalence (%) of obesity (body mass index [BMI] ≥ 30 kg/m^2) among adults in selected low- and middle-income countries in the Eastern Mediterranean Region. * BMI > 30 kg/m^2 (WHO recommendations for the Asia-Pacific Region). Sources: Sana'a, Yemen: Gunaid (2012) [1]; Islamic Republic of Iran: STEPS (2009) [2]; Syrian Arab Republic: STEPS (2003) [3]; Khartoum, Sudan: STEPS (2006) [4]; Tunisia: El Ati et al. (2012) [5]; Palestine: STEPS (2011) [6]; Jalalabad, Afghanistan: Saeed (2015) [7]; Lebanon: Sibai and Hwalla (2010) [8]; Multan, Pakistan: Aslam et al. (2010) [9]; Libya: STEPS (2009) [10]; Egypt: STEPS (2012) [11]; USA: Ogden et al. (2014) [12].



Cultural determinants of obesity: situation analysis and associations

The increase in the prevalence of obesity in Eastern Mediterranean populations has been associated with several sociocultural, behavioural, and environmental changes, such as the nutrition transition, changes in socioeconomic status, cultural and social factors, and urbanization, all of which have negatively affected the quality and the quantity of the food consumed and have encouraged sedentary behaviour.

Data from the Food and Agriculture Organization of the United Nations (FAO) food balance sheets and from food consumption surveys conducted in the EMR during the past four decades (between 1969–1971 and 2011) have shown a remarkable change in eating behaviour, marked by a shift away from the traditional diet, rich in fruits, vegetables, and whole grains, and towards a diet high in fat, sugar, and refined carbohydrates. Other factors, such as food marketing, body image, and early-life feeding practices, also appear to play an important role in the burden of obesity in the region. The interrelationships between the different sociocultural, behavioural, and environmental determinants of obesity in LMICs in the EMR are discussed in detail below.

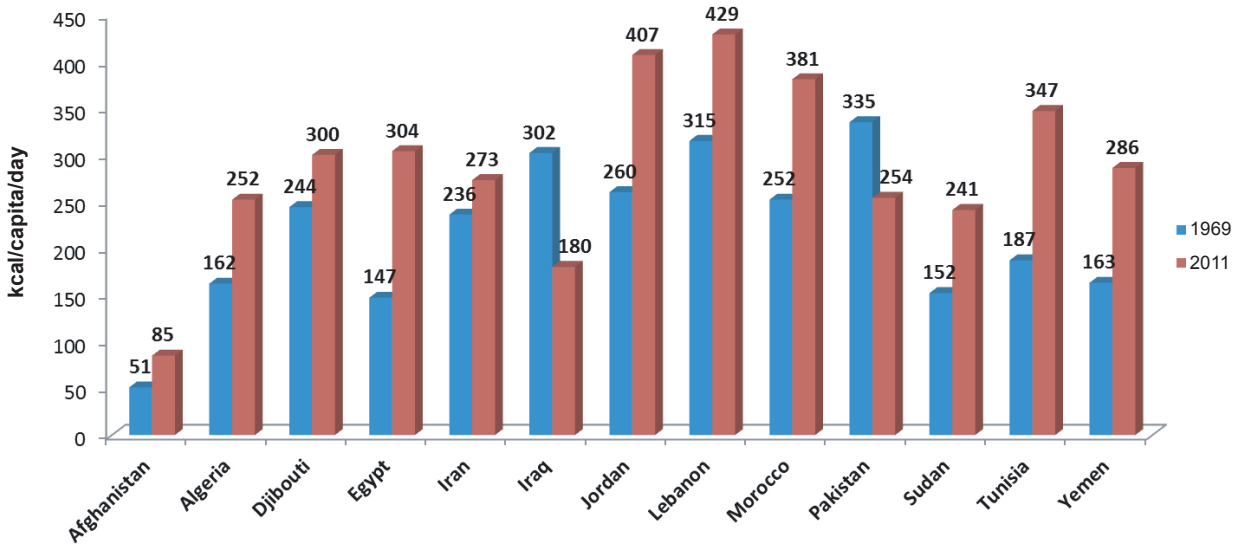
The nutrition transition

Food availability and consumption

To understand the nutrition transition in LMICs in the EMR, is it important to analyse the changes that have occurred in food availability and food consumption, to properly address these changes. Data from the FAO food balance sheets and from food consumption surveys between 1969–1971 and 2011 highlight a shift towards an increasingly energy-dense diet and high intakes of fat and sugar, coupled with a parallel decrease in consumption of carbohydrates [60–65]. Data from FAO also show that sugar availability, which is reported to be a predisposing factor to obesity, increased considerably during the same period (1969–2011) in several LMICs in the EMR, such as Afghanistan, Sudan, Tunisia, and Yemen, and doubled in Egypt. However, a reduction was noted in Iraq and Pakistan (Fig. 8.2) [60].

A strong association has been reported between high consumption of harmful food components (processed meat, red meat, trans-fatty acids, sugar-sweetened beverages, and sodium), low consumption of protective foods (fruits, vegetables and beans, nuts and seeds, whole grains, and omega-3 fatty acids [found in fish and seafood]), and increased risk of cardiometabolic disease deaths across all countries in the EMR; therefore, a food consumption pattern that is collectively high in harmful foods and low in protective foods is a strong predictor of cardiometabolic disease mortality

Fig. 8.2. Change in sugar availability (kcal/capita/day) between 1969 and 2011 in selected low- and middle-income countries in the Eastern Mediterranean Region. Source: FAO (2015) [60].



[66]. In addition, the dietary energy supply from the different food groups (harmful and protective) shows that the traditional diet has been modified, so that most of the countries have shown insufficient per capita consumption of protective foods, which fell well below recommended levels, as well as higher than recommended per capita consumption of harmful food components across all countries in the EMR [66].

The nutrition transition reflected in changes in food consumption patterns has been reported to be correlated with the prevalence of obesity in several countries in the EMR and across different age groups. High energy intake has been significantly associated with higher risk of obesity [15, 67]. The contribution of fat to energy intake was higher among obese individuals than among their non-obese counterparts, whereas the opposite was found for the contribution of carbohydrate to energy intake [68].

Countries have reported on the association of dietary patterns with obesity and metabolic diseases. In the Islamic Republic of Iran, a positive association was shown between an unhealthy dietary pattern and the risk of obesity in women, whereas the opposite was shown for a healthy dietary pattern [69]. A more recent cross-sectional study in a large cohort of Iranian adults found that adherence to a pattern of nutrient intake characterized by high consumption of thiamine, betaine, starch, folate, iron, selenium, niacin, calcium, and manganese was associated with a lower likelihood of general obesity (particularly in men), whereas a pattern of nutrient intake characterized by high consumption of glucose, fructose, sucrose, vitamin C, potassium, total dietary fibre, copper, and vitamin K was associated with a greater likelihood of general obesity in men [70]. In Lebanon, an unhealthy dietary pattern was also reported to be positively associated with high body mass index (BMI) and increased waist circumference, and tripled the risk of hyperglycaemia and metabolic syndrome among adults [71]. Table 8.1 summarizes the associations of different dietary and nutrient patterns with obesity in Lebanon and the Islamic Republic of Iran.

Food marketing

The contribution of food marketing to the rise in the prevalence of obesity in the EMR is governed by six major elements: availability, price, education and knowledge, labelling, food subsidy policies, and the impact of these policies.

LMICs in the EMR have been significantly affected by globalization, which has resulted in the wide spread of fast-food chains as well as different food retail industries and markets, making energy-dense and processed foods more readily available than ever before and easily accessible by consumers of all ages. This trend has been further exacerbated by the convenient and affordable prices of energy-dense foods and snacks compared with healthy food items, which tend to be more expensive.

In the EMR, knowledge and education about healthy food products are largely influenced by the media. Exposure to television commercials for fast foods, soft drinks, sweets, and chocolates may markedly influence the food choices and dietary habits of

Table 8.1. Association of dietary and nutrient patterns with obesity in Lebanon and the Islamic Republic of Iran

Country Dietary/nutrient pattern	Measure of obesity	
	Body mass index (general obesity)	Elevated waist circumference (abdominal obesity)
Lebanon		
Unhealthy dietary pattern[a]	Positive	Positive
Traditional/Lebanese dietary pattern[b]	None	None
Islamic Republic of Iran		
Healthy dietary pattern[c]	Negative	Negative
Unhealthy dietary pattern[d]	Positive	Positive
Traditional/Iranian dietary pattern[e]	None	None
First nutrient pattern[f]	None	None
Second nutrient pattern[g]	Negative (in men)	None
Third nutrient pattern[h]	Positive (in men)	None

[a] High in fast-food sandwiches, pizza, pies, desserts, carbonated beverages, butter, juices, and mayonnaise.

[b] High in fruits and vegetables, olives and olive oil, traditional dishes and desserts, eggs, and whole dairy products.

[c] High in fruits, other vegetables, tomatoes, poultry, legumes, cruciferous and green leafy vegetables, tea, fruit juices, and whole grains.

[d] High in refined grains, red meat, butter, processed meat, whole dairy products, sweets and desserts, pizza, potatoes, eggs, hydrogenated fats, and soft drinks, and low in other vegetables and low-fat dairy products.

[e] High in refined grains, potatoes, tea, whole grains, hydrogenated fats, legumes, and broth.

[f] High in fatty acids (including saturated, monounsaturated, and polyunsaturated fatty acids), cholesterol, vitamin B12, vitamin E, zinc, choline, protein, pyridoxine, phosphorus, and pantothenic acid.

[g] High in thiamine, betaine, starch, folate, iron, selenium, niacin, calcium, and manganese.

[h] High in glucose, fructose, sucrose, vitamin C, potassium, total dietary fibre, copper, and vitamin K.

Sources: Lebanon: Naja et al. (2014) [71]; Islamic Republic of Iran: Esmaillzadeh and Azadbakht (2008) [69], Salehi-Abargouei et al. (2015) [70].

the viewers, particularly children and adolescents. In Egypt, for example, television advertisements were found to be the main driver for the purchase of chocolate and sweets by school-age children [72]. Moreover, food labelling standards have not been mandatory in the EMR and have not been given enough consideration for public awareness and education about food content and portion sizes. As a result, consumers are either indifferent towards reading labels or find it challenging to understand the information on the label, especially consumers with low socioeconomic status.

Most countries in the EMR have opted to subsidize food items such as wheat, rice, vegetable oil, and sugar, hence possibly contributing to the high burden of obesity in the region by making consumers highly dependent on these energy-dense subsidized foods. In Egypt, mothers' BMI was found to be inversely correlated with the price of subsidized *baladi* bread and subsidized sugar but directly correlated with the price of healthier foods such as fruits, milk, and eggs [73]. Hence, reducing the price of healthy food items may contribute to weight reduction among mothers by better promoting the consumption of healthier food items, reducing the consumption of energy-dense foods, or both [73]. The impact of such policies can be understood through more robust research in the EMR on the influence of food marketing policies on consumer behaviour and dietary intake, as well as obesity.

Early-life feeding practices

Inadequate feeding practices in the first years of life have been reported to be associated with an increased risk of adult obesity [74]. A longer duration of exclusive breastfeeding was suggested to reduce the risk of overweight and obesity in children [75]. In addition, very early introduction of complementary foods has been shown to increase the risk of obesity and cardiovascular disease later in life [76].

In the EMR, suboptimal breastfeeding is highly prevalent, coupled with untimely complementary feeding. This may have led to the double burden of child malnutrition in the region, manifested by concomitant high rates of stunting and obesity among children younger than 5 years.

The available studies highlight the low rates of exclusive breastfeeding in the first 6 months in most countries in the EMR. The rates range from 5.3% to 58.4%, falling below the World Health Assembly's global nutrition target for 2025 of 50%, except in the Islamic Republic of Iran and Afghanistan [17, 41, 48–50, 58, 77–84].

Complementary feeding practices in the EMR are also suboptimal and fall short of global recommendations. In most countries in the region, solid foods are introduced before the

recommended age of 4–6 months, a practice that may have contributed to the high prevalence of obesity [85–87].

Data on the association between early feeding practices and the risk of obesity are scarce in the EMR. In the Islamic Republic of Iran, for example, a longer duration of breastfeeding was found to be significantly associated with a lower prevalence of overweight among school-aged children and adolescents [88–89]. In Lebanon, a high likelihood of overweight and obesity were observed among children (0–2 years) who were exclusively breastfed for less than 4 months or less than 6 months, who received formula milk in the first 6 months, and who had high intakes of carbohydrates, sugars, and total fat (Nasreddine et al., unpublished data).

Socioeconomic status

Countries in the EMR are classified into three income groups: low-income countries, middle-income countries, and high-income countries. The prevalence of obesity in middle-income countries is high and similar to the prevalence in high-income countries, whereas the prevalence of obesity is lower in low-income countries [90].

Several studies in EMR countries have shown a correlation between an individual's socioeconomic status and the likelihood of obesity. In general, obesity is more prevalent in unemployed people and in married individuals of both sexes [67, 91–95]. In the Islamic Republic of Iran, living in an urban area and having a higher education level increased the likelihood of obesity among adults [96], whereas in Lebanon, obesity was found to be inversely associated with the socioeconomic status of women, and the likelihood of obesity decreased significantly with higher education level, greater household assets, and lower crowding index [67]. Socioeconomic indicators were also correlated with paediatric obesity. Risk of obesity increased among adolescents in the Syrian Arab Republic who reported a low crowding index and whose parents had attained a higher education level [65] and among children and adolescents in Pakistan who were in a higher school grade (grade 4 vs grade 1) and living in an urban area with higher socioeconomic status [97]. Table 8.2 summarizes the association of socioeconomic indicators with obesity in these four countries.

Cultural and social factors

Cultural factors may play an important role in the occurrence of obesity in some countries in the region. For example, a culture that promotes plumpness as a sign of beauty, health, and affluence has been suggested to be an underlying factor for the high prevalence of obesity in the high-income countries in the EMR. Additional factors that may contribute significantly to the rise in the prevalence of obesity are eating habits (plate sharing) and the types of traditional clothing (*abaya* or wide gowns) worn by a substantial number of women in the region [98].

The influence of men in determining women's attitudes towards body size is an important issue in some countries in the EMR. In Qatar, for example, about 43% of the Arab women surveyed believed that men preferred plump women [99]. Similar findings were reported in Morocco, where a cultural preference for body fatness among women exists [100].

The traditional long, wide dress for men or women in some countries may hide body fat and consequently reduce a person's motivation to lose weight [101]. In some countries in the EMR, women are mandated by law to wear full-body covering when they are in public. This covering makes it difficult to observe the size and shape of the female body, thereby reducing the emphasis on these features and possibly acting as a protective factor against body image concerns [102].

Table 8.2. Association of socioeconomic indicators with obesity in selected low- and middle-income countries in the Eastern Mediterranean Region

Country (population)	High education level	High socioeconomic status[a]
Islamic Republic of Iran (adults ≥ 19 years)	Increasing obesity	Increasing obesity
Lebanon (women ≥ 20 years)	Decreasing obesity	Decreasing obesity
Syrian Arab Republic (adolescents 15–18 years)	Increasing obesity[b]	Increasing obesity
Pakistan (children and adolescents 5–12 years)	Increasing obesity	Increasing obesity

[a] High socioeconomic status is reflective of: living in an urban area in the Islamic Republic of Iran; high household assets and low crowding index in Lebanon; low crowding index in the Syrian Arab Republic; and living in an urban area with high socioeconomic status in Pakistan.

[b] Association of obesity in adolescents with educational attainment of their parents.

Sources: Islamic Republic of Iran: Tavassoli et al. (2010) [96]; Lebanon: Chamieh et al. (2015) [67]; Syrian Arab Republic: Nasreddine et al. (2010) [65]; Pakistan: Mushtaq et al. (2011) [97].

Studies on the association of culture with obesity in the EMR are scarce. The prevalence of obesity was found to be greater among Iraqi women who wore traditional clothing (*abaya*), and the prevalence of obesity was higher among those who shared the plate with family members (77.5%) than among those who had individual plates (69.4%) [98].

Urbanization

LMICs in the EMR have been undergoing rapid urbanization, characterized by large movements from rural to urban areas, coupled with increased growth of large cities [103, 104]. Urbanization is suggested to intensify the burden of obesity [105].

In most of the countries in the EMR, obesity is more prevalent in urban sectors than in rural sectors for both sexes [93, 106–108]. After adjustment for possible confounding factors, including demographic and socioeconomic factors in a binary regression model, urban dwelling remained a major determinant of obesity in the Islamic Republic of Iran [109]. A similar pattern was found in Palestine, where BMI levels of urban women and men were significantly higher than those of their rural counterparts [108].

Physical inactivity

Most of the available studies on physical activity in the EMR are hampered by the limited amount of reliable data, the varying methodology, and the different physical activity instruments used by different researchers [110]. WHO has provided crude estimates of the prevalence of insufficient physical activity among adults (≥ 18 years) and adolescents (11–17 years) in selected LMICs of the EMR where data are available. The prevalence of insufficient physical activity among adults differed across countries and ranged from 15.6% in Jordan to 49.3% in Iraq, whereas it reached alarming levels (> 75%) among adolescents, ranging from 76.7% in Lebanon to 91.9% in Sudan (Fig. 8.3) [111].

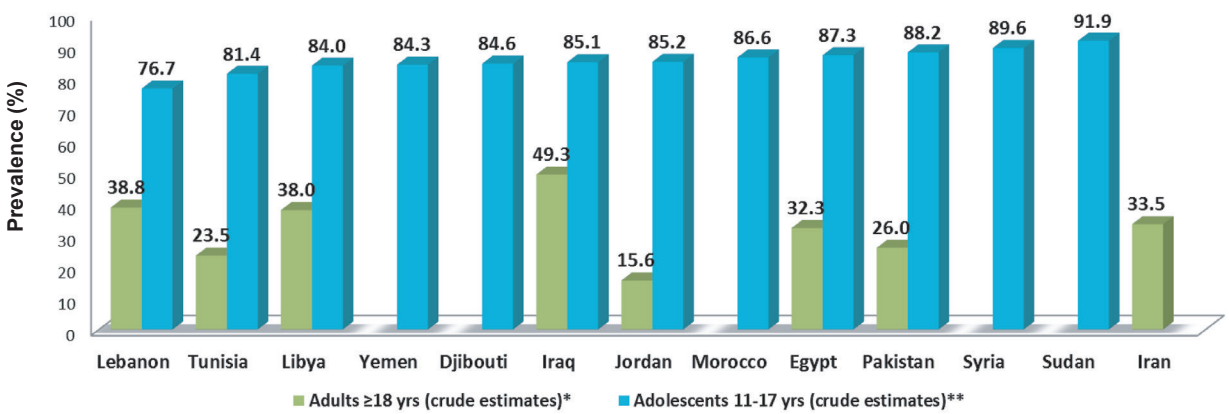
According to the Global School-based Student Health Survey from 2003–2007, the proportion of schoolchildren (13–15 years) who spent 3 hours or more per day on sedentary activities (sitting and watching television, playing computer games, talking with friends, or doing other seated activities) in some countries in the EMR was relatively high, ranging from 22.4% in Egypt to 42.0% in Jordan [112].

In most countries in the EMR, labour-saving changes in occupations, a high dependence on cars and buses for transportation, massive urbanization, satellite television, and increased reliance on computers and telecommunication technology may all have contributed to an increase in the burden of obesity [113]. Outdoor activities are hampered by the overall lack of public parks and walking and bicycle lanes, and by the hot climate [114]. In the region, women face more barriers to participating in physical activity compared with men. This is because men, in general, have more freedom and more places to practise sport and other recreational activities, whereas women are often restricted due to cultural and religious beliefs, which make them unable to publicly and freely participate in physical activity [115].

Conclusions

LMICs in the EMR have been undergoing a nutrition transition, with a parallel increase in obesity rates

Fig. 8.3. Prevalence (%) of insufficient physical activity among adults and adolescents in selected low- and middle-income countries in the Eastern Mediterranean Region. * < 150 minutes per week of moderate-intensity physical activity, or < 75 minutes per week of vigorous-intensity physical activity, or equivalent; ** < 60 minutes per day of moderate- to vigorous-intensity physical activity. Source: WHO (2010) [111].



across all age groups and among both sexes, which can be attributed to socioeconomic, cultural, and social factors, as well as urbanization. Many factors may have contributed to the escalating burden of obesity in the region, including an unhealthy dietary pattern, low breastfeeding rates coupled with untimely and faulty complementary feeding practices, unemployment, low education levels, physical inactivity, perceptions of beauty and a preference for plumpness in women, and cultural habits such as plate sharing and traditional clothing (*abaya*).

Intervention strategies to combat obesity should adopt a holistic approach in addressing the obesogenic factors comprehensively. A single intervention alone may not be viable and economically efficient for a multifaceted problem like obesity, which involves complex interactions. Therefore, adopting a model as suggested by Amarasinghe and D'Souza [116], which is adapted to Eastern Mediterranean populations and which encompasses economic, environmental, social, and individual elements, would constitute a promising approach to curb the rising burden of obesity in the region.

Key points

- There is a high burden of obesity and an increasing trend in the prevalence across all age groups in LMICs in the EMR.
- Obesity in LMICs in the EMR is associated with sociocultural, behavioural, and environmental determinants (e.g. the nutrition transition, socioeconomic status, cultural and social factors, and urbanization) that are closely interrelated.
- An unhealthy dietary pattern, food marketing that promotes consumption of energy-dense foods, faulty and untimely early feeding practices, unemployment, low education levels, physical inactivity, perceptions of beauty and a preference for plumpness in women, as well as plate sharing and traditional clothing are all factors implicated in the escalating burden of obesity in LMICs in the EMR.

Research needs

- Adequate research data are needed on sociocultural determinants of obesity in LMICs in the EMR.
- There is a need for the development of intervention strategies and the assessment of their impact in addressing obesity prevention in LMICs in the EMR.
- Cohort studies are needed to adequately investigate culturally related early-life infant and young child feeding practices and their future impact on obesity in LMICs in the EMR.

References

1. Gunaid AA (2012). Obesity, overweight and underweight among adults in an urban community in Yemen. East Mediterr Health J. 18(12):1187–93. PMID:23301392

2. STEPS (2009). WHO STEPS chronic disease risk factor surveillance: Iran STEPS Survey 2009 Fact Sheet 1388. Available from: http://www.who.int/chp/steps/Iran_2009_STEPS_FactSheet.pdf?ua=1.

3. STEPS (2003). WHO STEPS noncommunicable disease risk factor surveillance: Syrian Arab Republic 2003 STEPS Survey Fact Sheet [in Arabic]. Available from: http://www.who.int/chp/steps/SyrianArabRepublicSTEPSReport.PDF?ua=1.

4. STEPS (2006). WHO STEPS chronic disease risk factor surveillance: Khartoum State/Sudan STEPS Survey 2005–2006 Fact Sheet. Available from: http://www.who.int/chp/steps/STEPS_FactSheet_Sudan.pdf?ua=1.

5. El Ati J, Traissac P, Delpeuch F, Aounallah-Skhiri H, Béji C, Eymard-Duvernay S, et al. (2012). Gender obesity inequities are huge but differ greatly according to environment and socio-economics in a North African setting: a national cross-sectional study in Tunisia. PLoS One. 7(10):e48153. http://dx.doi.org/10.1371/journal.pone.0048153 PMID:23118943

6. STEPS (2011). WHO STEPS chronic disease risk factor surveillance (6-3C-1): Palestine STEPS Survey 2010–2011 Fact Sheet. Available from: http://www.who.int/chp/steps/Palestine_FactSheet_2010-11.pdf?ua=1.

7. Saeed KMI (2015). Prevalence and associated risk factors for obesity in Jalalabad city – Afghanistan. Alex J Med. 51(4):347–52. http://dx.doi.org/10.1016/j.ajme.2014.12.004

8. Sibai A, Hwalla N (2010). WHO STEPS chronic disease risk factor surveillance: data book for Lebanon. Available from: http://www.who.int/chp/steps/2008_STEPS_Lebanon.pdf?ua=1.

9. Aslam M, Saeed A, Pasha GR, Altaf S (2010). Gender differences of body mass index in adults of Pakistan: a case study of Multan city. Pak J Nutr. 9(2):162–6. http://dx.doi.org/10.3923/pjn.2010.162.166

10. STEPS (2009). WHO STEPS noncommunicable disease risk factor surveillance: Libya 2009 STEPS Survey Report [in Arabic]. Available from: http://www.who.int/chp/steps/2009_STEPS_Libya.pdf?ua=1.

11. STEPS (2012). WHO STEPS chronic disease risk factor surveillance (6-3C-1): Egypt STEPS Survey 2011–12 Fact Sheet. Available from: http://www.who.int/chp/steps/2011-2012_Egypt_FactSheet.pdf?ua=1.

12. Ogden CL, Carroll MD, Kit BK, Flegal KM (2014). Prevalence of childhood and adult obesity in the United States, 2011-2012. JAMA. 311(8):806–14. http://dx.doi.org/10.1001/jama.2014.732 PMID:24570244

13. Khader Y, Batieha A, Ajlouni H, El-Khateeb M, Ajlouni K (2008). Obesity in Jordan: prevalence, associated factors, comorbidities, and change in prevalence over ten years. Metab Syndr Relat Disord. 6(2):113–20. http://dx.doi.org/10.1089/met.2007.0030 PMID:18510436

14. Nasreddine L, Naja F, Chamieh MC, Adra N, Sibai A-M, Hwalla N (2012). Trends in overweight and obesity in Lebanon: evidence from two national cross-sectional surveys (1997 and 2009). BMC Public Health. 12(1):798. http://dx.doi.org/10.1186/1471-2458-12-798 PMID:22984791

15. Mokhtar N, Elati J, Chabir R, Bour A, Elkari K, Schlossman NP, et al. (2001). Diet culture and obesity in northern Africa. J Nutr. 131(3):887S–92S. PMID:11238780

16. MOPH (2005). Summary Report of the National Nutrition Survey, Afghanistan, 2004. Kabul: Ministry of Public Health of the Islamic Republic of Afghanistan, UNICEF, Centers for Disease Control and Prevention, National Institute for Research on Food and Nutrition-Italy, and Tufts University.

17. MOPH (2013). National Nutrition Survey, Afghanistan (2013): survey report. Kabul: Ministry of Public Health of the Islamic Republic of Afghanistan and UNICEF. Available from: http://reliefweb.int/sites/reliefweb.int/files/resources/Report NNS Afghanistan 2013 (July 26-14).pdf.

18. WHO (2007). The WHO child growth standards. Geneva, Switzerland: World Health Organization. Available from: http://www.who.int/childgrowth/en/.

19. Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, et al. (2002). 2000 CDC growth charts for the United States: methods and development. National Center for Health Statistics. Vital Health Stat. 11(246). Available from: https://www.cdc.gov/nchs/data/series/sr_11/sr11_246.pdf.

20. GSHS (2009). Global School-based Student Health Survey (GSHS): Pakistan 2009 Fact Sheet. Available from: http://www.who.int/chp/gshs/Pakistan_2009_FS.pdf?ua=1.

21. GSHS (2010). Global School-based Student Health Survey (GSHS): Morocco 2010 Fact Sheet. Available from: http://www.who.int/chp/gshs/Morocco_2010_GSHS_FS.pdf?ua=1.

22. GSHS (2012). Global School-based Student Health Survey (GSHS): Sudan 2012 Fact Sheet. Available from: http://www.who.int/chp/gshs/2012_Sudan_GSHS_FS.pdf?ua=1.

23. GSHS (2008). Global School-based Student Health Survey (GSHS): Yemen 2008 Fact Sheet. Available from: http://www.who.int/chp/gshs/2008_Yemen_fact_sheet.pdf?ua=1.

24. GSHS (2007). Global School-based Student Health Survey (GSHS): Djibouti 2007 Fact Sheet. Available from: http://www.who.int/chp/gshs/Djibouti_2007_Fact_Sheet.pdf?ua=1.

25. GSHS (2007). Global School-based Student Health Survey (GSHS): Jordan 2007 Fact Sheet. Available from: http://www.who.int/chp/gshs/gshs_fs_jordan_2007.pdf?ua=1.

26. Aounallah-Skhiri H, El Ati J, Traissac P, Ben Romdhane H, Eymard-Duvernay S, Delpeuch F, et al. (2012). Blood pressure and associated factors in a North African adolescent population: a national cross-sectional study in Tunisia. BMC Public Health. 12(1):98. http://dx.doi.org/10.1186/1471-2458-12-98 PMID:22305045

27. GSHS (2010). Global School-based Student Health Survey (GSHS): Syria 2010 Fact Sheet. Available from: http://www.who.int/chp/gshs/Syria_2010_GSHS_FS.pdf?ua=1.

28. GSHS (2011). Global School-based Student Health Survey (GSHS): Lebanon 2011 Fact Sheet. Available from: http://www.who.int/chp/gshs/2011_GSHS_FS_Lebanon.pdf?ua=1.

29. GSHS (2011). Global School-based Student Health Survey (GSHS): Egypt 2011 Fact Sheet. Available from: http://www.who.int/chp/gshs/Egypt_GSHS_FS_2011.pdf?ua=1.

30. GSHS (2012). Global School-based Student Health Survey (GSHS): Iraq 2012 Fact Sheet. Available from: http://www.who.int/chp/gshs/2012_Iraq_GSHS_FS.pdf?ua=1.

31. GSHS (2007). Global School-based Student Health Survey (GSHS): Libya 2007 Fact Sheet. Available from: http://www.who.int/chp/gshs/Libya_2007_fact_sheet.pdf?ua=1.

32. Bahreynian M, Motlagh ME, Qorbani M, Heshmat R, Ardalan G, Kelishadi R (2015). Prevalence of growth disorders in a nationally representative sample of Iranian adolescents according to socioeconomic status: the CASPIAN-III study. Pediatr Neonatol. 56(4):242–7. http://dx.doi.org/10.1016/j.pedneo.2014.12.001 PMID:25603727

33. Kelishadi R, Haghdoost A-A, Sadeghirad B, Khajehkazemi R (2014). Trend in the prevalence of obesity and overweight among Iranian children and adolescents: a systematic review and meta-analysis. Nutrition. 30(4):393–400. http://dx.doi.org/10.1016/j.nut.2013.08.011 PMID:24332523

34. Kelishadi R, Ardalan G, Gheiratmand R, Majdzadeh R, Hosseini M, Gouya MM, et al.; Caspian Study Group (2008). Thinness, overweight and obesity in a national sample of Iranian children and adolescents: CASPIAN Study. Child Care Health Dev. 34(1):44–54. PMID:18171443

35. Mirmohammadi S-J, Hafezi R, Mehrparvar AH, Rezaeian B, Akbari H (2011). Prevalence of overweight and obesity among Iranian school children in different ethnicities. Iran J Pediatr. 21(4):514–20. PMID:23056841

36. GSHS (2005). Global School-based Student Health Survey (GSHS): Lebanon 2005 Fact Sheet. Available from: http://www.who.int/chp/gshs/2005_Lebanon_Fact_Sheet.pdf?ua=1.

37. Nasreddine L, Naja F, Akl C, Chamieh MC, Karam S, Sibai AM, et al. (2014). Dietary, lifestyle and socio-economic correlates of overweight, obesity and central adiposity in Lebanese children and adolescents. Nutrients. 6(3):1038–62. http://dx.doi.org/10.3390/nu6031038 PMID:24618510

38. Aounallah-Skhiri H, El Ati J, Traissac P, Ben Romdhane H, Bougatef S, Béji C, et al. (2009). Evolution de la consommation alimentaire et de la corpulence des adolescents tunisiens entre 1996 et 2005. 4ème Congrès de la Société Française de Nutrition, Montpellier (France), 10–12 décembre 2009.

39. Republic of Yemen Ministry of Public Health and Population and Central Statistical Organization (2015). Yemen National Health and Demographic Survey 2013. Sana'a, Yemen: Ministry of Public Health and Population and Central Statistical Organization; Cairo, Egypt: Pan Arab Project for Family Health (PAPFAM); Rockville (MD), USA: The Demographic and Health Surveys (DHS) Program, ICF International. Available from: https://dhsprogram.com/pubs/pdf/FR296/FR296.pdf.

40. Government of Sudan Federal Ministry of Health and Central Bureau of Statistics (2012). Sudan Household Health Survey – Round 2, 2010: national report. Khartoum, Sudan: Federal Ministry of Health and Central Bureau of Statistics. Available from: https://mics-surveys-prod.s3.amazonaws.com/MICS4/Middle%20East%20and%20North%20Africa/Sudan/2010/Final/Sudan%202010%20MICS_English.pdf.

41. Jordan Department of Statistics (2013). Jordan Population and Family Health Survey, 2012. Amman, Jordan: Department of Statistics; Calverton (MD), USA: ICF International. Available from: https://dhsprogram.com/pubs/pdf/FR282/FR282.pdf.

42. de Onis M, Blössner M, Borghi E (2010). Global prevalence and trends of overweight and obesity among preschool children. Am J Clin Nutr. 92(5):1257–64. http://dx.doi.org/10.3945/ajcn.2010.29786 PMID:20861173

43. Palestinian Central Bureau of Statistics (2013). Palestinian Family Survey, 2010: final report. Ramallah, Palestine: Palestinian Central Bureau of Statistics, UNICEF, and UNFPA. Available from: www.pcbs.gov.ps/Portals/_PCBS/Downloads/book1941.pdf.

44. Aga Khan University (2012). National Nutrition Survey Pakistan, 2011. Islamabad, Pakistan: Aga Khan University, Pakistan Medical Research Council (PMRC), Government of Pakistan, and UNICEF Pakistan. Available from: https://www.humanitarianresponse.info/system/files/documents/files/59_National Nutrition Survey-2011.pdf.

45. Ministère de la Santé, Maroc (2012). Enquête Nationale sur la Population et la Santé Familiale (ENPSF) 2011: rapport préliminaire. Rabat, Morocco: Ministère de la Santé, Direction de la Planification et des Ressources Financières, Division de la Planification et des Etudes, Service des Etudes et de l'Information Sanitaire. Available from: http://www.sante.gov.ma/Publications/Etudes_enquete/Documents/Rapport synthese_ENPSF-2011.pdf.

46. WHO (2015). Global database on child growth and malnutrition. Countries and territories. Geneva, Switzerland: World Health Organization. Available from: http://www.who.int/nutgrowthdb/database/countries/en/.

47. Iraq Central Statistics Organization and Kurdistan Regional Statistics Office (2012). Iraq Multiple Indicator Cluster Survey (MICS) 2011: final report. Baghdad, Iraq: Central Statistical Organization (CSO) and Kurdistan Regional Statistics Office (KRSO).

48. Tunisia Ministry of Development and International Cooperation (2013). Monitoring the situation of children and women in Tunisia, MICS 2011–2012: final report [in French]. Tunis, Tunisia: Ministry of Development and International Cooperation, National Institute of Statistics, and UNICEF. Available from: https://mics-surveys-prod.s3.amazonaws.com/MICS4/Middle%20East%20and%20North%20Africa/Tunisia/2011-2012/Final/Tunisia%202011-12%20MICS_French.pdf.

49. Egypt Ministry of Health and Population (2014). Egypt Demographic and Health Survey (EDHS) 2014: main findings. Cairo, Egypt: Ministry of Health and Population; Rockville (MD), USA: The DHS Program, ICF International. Available from: http://dhsprogram.com/pubs/pdf/PR54/PR54.pdf.

50. League of Arab States and Syrian Arab Republic (2011). Family Health Survey of the Arab Republic of Syria, 2009: principal report (PAPFAM). Cairo, Egypt: League of Arab States.

51. Libyan National Center for Infectious and Chronic Disease Control and Pan Arab Project for Family Health (2008). Libyan National Survey of Family Health (PAPFAM), 2007. Cairo, Egypt: League of Arab States.

52. General Committee for Health and Social Security (1996). Libya Maternal and Child Health Survey 1995: preliminary report. Tripoli, Libya: General Committee for Health and Social Security; Cairo, Egypt: League of Arab States (PAPCHILD).

53. Ministère de la Santé Publique (2008). Enquête sur la santé et le bien être de la mère et l'enfant: MICS 3. Tunis, Tunisia: Ministère de la Santé Publique, Office National de la Famille et de la Population, and UNICEF.

54. League of Arab States (PAPFAM) and Syrian Arab Republic Central Bureau of Statistics (2002). The Family Health Survey in the Syrian Arab Republic: principal report. Cairo, Egypt: League of Arab States (PAPFAM) and Syrian Arab Republic, Office of the Prime Minister, Central Bureau of Statistics. Available from: http://s3.amazonaws.com/zanran_storage/www.un.org.sy/ContentPages/47530865.pdf.

55. Ministère de la Santé, Maroc (2005). Enquête sur la Population et la Santé Familiale (EPSF) 2003–2004. Rabat, Morocco: Ministère de la Santé; Calverton (MD), USA: ORC Macro. Available from: http://dhsprogram.com/pubs/pdf/FR155/FR155.pdf.

56. Arab League and Republic of Lebanon (2006). Lebanon Family Health Survey 2004: principal report. Tutelian M, Khayyat M, Monem AA, editors. Arab League, Lebanon Central Administration of Statistics, and Pan Arab Project for Family Health (PAPFAM). Available from: http://s3.amazonaws.com/zanran_storage/www.pdslebanon.org/ContentPages/2504898874.pdf.

57. El-Zanaty F, Way A (2009). Egypt Demographic and Health Survey 2008. Cairo, Egypt: Ministry of Health. Available from: https://dhsprogram.com/pubs/pdf/fr220/fr220.pdf.

58. Yemen Ministry of Health and Population (2004). Yemen Family Health Survey: principal report. Cairo, Egypt: Yemen Ministry of Health and Population, Central Statistical Organization, and League of Arab States (PAPFAM).

59. Government of National Unity and Government of South Sudan (2007). Sudan Household Health Survey (SHHS), 2006. Khartoum, Sudan: Government of National Unity; Juba, South Sudan: Government of South Sudan (additional analysis conducted by PAPFAM, June 2013).

60. FAO (2015). FAOSTAT: food and agriculture data. Food and Agriculture Organization of the United Nations. Available from: http://faostat3.fao.org/home/E.

61. Nasreddine L, Naja FA, Sibai AM, Helou K, Adra N, Hwalla N (2014). Trends in nutritional intakes and nutrition-related cardiovascular disease risk factors in Lebanon: the need for immediate action. J Med Liban. 62(2):83–91. http://dx.doi.org/10.12816/0004102 PMID:25011369

62. Kelishadi R, Gheisari A, Zare N, Farajian S, Shariatinejad K (2013). Salt intake and the association with blood pressure in young Iranian children: first report from the Middle East and North Africa. Int J Prev Med. 4(4):475–83. PMID:23671781

63. Ahmadi A, Moazen M, Mosallaei Z, Mohammadbeigi A, Amin-Iari F (2014). Nutrient intake and growth indices for children at kindergartens in Shiraz, Iran. J Pak Med Assoc. 64(3):316–21. PMID:24864607

64. Shab-Bidar S, Hosseini-Esfahani F, Mirmiran P, Hosseinpour-Niazi S, Azizi F (2014). Metabolic syndrome profiles, obesity measures and intake of dietary fatty acids in adults: Tehran Lipid and Glucose Study. J Hum Nutr Diet. 27(Suppl 2):98–108. http://dx.doi.org/10.1111/jhn.12117 PMID:23731333

65. Nasreddine L, Mehio-Sibai A, Mrayati M, Adra N, Hwalla N (2010). Adolescent obesity in Syria: prevalence and associated factors. Child Care Health Dev. 36(3):404–13. http://dx.doi.org/10.1111/j.1365-2214.2009.01042.x PMID:19961497

66. Afshin A, Micha R, Khatibzadeh S, Fahimi S, Shi P, Powles J, et al.; 2010 Global Burden of Diseases, Injuries, and Risk Factors Study: NUTRItrition and ChrOnic Diseases Expert Group (NUTRICODE), and Metabolic Risk Factors of ChrOnic Diseases Collaborating Group (2015). The impact of dietary habits and metabolic risk factors on cardiovascular and diabetes mortality in countries of the Middle East and North Africa in 2010: a comparative risk assessment analysis. BMJ Open. 5(5):e006385. http://dx.doi.org/10.1136/bmjopen-2014-006385 PMID:25995236

67. Chamieh MC, Moore HJ, Summerbell C, Tamim H, Sibai AM, Hwalla N (2015). Diet, physical activity and socio-economic disparities of obesity in Lebanese adults: findings from a national study. BMC Public Health. 15(1):279. http://dx.doi.org/10.1186/s12889-015-1605-9 PMID:25880751

68. Musaiger AO (2007). Overweight and obesity in the Arab countries: the need for action. Bahrain: Arab Center for Nutrition. Available from: www.acnut.com/v/images/stories/pdf/overweight_and_obesity_in_arab_countries.pdf.

69. Esmaillzadeh A, Azadbakht L (2008). Major dietary patterns in relation to general obesity and central adiposity among Iranian women. J Nutr. 138(2):358–63. PMID:18203904

70. Salehi-Abargouei A, Esmaillzadeh A, Azadbakht L, Keshteli AH, Feizi A, Feinle-Bisset C, et al. (2016). Nutrient patterns and their relation to general and abdominal obesity in Iranian adults: findings from the SEPAHAN study. Eur J Nutr. 55(2):505–18. http://dx.doi.org/10.1007/s00394-015-0867-4 PMID:25733164

71. Naja F, Nasreddine L, Itani L, Dimassi H, Sibai AM, Hwalla N (2014). Dietary patterns in cardiovascular diseases prevention and management: review of the evidence and recommendations for primary care physicians in Lebanon. J Med Liban. 62(2):92–9. http://dx.doi.org/10.12816/0004103 PMID:25011370

72. Jaweesh KS (2002). Television advertisements as a factor influencing children food habits. Arab J Food Nutr. 3(6):392–408.

73. Asfaw A (2007). Do government food price policies affect the prevalence of obesity? Empirical evidence from Egypt. World Dev. 35(4):687–701. http://dx.doi.org/10.1016/j.worlddev.2006.05.005

74. Caulfield LE, de Onis M, Blössner M, Black RE (2004). Undernutrition as an underlying cause of child deaths associated with diarrhea, pneumonia, malaria, and measles. Am J Clin Nutr. 80(1):193–8. PMID:15213048

75. Horta BL, Victora CG (2013). Long-term effects of breastfeeding: a systematic review. Geneva, Switzerland: World Health Organization. Available from: http://apps.who.int/iris/bitstream/10665/79198/1/9789241505307_eng.pdf.

76. Wilson AC, Forsyth JS, Greene SA, Irvine L, Hau C, Howie PW (1998). Relation of infant diet to childhood health: seven year follow up of cohort of children in Dundee infant feeding study. BMJ. 316(7124):21–5. http://dx.doi.org/10.1136/bmj.316.7124.21 PMID:9451261

77. Kassim IAR, Seal A, Moloney G, Erhardt J, Jooste P, et al. (2010). National Micronutrient and Anthropometric Nutrition Survey, Somalia 2009. Food Security and Nutrition Analysis Unit (FSNAU), Food and Agriculture Organization of the United Nations. Available from: http://www.humanitarianresponse.info/system/files/Somalia-National-Micronutrient-Study.pdf.

78. FAO (2014). Food and nutrition in numbers 2014. Food and Agriculture Organization of the United Nations. Available from: http://www.fao.org/3/a-i4175e.pdf.

79. Lebanon Central Administration of Statistics in and UNICEF Beirut (2009). Multiple Indicators Cluster Survey, round 3 (MICS3) Lebanon. Lebanon Central Administration of Statistics.

80. WHO (2014). Global Health Observatory data repository. Exclusive breastfeeding under 6 months: data by country. Geneva, Switzerland: World Health Organization. Available from: http://apps.who.int/gho/data/view.main.NUT1730?lang=eng.

81. Geneva Infant Feeding Association (IBFAN-GIFA) IBFAN Global Liaison Office (2014). The Convention on the Rights of the Child, Session 67/September 2014: Report on the situation of infant and young child feeding in Morocco. International Baby Food Action Network (IBFAN). Available from: http://tbinternet.ohchr.org/Treaties/CRC/Shared Documents/MAR/INT_CRC_NGO_MAR_17890_E.pdf.

82. Palestinian Central Bureau of Statistics (2015). Palestinian Multiple Indicator Cluster Survey (MICS) 2014: key findings. Ramallah, Palestine: Palestinian Central Bureau of Statistics. Available from: www.pcbs.gov.ps/Downloads/book2099.pdf.

83. UNICEF (2013). UNICEF Annual Report 2013 – Djibouti. Available from: http://www.unicef.org/about/annualreport/files/Djibouti_COAR_2013.pdf.

84. Kalantari N, Roudsari AH (2013). Breastfeeding promotion in Iran: opportunities and challenges. J Compr Pediatr. 3(5):165–6. http://dx.doi.org/10.17795/compreped-12327

85. Abdul Ameer AJ, Al-Hadi AH, Abdulla MM (2008). Knowledge, attitudes and practices of Iraqi mothers and family child-caring women regarding breastfeeding. East Mediterr Health J. 14(5):1003–14. PMID:19161071

86. Batal M, Boulghourjian C, Akik C (2010). Complementary feeding patterns in a developing country: a cross-sectional study across Lebanon. East Mediterr Health J. 16(2):180–6. PMID:20799572

87. Shembesh NM, Balo NNM, Singh R (1997). Breast-feeding and weaning patterns in Benghazi, Libyan Arab Jamahiriya. East Mediterr Health J. 3(2):251–7.

88. Kelishadi R, Pour MH, Sarraf-Zadegan N, Sadry GH, Ansari R, Alikhassy H, et al. (2003). Obesity and associated modifiable environmental factors in Iranian adolescents: Isfahan Healthy Heart Program - Heart Health Promotion from Childhood. Pediatr Int. 45(4):435–42. http://dx.doi.org/10.1046/j.1442-200X.2003.01738.x PMID:12911481

89. Fallahzadeh H, Golestan M, Rezvanian T, Ghasemian Z (2009). Breast-feeding history and overweight in 11 to 13-year-old children in Iran. World J Pediatr. 5(1):36–41. http://dx.doi.org/10.1007/s12519-009-0006-5 PMID:19172330

90. Musaiger AO (2011). Overweight and obesity in Eastern Mediterranean Region: prevalence and possible causes. J Obes. 2011:407237. http://dx.doi.org/10.1155/2011/407237 PMID:21941635

91. Ahmad MN, Tukan SK, Takruri HR (2006). Obesity and overweight in young adult females of Northern Badia of Jordan. Malays J Nutr. 12(2):157–66.

92. Ainy E, Azizi F (2007). Women, occupation and cardiovascular risk factors: findings from the Tehran Lipid and Glucose Study. Public Health. 121(12):950–3. http://dx.doi.org/10.1016/j.puhe.2006.12.016 PMID:17645903

93. Janghorbani M, Amini M, Willett WC, Mehdi Gouya M, Delavari A, Alikhani S, et al. (2007). First nationwide survey of prevalence of overweight, underweight, and abdominal obesity in Iranian adults. Obesity (Silver Spring). 15(11):2797–808. http://dx.doi.org/10.1038/oby.2007.332 PMID:18070771

94. Batnitzky A (2008). Obesity and household roles: gender and social class in Morocco. Sociol Health Illn. 30(3):445–62. http://dx.doi.org/10.1111/j.1467-9566.2007.01067.x PMID:18373507

95. Veghari G, Sedaghat M, Joshaghani H, Hoseini A, Niknezhad F, Angizeh A, et al. (2010). The prevalence of obesity and its related risk factor in the north of Iran in 2006. J Res Health Sci. 10(2):116–21. PMID:22911934

96. Tavassoli AA, Gharipour M, Khosravi A, Kelishadi R, Siadat ZD, Bahonar A, et al. (2010). Gender differences in obesogenic behaviour, socioeconomic and metabolic factors in a population-based sample of Iranians: the IHHP study. J Health Popul Nutr. 28(6):602–9. http://dx.doi.org/10.3329/jhpn.v28i6.6609 PMID:21261206

97. Mushtaq MU, Gull S, Abdullah HM, Shahid U, Shad MA, Akram J (2011). Prevalence and socioeconomic correlates of overweight and obesity among Pakistani primary school children. BMC Public Health. 11(1):724. http://dx.doi.org/10.1186/1471-2458-11-724 PMID:21943029

98. Al-Tawil NG, Abdulla MM, Abdul Ameer AJ (2007). Prevalence of and factors associated with overweight and obesity among a group of Iraqi women. East Mediterr Health J. 13(2):420–9. PMID:17684862

99. Musaiger AO, Shahbeek NE, Al-Mannai M (2004). The role of social factors and weight status in ideal body-shape preferences as perceived by Arab women. J Biosoc Sci. 36(6):699–707. http://dx.doi.org/10.1017/S0021932003006412 PMID:15535459

100. Rguibi M, Belahsen R (2004). Overweight and obesity among urban Sahraoui women of South Morocco. Ethn Dis. 14(4):542–7. PMID:15724774

101. Musaiger AO, Qashqari K (2005). The relation between dressing and obesity among women in Saudi Arabia. Arab J Food Nutr. 6:292–302.

102. Abdollahi P, Mann T (2001). Eating disorder symptoms and body image concerns in Iran: comparisons between Iranian women in Iran and in America. Int J Eat Disord. 30(3):259–68. http://dx.doi.org/10.1002/eat.1083 PMID:11746285

103. Mirkin B (2010). Population levels, trends and policies in the Arab region: challenges and opportunities. Arab Human Development Report research paper series. United Nations Development Programme, Regional Bureau for Arab States. Available from: www.undp.org/content/dam/rbas/report/Population%20Levels,Trends.pdf.

104. Misra A, Khurana L (2008). Obesity and the metabolic syndrome in developing countries. J Clin Endocrinol Metab. 93(11 Suppl 1): S9–30. http://dx.doi.org/10.1210/jc.2008-1595 PMID:18987276

105. Monteiro CA, Moura EC, Conde WL, Popkin BM (2004). Socioeconomic status and obesity in adult populations of developing countries: a review. Bull World Health Organ. 82(12):940–6. PMID:15654409

106. Galal OM (2002). The nutrition transition in Egypt: obesity, undernutrition and the food consumption context. Public Health Nutr. 5(1A):141–8. http://dx.doi.org/10.1079/PHN2001286 PMID:12027277

107. Benjelloun S (2002). Nutrition transition in Morocco. Public Health Nutr. 5(1A):135–40. http://dx.doi.org/10.1079/PHN2001285 PMID:12027276

108. Abdul-Rahim HF, Holmboe-Ottesen G, Stene LCM, Husseini A, Giacaman R, Jervell J, et al. (2003). Obesity in a rural and an urban Palestinian West Bank population. Int J Obes Relat Metab Disord. 27(1):140–6. http://dx.doi.org/10.1038/sj.ijo.0802160 PMID:12532166

109. Esmaeily H, Azimi-Nezhad M, Ghayour-Mobarhan M, Parizadeh M-R, Safarian M, Parizadeh M-J, et al. (2009). Association between socioeconomic factors and obesity in Iran. Pak J Nutr. 8(1):53–6. http://dx.doi.org/10.3923/pjn.2009.53.56

110. Al-Hazzaa HM (2004). The public health burden of physical inactivity in Saudi Arabia. J Family Community Med. 11(2):45–51. PMID:23012048

111. WHO (2010). Global Health Observatory (GHO) data. Prevalence of insufficient physical activity: by country. Geneva, Switzerland: World Health Organization. Available from: http://www.who.int/gho/ncd/risk_factors/physical_activity/en/.

112. Guthold R, Cowan MJ, Autenrieth CS, Kann L, Riley LM (2010). Physical activity and sedentary behavior among schoolchildren: a 34-country comparison. J Pediatr. 157(1):43–49.e1. http://dx.doi.org/10.1016/j.jpeds.2010.01.019 PMID:20304415

113. Musaiger AO, Al-Hazzaa HM (2012). Prevalence and risk factors associated with nutrition-related noncommunicable diseases in the Eastern Mediterranean region. Int J Gen Med. 5:199–217. http://dx.doi.org/10.2147/IJGM.S29663 PMID:22399864

114. Yount KM, Sibai AM (2009). The demography of aging in Arab societies. In: Uhlenberg P, editor. International handbook of the demography of aging. 9th ed. Dordrecht, Netherlands: Springer. http://dx.doi.org/10.1007/978-1-4020-8356-3_13

115. Musaiger AO, Al-Ansari MS (2000). Barriers to practicing physical activity in the Arab countries. In: Musaiger AO, Meladi SS, editors. Nutrition and physical activity in the Arab countries of the Near East. Cairo, Egypt: FAO Regional Office.

116. Amarasinghe A, D'Souza G (2012). Individual, social, economic, and environmental model: a paradigm shift for obesity prevention. ISRN Public Health. 2012:571803. http://dx.doi.org/10.5402/2012/571803

CHAPTER 9.

Potential mechanisms in childhood obesity: causes and prevention

Youfa Wang

This chapter reviews the scientific evidence on obesity in children. It provides a synthesis of research findings, including the scope of the global problem, prevalence trends, risk factors, prevention, and recommendations made by leading experts and health organizations. In this chapter, we use "children" to mean both children and adolescents, including the age range 0–19 years.

Childhood obesity rates have increased over the past two decades in most countries worldwide, while the prevalence seems to have plateaued in certain high-income countries [1]. This stabilization in some high-income countries is due in part to campaigns and policy changes made by those countries within the past decade. The trends in childhood obesity rates and the large variations in the rates and trends between countries provide useful insights into the drivers of the epidemic. Multiple biological, behavioural, family, and societal factors affect a child's risk of developing obesity. Because children are different from adults, special attention and efforts are needed to help them develop healthy eating patterns and physical activity behaviours and maintain an optimal body weight. Furthermore, childhood is an important stage in life at which to tackle the obesity epidemic, considering that childhood obesity tends to track into adulthood.

The global childhood obesity epidemic: trends and variation between countries

The obesity epidemic has become a global public health crisis. Childhood obesity (including overweight and obesity) is an important contributor to adult obesity, diabetes, and other noncommunicable chronic diseases worldwide. Data have shown a substantial increase during the past three decades in the prevalence of obesity in children in both high-income countries and low- and middle-income countries, although there are large differences between countries in the prevalence rates and increasing trends [2–7]. Over the past two decades, many developing countries, such as Mexico, China, and Brazil, have experienced an increase in the prevalence of obesity that is more rapid than the increase in some developed countries, even though the prevalence rates are lower in developing countries. This suggests that childhood obesity is a growing problem in many developing countries, and thus it is an opportune moment for researchers to intervene.

A recent comprehensive study estimated the global, regional, and national prevalence of overweight and obesity in children and adults in 1980–2013 using data collected from a large number of countries [6].

The study reported that the prevalence had increased substantially in children in developed countries; in 2013, 23.8% (95% uncertainty interval [UI], 22.9–24.7%) of boys and 22.6% (95% UI, 21.7–23.6%) of girls were overweight or obese. The prevalence had also increased in children in developing countries from 1980 to 2013, for boys from 8.1% (95% UI, 7.7–8.6%) to 12.9% (95% UI, 12.3–13.5%) and for girls from 8.4% (95% UI, 8.1–8.8%) to 13.4% (95% UI, 13.0–13.9%). A large variation in the prevalence between countries was observed. The study concluded that obesity has become a major global health challenge; not only is the prevalence of obesity increasing, but also no national success stories have been reported during the past three decades. Urgent global action is needed to help countries to intervene effectively. Some of the study's conclusions are consistent with those of a previous study based on findings from approximately 75 countries, which also projected that the prevalence of childhood obesity would continue to increase unless effective programmes were implemented [7].

Recent data indicate that the prevalence of childhood obesity in some developed countries (e.g. some European countries and the USA) seems to have reached a plateau [1, 5, 8]. The stabilization is thought to be a result of programmes, including national policies, designed to prevent childhood obesity in those countries.

The global patterns of the childhood obesity epidemic (consistent increasing trends in a large number of countries, the large variations in the prevalence of obesity by country, the increasing trends within countries, and the levelling off or decline in some developed countries) also provide useful insights into the causes of the problem.

Causes and drivers of the global childhood obesity epidemic

Obesity is a result of a positive energy balance (i.e. energy intake that exceeds energy expenditure). Many factors affect an individual's eating and physical activity behaviours. The factors are more complex for children than for adults, because of the many differences between them. Many factors have contributed to the increase in the prevalence of obesity in children. Briefly, these factors include unhealthy eating patterns, lack of physical activity, increased sedentary behaviours (i.e. screen time), and short sleep duration (which results in a positive energy balance, and thus excessive weight gain), as well as other factors, such as parenting and family factors, school factors, social norms, and community food and physical activity environments that affect children's eating and physical activity behaviours [4, 9, 10].

During recent years, researchers and key related public health organizations, including the World Health Organization (WHO) and the United States Institute of Medicine (now known as the National Academy of Medicine), have argued that the increase in the prevalence of childhood obesity results from many changes in society; in particular, it is due to social and economic development and policies in the areas of agriculture, transportation, urban planning, the environment, education, and food processing, distribution, and marketing. These factors have contributed to unhealthy eating patterns, lack of physical activity, and increased sedentary behaviours in children. The worldwide increases in the prevalence of childhood obesity are attributable to a global shift in dietary patterns towards increased intake of energy-dense foods that are high in fats (saturated and trans-fatty acids) and in sugars but low in other, healthy micronutrients. The trend towards decreased physical activity levels – because of the increasingly sedentary nature of recreational activities, changing modes of transportation, and urbanization – is an additional driver that compounds the global childhood obesity epidemic [5].

Table 9.1 lists a set of risk factors for excessive weight gain in children. Some of the biological, genetic, life-stage, lifestyle, and environmental risk factors are highlighted here.

Genetic factors (and gene–environment interactions)

A large body of evidence, including studies on twins, siblings, nuclear families, and extended pedigrees, has shown the heritability of obesity, including measures of body mass index (BMI) and body fat, especially in twin studies [11–13]. Advances in genotyping technologies have raised hopes and expectations that genetic testing will pave the way to personalized medicine and that complex traits such as obesity will be prevented even before birth [11]. For example, a recent systematic review and meta-regression analysis examined BMI heritability and differences in BMI heritability by population characteristics, such as sex, age, time period of observation, and average BMI, as well as by broad national-level socioenvironmental factors [13]. Based on findings from 32 twin studies in various countries worldwide, BMI heritability was found to range from approximately 30% to 90%, and the heterogeneity of BMI heritability was found to be significantly attributable to differences in study subjects' age, time period of observation, average BMI, and the economic development levels of the study populations.

Given the shifts in people's dietary and physical activity patterns under the influence of obesogenic

Table 9.1. Risk factors contributing to excessive weight gain in children

Category	Specific factors and examples
Genetic and biological predisposition	Some minority ethnic groups (e.g. Native Americans in the USA), high birth weight, rapid weight gain during infancy, early adiposity rebound
Dietary intake/food choices	Child feeding practices, energy intake, energy density of diet, consumption of sugar-sweetened beverages, large portion size, snacking
Physical activity and sedentary behaviours	Screen time, automobile use for transportation, decline in walking/cycling to school
Parental and family characteristics	Low family socioeconomic status in developed countries, high-income groups in developing countries, parental obesity, maternal diabetes, smoking during pregnancy, mothers who were overweight before the pregnancy, social deprivation, parenting practices, parental eating patterns and physical activity
Environmental risk factors	Community and school environments that contribute to energy overconsumption and inadequate physical activity, fast-food outlets, lack of park and recreation space, lack of health clubs, technological development
Factors with conflicting evidence or lack of adequate evidence (partially due to limited research)	Gut microbiota, duration of breastfeeding, maternal parity, maternal marital status at birth, delivery type, gestational weight gain, maternal postpartum weight loss, social norms, peer influence, ideal body type

environments, the fact that not all children become obese indicates the presence of susceptibility and resistance, as well as the importance of the effect of the interaction between genetic and environmental factors on development of childhood obesity. Paediatric obesity is a complex phenotype and is modulated by unique gene–environment interactions that occur during early periods of life. Susceptibility could be mediated through a failure of appetite regulation, leading to increased energy intake, or via diminished energy expenditure.

Risk factors during early life stages, including prenatal factors

Experiences during early life stages (including prenatal factors, such as exposures that women experience, and postnatal factors, such as infant and young child feeding) can have important, long-term impacts on future health. According to the International Society for Developmental Origins of Health and Disease (DOHaD Society), a poor start to life is associated with an increased risk of several disorders, especially non-communicable diseases, throughout the life-course [14]. These diseases include obesity, cardiovascular disease, type 2 diabetes, osteoporosis, some forms of cancer, and some other diseases. The environmental exposures that affect future health and disease risk include parental lifestyle and diet, smoking, obesity, and exposure to chemicals that are endocrine disrupters or toxins. A growing body of evidence supports the statement of the DOHaD Society and argues for related interventions that target women, including young women, to ensure better pregnancy outcomes [14].

Many studies have been conducted to examine the effects of early-life factors on the risk of childhood obesity. Both prenatal factors, such as gestational weight gain, and postnatal factors, such as feeding practices during infancy, have been studied. Gestational weight gain is used as an indicator of prenatal factors. Research suggests that the offspring of overweight or obese women tend to have higher birth weights and more body fat, and have increased risks of developing obesity later in life [15]. A recent meta-analysis of findings from 12 cohort studies reported that the risk of childhood overweight/obesity was significantly associated with excessive gestational weight gain. The combined odds ratio of excessive gestational weight gain and childhood overweight/obesity was 1.33 (95% confidence interval [CI], 1.18–1.50). The association was found to be robust. Adjustment for maternal BMI, investigation area, age of children, research type, and omission of any single study had little effect on the pooled estimate [16]. The mother–child association for childhood obesity may be partly related to the increased risk of gestational diabetes [15, 17].

A 2012 systematic review and meta-analysis examined the risk factors for childhood obesity that can be identified during infancy based on findings from 30 prospective observational studies that followed up children from birth to at least age 2 years [18]. The study reported significant and strong independent associations between childhood obesity and mothers who were overweight before the pregnancy, high infant birth weight, and rapid weight gain during the first year of life. The meta-analysis compared breastfed infants with non-breastfed infants and found a 15% decrease for breastfed infants in the likelihood of childhood overweight

(adjusted odds ratio, 0.85; 95% CI, 0.74–0.99; I^2 = 73.3%; n = 10). For children of mothers who smoked during pregnancy, there was a 47% increase in the likelihood of childhood overweight (adjusted odds ratio, 1.47; 95% CI, 1.26–1.73; I^2 = 47.5%; n = 7). The study reported that there was some evidence that the early introduction of solid foods was associated with childhood overweight. Conflicting evidence was found for duration of breastfeeding, socioeconomic status at birth, maternal parity, and maternal marital status at birth. There was inconclusive evidence (due to the limited number of studies) for delivery type, gestational weight gain, maternal postpartum weight loss, and "fussy" infant temperament [18].

A systematic review of 10 studies investigated the relationship between the types of food consumed by infants during the complementary feeding period and risk of overweight/obesity during childhood. The review concluded that high intakes of energy and protein, particularly dairy protein, during infancy could be associated with an increase in BMI and body fatness [19]. Another recent systematic review of 23 studies concluded that there is no clear association between the timing of the introduction of complementary foods and risk of childhood obesity, but that some evidence suggests that very early introduction of complementary foods (before age 4 months), rather than at age 4–6 months or after age 6 months, may increase the risk of childhood obesity [20].

Family environment, socioeconomic status, and parenting

Family environment is important for children's health behaviours and outcomes. The relationship between family socioeconomic status and obesity is complex, has changed over time, and varies between countries and even between population groups within the same country [21, 22]. In developed countries, children from a family with low socioeconomic status are more likely to be obese [23], whereas in developing countries, children from a family with higher socioeconomic status have a higher risk of being overweight or obese [24, 25].

The role of the environment in the link between parental obesity and child obesity is difficult to study directly and to quantify, but two lines of evidence suggest a non-genetic component: (i) studies that document dramatic increases in the prevalence of childhood obesity in developing countries where the populations adopt lifestyles typical of industrialized countries; and (ii) studies in developing countries that document the coexistence of underweight and overweight within the same family [26].

A growing number of studies are attempting to examine the effects of parenting practices on childhood obesity, but the understanding remains very limited [27–29].

Lifestyle factors

Dietary intake

Unhealthy dietary patterns, such as those that include energy-dense fast foods and processed foods, are risk factors for obesity [4]. Research, including intervention trials, has indicated that the consumption of sugar-sweetened beverages and the fructose they contain increases the risk of obesity and has contributed to the rising epidemic of childhood obesity [30–32]. Meta-analyses suggest that consumption of sugar-sweetened beverages may increase the risks of obesity, diabetes, metabolic syndrome, and cardiovascular disease in both children and adults [30, 32].

Short sleep duration

Systematic reviews and meta-analyses have reported an association between short sleep duration and risk of obesity in children [33, 34]. Recently, Fatima et al. reviewed 22 longitudinal studies, with subjects from diverse backgrounds, and reported an inverse association between sleep duration and BMI. The meta-analysis of 11 longitudinal studies, including 24 821 participants, showed that children who slept for a short duration had twice the risk of being overweight/obese compared with children who slept for a long duration (odds ratio, 2.15; 95% CI, 1.64–2.81) [33].

Screen time

Screen time is a major source of inactivity among children in many countries. Recently, the source of increased screen time has shifted from television viewing to the use of other devices, including smartphones and tablets. Previously, well-documented evidence, including from intervention trials, has linked time spent watching television with risk of obesity in children [35]. It is likely that the increasing use and influence of social media in children's lives have also affected their eating patterns and physical activity behaviours, and thus could affect their weight. However, few recent studies have examined the impact of overall screen time and the impact of social media on risk of obesity in children.

Snacking

Children eat snacks often, which may contribute to their total energy consumption, especially in developed countries. The types of foods commonly consumed as snacks are often high in fats (saturated and trans-fatty acids) or sugars (i.e. potato chips, cookies) and thus add

considerably to daily energy intake and may affect energy balance.

Built and social environments

Built environment

The local community and school food environments, facilities, and services affect children's eating and physical activity behaviours. Children may buy food and beverage products from food stores close to home and school. School nutrition services, in particular school lunch, and school physical education affect children's energy balance. In addition, parental concerns about safety issues may limit a child's ability to play outdoors or walk to school.

Social norms and body image

Social norms affect people's behaviours, including eating and physical activity. Peer influence as a part of social norms may have an even greater impact on adolescents. Differences exist between countries and between ethnic groups with respect to ideal body type.

Other risk factors

Adiposity rebound

The timing of the adiposity rebound (the rebound in BMI in childhood) predicts later obesity. An early adiposity rebound in childhood predicts higher BMI levels in adolescence and adulthood and an increased risk for children of becoming obese as adults [36, 37].

The gut microbiota, prebiotics, and probiotics

Recent evidence suggests that the gut microbiota is involved in the control of body weight, energy homeostasis, and inflammation, and thus plays a role in risk of obesity; prebiotics and probiotics have physiological functions that contribute to changes in the composition of the gut microbiota and may also affect appetite and weight status [38].

Stress

Some research suggests that stress during childhood and adolescence, including peer influence, is associated with obesity risk, but this is still not well understood [39, 40]. It has been suggested that high levels of stress may change eating patterns and increase consumption of highly palatable foods. Repeated high levels of stress and/or chronic stress may alter the biology of stress regulation and appetite/energy regulation; both of these components directly affect neural mechanisms that contribute to stress-induced and food cue-induced overeating of highly palatable foods [40].

Prevention of childhood obesity

Many studies have examined the prevention and management of obesity in children. Most of these studies have been conducted in high-income countries, and very little is known about the situation in low- and middle-income countries. Nevertheless, many useful lessons have been learned and some recommendations have been made (Table 9.2). The growing obesity problem is societal, and thus it demands a population-based, multisectoral, multidisciplinary, and culturally relevant approach [41]. Unlike most adults, children do not have much power to choose the environment in which they live and the food they eat. Furthermore, they also have a limited ability to understand the long-term consequences of their behaviours. Therefore, special attention and efforts are needed to help them develop healthy lifelong habits, to prevent obesity.

Various interventions conducted in countries worldwide have been reviewed to determine which programmes are successful and what research is needed for the prevention of childhood obesity [42, 5, 43, 44]. Many studies have been conducted to study prevention of childhood obesity, and mixed results have been reported [44–46]. Adequate evidence has been accumulated to support that interventions, especially school-based programmes, could be effective in preventing childhood obesity. Even if some of the interventions cannot reduce the prevalence of childhood obesity, they may still result in beneficial changes in other health outcomes, such as lowered blood pressure and improved blood lipid profile, as shown by recent systematic reviews and meta-analyses [42, 45–48].

In the most comprehensive systematic examination of childhood obesity prevention studies reported to date, the effectiveness of various childhood obesity prevention programmes was evaluated [42, 44, 47, 48]. The findings could help various stakeholders to understand the effectiveness of obesity prevention programmes for children and offer insights for future research and intervention development. The evaluation assessed 139 studies conducted in multiple settings in high-income countries during the past three decades, focusing on adiposity-related outcomes and strength of evidence. The strength of evidence varied by intervention strategy and setting. There was at least moderate evidence for school-based interventions, and about 50% of them reported statistically significant desirable effects for adiposity-related measures. The school-based studies that also included a home-based component had the highest proportion of studies with favourable results. Also, interventions conducted in multiple settings had more favourable

Table 9.2. Recommendations for promoting healthy eating and physical activity for obesity prevention in young people[a]

Setting	Age group	Recommendations related to nutrition	Recommendations related to physical activity
Home	Infants and young children	• Breastfeed exclusively for the first 6 months of life. • Continuously breastfeed until age 2 years and beyond, complemented with a variety of adequate, safe, and nutrient-dense complementary foods. • Avoid the use of added sugars and starches when feeding formula. • Accept the child's ability to regulate energy intake rather than feeding until the plate is empty. • Ensure the appropriate micronutrient intake needed to promote optimal linear growth. • Avoid rewarding children with candies.	• Daily "tummy time" for infants younger than 6 months. • Adult–infant interactions on the ground each day. • Free exploration under adult supervision. • Parents joining children in physical activity. • Avoid punishing children for being physically active and withholding physical activity as a punishment.
	Children and adolescents	• Provide a healthy breakfast before each school day. • Serve healthy school snacks to children (whole grains, vegetables, and fruits). • Promote intake of fruits and vegetables. • Restrict intake of energy-dense, micronutrient-poor foods. • Restrict intake of sugar-sweetened beverages. • Ensure opportunities for family meals. • Limit exposure to marketing practices. • Teach children to resist temptation and marketing strategies. • Provide information and skills to make healthy food choices.	• Reduce non-active time (e.g. television viewing, computer use). • Encourage safe walking/bicycling to school and to other social activities. • Make physical activity part of the family's daily routine, such as designating time for family walks or playing active games together. • Ensure that the activity is age-appropriate, and provide protective equipment such as helmets, wrist pads, and knee pads.
Childcare/ school	Infants and young children	• Provide school food programmes to increase the availability of healthy food in schools. • Ensure that food served in schools adheres to minimum nutrition standards. • Promote parental involvement.	• Use cribs, car seats, and high chairs for their primary use only. • Limit use of equipment (strollers, swings, and bouncer seats). • Implement activities for toddlers and preschoolers that limit sitting or standing to no more than 30 minutes at a time.
	Children and adolescents	• Provide health education to help students acquire knowledge, attitudes, beliefs, and skills that are needed to make informed decisions, practise healthy behaviours, and create conditions that are conducive to health. • Provide school food programmes to increase the availability of healthy food in schools. • Have vending machines only if they sell healthy options, such as water, milks, juices without added sugars, fruits and vegetables, sandwiches, and low-fat snacks. • Ensure that food served in schools adheres to minimum nutrition standards. • Provide school health services for students and staff of the school, to help foster health and well-being as well as prevent, reduce, monitor, treat, and refer important health problems or conditions for students and staff of the school. • Use school gardens as a tool to develop awareness about food origins. • Promote parental involvement.	• Offer daily physical education classes with a variety of activities, so that the maximum number of students' needs, interests, and abilities are addressed. • Offer extracurricular activities. • Encourage safe, non-motorized modes of transportation to school and other social activities. • Provide access to adequate physical activity facilities to students and the community. • Encourage students, teachers, parents, and the community to become physically active.
Health-care providers	All ages	• Monitor growth in children (consider the rate of weight gain, body mass index [BMI], and parental weight status as risk factors for later obesity). • Address weight management and lifestyle issues with all patients, regardless of presenting weight, at least once a year. • Counsel on the following: (i) limiting consumption of sugar-sweetened beverages; (ii) encouraging diets with recommended quantities of fruits and vegetables; (iii) eating breakfast daily; (iv) limiting eating at restaurants, particularly fast-food restaurants; (v) encouraging family meals in which parents and children eat together; and (vi) limiting portion sizes.	• Counsel parents and children's caregivers on the following: (i) not to permit televisions, computers, or other digital media devices in children's bedrooms or other sleeping areas; (ii) eating a diet rich in calcium; (iii) eating a diet high in fibre; (iv) eating a diet with balanced macronutrients; (v) initiating and maintaining breastfeeding; (vi) participating in 60 minutes of moderate to vigorous physical activity per day for children of healthy weight; and (vii) limiting consumption of energy-dense foods.

Table 9.2. Recommendations for promoting healthy eating and physical activity for obesity prevention in young people[a] (continued)

Setting	Age group	Recommendations related to nutrition	Recommendations related to physical activity
Policies and regulations	All ages	• Develop and implement assistance programmes to facilitate healthy eating and physical activity for low-income and vulnerable populations. • Establish and monitor the implementation of uniform voluntary national nutrition and marketing standards for food and beverage products marketed to children. • Have sound economic development plans and urban planning to create healthful environments and facilitate healthy eating and physical activity behaviours.	

[a] Some of these are based on experts' opinions.

Sources: WHO (2017) [41], Barlow and the Expert Committee (2007) [49], Davis et al. (2007) [50], IOM (2011) [51].

outcomes than single-setting interventions. The interventions with the highest strength of evidence were physical activity-only interventions delivered in schools with home involvement and combined diet–physical activity interventions delivered in schools with both home and community components. Overall, a greater proportion of multisetting studies demonstrated significant and beneficial results compared with single-setting interventions. For all settings combined, the highest proportion of significant and favourable impacts on adiposity-related outcomes was attributable to diet-only interventions, whereas the lowest proportion of successes was for physical activity-only interventions. The strength of evidence for the effectiveness of interventions in settings other than schools and homes was insufficient.

Both healthy eating and physical activity should be targeted in obesity prevention. Some researchers have argued that it may be more feasible and effective to target energy intake control by use of national policies. Nutrition policies are needed to tackle childhood obesity, promote healthy growth, ensure nutritional security in every household, and protect children from lifestyle choices that lead to inactivity or to the overconsumption of foods with poor nutritional quality [5]. Public health efforts are needed to protect children from the marketing of sedentary activities and energy-dense, nutrient-poor foods and beverages. The governance of food supply and food markets should be improved, and commercial activities need to be monitored and regulated. Childhood obesity prevention efforts need to be broadened to include interventions that change the nature of the food and consumer environment, including the availability, price, and formulation of different types of food products and the marketing practices that influence food choices and preference.

Conclusions

Multiple factors at the individual, family, school, society, and global levels affect children's energy balance-related behaviours and have contributed to the increases in the prevalence of childhood obesity worldwide. Although genetic factors play an important role in affecting individuals' susceptibility to developing obesity, environmental factors should be the key targets of intervention efforts to fight the epidemic, because they are modifiable.

To prevent obesity, it is recommended that children should do the following: (i) increase consumption of fruits and vegetables, legumes, whole grains, and nuts; (ii) limit energy intake; (iii) limit the intake of high-energy-density foods, such as fried foods, fast foods, processed foods, and sugars, as well as sugar-sweetened beverages; and (iv) be physically active and reduce sedentary behaviours, to accumulate at least 60 minutes of moderate to vigorous activity each day and to limit screen time.

Of greater urgency and importance is developing sustainable and effective interventions to control the childhood obesity epidemic; the collaboration and strong commitment of government, industry, and other stakeholders is needed. These stakeholders can and should play key roles in creating healthy environments by facilitating the availability of healthier options that improve eating patterns and physical activity behaviours among children.

Key points

- Childhood obesity rates have increased over the past two decades in most countries worldwide, while the prevalence seems to have reached a plateau in some high-income countries in recent years, due in part to national campaigns, including policy changes.
- In developed countries in 2013, about 23% of children were overweight or obese.
- The trends in childhood obesity rates and the large variations in the rates and trends between countries provide useful insights into the drivers of the epidemic.
- Many factors have contributed to the increase in the prevalence of obesity in children, including unhealthy eating patterns, lack of physical activity, increased sedentary behaviours (i.e. screen time), and shorter sleep duration, as well as other factors, such as parenting and family factors, school factors, social norms, and community food and physical activity environments that affect children's eating and physical activity behaviours.
- Experiences during early life stages (including prenatal factors, such as exposures that women experience, and postnatal factors, such as infant and young child feeding) can have important, long-term impacts on future health, including risk of obesity.
- Family environment is important for children's health behaviours and outcomes. The relationship between family socioeconomic status and obesity is complex, has changed over time, and varies between population groups and between countries.
- The global childhood obesity epidemic demands a population-based, multisectoral, multidisciplinary, and culturally relevant approach. Children need assistance and special efforts to help them develop healthy eating patterns and physical activity behaviours and maintain an optimal body weight.
- To prevent obesity, it is recommended that children should: (i) increase consumption of fruits and vegetables, legumes, whole grains, and nuts; (ii) limit energy intake; (iii) limit the intake of high-energy-density foods, such as fried foods, fast foods, processed foods, and sugars, as well as sugar-sweetened beverages; and (iv) be physically active and reduce sedentary behaviours (accumulate at least 60 minutes of moderate to vigorous activity each day, and limit screen time).

Research needs

The following list is based on the recommendations from Wang et al. (2015) [42].

- Further research is needed on the key drivers of the childhood obesity epidemic worldwide, their relative effects, and the differences between countries and between population groups within countries.
- Studies are lacking on the changing roles of family and parents and how these affect childhood obesity. Given the many social and environmental changes, including technological development and changes in the labour force, it is likely that parental and family roles may have changed.
- Intervention studies conducted in non-school-based settings are needed. The literature on interventions that do not include a school component is sparse. More studies are needed that test environmental and policy-based interventions. Also, very few preventive studies have taken place in clinical settings, such as within a primary care practice. Primary health-care providers could play an important role in the prevention and management of childhood obesity.
- Innovative study design and intervention approaches are needed. Drawing on established behavioural theories and using innovative intervention strategies when designing interventions may help to increase their success in prevention of childhood obesity.
- Systems science-guided intervention studies are needed. Obesity is the result of a complex mixture of biological, behavioural, social, economic, and environmental factors. An effective and sustainable strategy for obesity prevention may have to target many factors. Applying a systems science approach in intervention design, implementation, and evaluation can take into account multiple risk factors as well as the complex interactions and feedback loops between them.
- The cost–effectiveness of interventions should be assessed. Cost–effectiveness analyses will add important value to the evaluation of an intervention and are also important for the promotion and dissemination of effective interventions.
- The implementation of intervention programmes may also have potential harms, such as unintentionally increasing weight-based stigma when programmes are implemented on a large scale for many children. Few studies have assessed and reported on potential harms.
- There are many promising opportunities and also challenges for international collaboration on childhood obesity prevention. More research is needed to learn about how to effectively facilitate such collaboration and overcome the barriers.

References

1. Wabitsch M, Moss A, Kromeyer-Hauschild K (2014). Unexpected plateauing of childhood obesity rates in developed countries. BMC Med. 12(1):17. http://dx.doi.org/10.1186/1741-7015-12-17 PMID:24485015

2. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, de Onis M, et al.; Maternal and Child Nutrition Study Group (2013). Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet. 382(9890):427–51. http://dx.doi.org/10.1016/S0140-6736(13)60937-X PMID:23746772

3. de Onis M, Blössner M, Borghi E (2010). Global prevalence and trends of overweight and obesity among preschool children. Am J Clin Nutr. 92(5):1257–64. http://dx.doi.org/10.3945/ajcn.2010.29786 PMID:20861173

4. Lobstein T, Baur L, Uauy R; IASO International Obesity TaskForce (2004). Obesity in children and young people: a crisis in public health. Obes Rev. 5(Suppl 1):4–104. http://dx.doi.org/10.1111/j.1467-789X.2004.00133.x PMID:15096099

5. Lobstein T, Jackson-Leach R, Moodie ML, Hall KD, Gortmaker SL, Swinburn BA, et al. (2015). Child and adolescent obesity: part of a bigger picture. Lancet. 385(9986):2510–20. http://dx.doi.org/10.1016/S0140-6736(14)61746-3 PMID:25703114

6. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. (2014). Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 384(9945):766–81. http://dx.doi.org/10.1016/S0140-6736(14)60460-8 PMID:25155414

7. Wang Y, Lobstein T (2006). Worldwide trends in childhood overweight and obesity. Int J Pediatr Obes. 1(1):11–25. http://dx.doi.org/10.1080/17477160600586747 PMID:17902211

8. Wang Y, Baker JL, Hill JO, Dietz WH (2012). Controversies regarding reported trends: has the obesity epidemic leveled off in the United States? Adv Nutr. 3(5):751–2. http://dx.doi.org/10.3945/an.112.002790 PMID:22983865

9. Reilly JJ, Armstrong J, Dorosty AR, Emmett PM, Ness A, Rogers I, et al.; Avon Longitudinal Study of Parents and Children Study Team (2005). Early life risk factors for obesity in childhood: cohort study. BMJ. 330(7504):1357. http://dx.doi.org/10.1136/bmj.38470.670903.E0 PMID:15908441

10. WHO (2017). Global strategy on diet, physical activity and health: what are the causes? Geneva, Switzerland: World Health Organization. Available from: http://www.who.int/dietphysicalactivity/childhood_why/en/index.html.

11. Manco M, Dallapiccola B (2012). Genetics of pediatric obesity. Pediatrics. 130(1):123–33. http://dx.doi.org/10.1542/peds.2011-2717 PMID:22665408

12. Cecil J, Dalton M, Finlayson G, Blundell J, Hetherington M, Palmer C (2012). Obesity and eating behaviour in children and adolescents: contribution of common gene polymorphisms. Int Rev Psychiatry. 24(3):200–10. http://dx.doi.org/10.3109/09540261.2012.685056 PMID:22724641

13. Min J, Chiu DT, Wang Y (2013). Variation in the heritability of body mass index based on diverse twin studies: a systematic review. Obes Rev. 14(11):871–82. http://dx.doi.org/10.1111/obr.12065 PMID:23980914

14. DOHaD Society (2017). International Society for Developmental Origins of Health and Disease. Available from: https://dohadsoc.org/.

15. Symonds ME, Mendez MA, Meltzer HM, Koletzko B, Godfrey K, Forsyth S, et al. (2013). Early life nutritional programming of obesity: mother-child cohort studies. Ann Nutr Metab. 62(2):137–45. http://dx.doi.org/10.1159/000345598 PMID:23392264

16. Tie HT, Xia Y-Y, Zeng Y-S, Zhang Y, Dai C-L, Guo JJ, et al. (2014). Risk of childhood overweight or obesity associated with excessive weight gain during pregnancy: a meta-analysis. Arch Gynecol Obstet. 289(2):247–57. http://dx.doi.org/10.1007/s00404-013-3053-z PMID:24141389

17. Frias AE, Grove KL (2012). Obesity: a transgenerational problem linked to nutrition during pregnancy. Semin Reprod Med. 30(6):472–8. http://dx.doi.org/10.1055/s-0032-1328875 PMID:23074005

18. Weng SF, Redsell SA, Swift JA, Yang M, Glazebrook CP (2012). Systematic review and meta-analyses of risk factors for childhood overweight identifiable during infancy. Arch Dis Child. 97(12):1019–26. http://dx.doi.org/10.1136/archdischild-2012-302263 PMID:23109090

19. Pearce J, Langley-Evans SC (2013). The types of food introduced during complementary feeding and risk of childhood obesity: a systematic review. Int J Obes (Lond). 37(4):477–85. http://dx.doi.org/10.1038/ijo.2013.8 PMID:23399778

20. Pearce J, Taylor MA, Langley-Evans SC (2013). Timing of the introduction of complementary feeding and risk of childhood obesity: a systematic review. Int J Obes (Lond). 37(10):1295–306. http://dx.doi.org/10.1038/ijo.2013.99 PMID:23736360

21. McLaren L (2007). Socioeconomic status and obesity. Epidemiol Rev. 29(1):29–48. http://dx.doi.org/10.1093/epirev/mxm001 PMID:17478442

22. Wang Y, Zhang Q (2006). Are American children and adolescents of low socioeconomic status at increased risk of obesity? Changes in the association between overweight and family income between 1971 and 2002. Am J Clin Nutr. 84(4):707–16. PMID:17023695

23. Brophy S, Cooksey R, Gravenor MB, Mistry R, Thomas N, Lyons RA, et al. (2009). Risk factors for childhood obesity at age 5: analysis of the Millennium Cohort Study. BMC Public Health. 9(1):467. http://dx.doi.org/10.1186/1471-2458-9-467 PMID:20015353

24. Mistry SK, Puthussery S (2015). Risk factors of overweight and obesity in childhood and adolescence in South Asian countries: a systematic review of the evidence. Public Health. 129(3):200–9. http://dx.doi.org/10.1016/j.puhe.2014.12.004 PMID:25746156

25. Su C, Zhang B, Wang YF, Jia XF, Xue H, Wang HJ (2015). Epidemics of overweight and obesity among growing childhood in China between 1997 and 2009: impact of family income, dietary intake, and physical activity dynamics. Chin Med J (Engl). 128(14):1879–86. http://dx.doi.org/10.4103/0366-6999.160648 PMID:26168826

26. Florêncio TMDT, Ferreira HS, de França AP, Cavalcante JC, Sawaya AL (2001). Obesity and undernutrition in a very-low-income population in the city of Maceió, northeastern Brazil. Br J Nutr. 86(2):277–84. http://dx.doi.org/10.1079/BJN2001396 PMID:11502242

27. Anzman SL, Rollins BY, Birch LL (2010). Parental influence on children's early eating environments and obesity risk: implications for prevention. Int J Obes (Lond). 34(7):1116–24. http://dx.doi.org/10.1038/ijo.2010.43 PMID:20195285

28. Birch LL, Ventura AK (2009). Preventing childhood obesity: what works? Int J Obes (Lond). 33(Suppl 1):S74–81. http://dx.doi.org/10.1038/ijo.2009.22 PMID:19363514

29. Grossklaus H, Marvicsin D (2014). Parenting efficacy and its relationship to the prevention of childhood obesity. Pediatr Nurs. 40(2):69–86. PMID:24941509

30. Pérez-Morales E, Bacardí-Gascón M, Jiménez-Cruz A (2013). Sugar-sweetened beverage intake before 6 years of age and weight or BMI status among older children; systematic review of prospective studies. Nutr Hosp. 28(1):47–51. PMID:23808429

31. Morgan RE (2013). Does consumption of high-fructose corn syrup beverages cause obesity in children? Pediatr Obes. 8(4):249–54. http://dx.doi.org/10.1111/j.2047-6310.2013.00173.x PMID:23630060

32. Bray GA, Popkin BM (2013). Calorie-sweetened beverages and fructose: what have we learned 10 years later. Pediatr Obes. 8(4):242–8. http://dx.doi.org/10.1111/j.2047-6310.2013.00171.x PMID:23625798

33. Fatima Y, Doi SAR, Mamun AA (2015). Longitudinal impact of sleep on overweight and obesity in children and adolescents: a systematic review and bias-adjusted meta-analysis. Obes Rev. 16(2):137–49. http://dx.doi.org/10.1111/obr.12245 PMID:25589359

34. Chen X, Beydoun MA, Wang Y (2008). Is sleep duration associated with childhood obesity? A systematic review and meta-analysis. Obesity (Silver Spring). 16(2):265–74. http://dx.doi.org/10.1038/oby.2007.63 PMID:18239632

35. Robinson TN (1999). Reducing children's television viewing to prevent obesity: a randomized controlled trial. JAMA. 282(16):1561–7. http://dx.doi.org/10.1001/jama.282.16.1561 PMID:10546696

36. Papadimitriou A (2015). Timing of adiposity rebound and prevalence of obesity. J Pediatr. 167(2):498–498. http://dx.doi.org/10.1016/j.jpeds.2015.04.072 PMID:26001317

37. Whitaker RC, Pepe MS, Wright JA, Seidel KD, Dietz WH (1998). Early adiposity rebound and the risk of adult obesity. Pediatrics. 101(3):E5. PMID:9481024

38. Sanchez M, Panahi S, Tremblay A (2014). Childhood obesity: a role for gut microbiota? Int J Environ Res Public Health. 12(1):162–75. http://dx.doi.org/10.3390/ijerph120100162 PMID:25546278

39. Wilson SM, Sato AF (2014). Stress and paediatric obesity: what we know and where to go. Stress Health. 30(2):91–102. http://dx.doi.org/10.1002/smi.2501 PMID:23818395

40. Sinha R, Jastreboff AM (2013). Stress as a common risk factor for obesity and addiction. Biol Psychiatry. 73(9):827–35. http://dx.doi.org/10.1016/j.biopsych.2013.01.032 PMID:23541000

41. WHO (2017). Global strategy on diet, physical activity and health: what can be done to fight the childhood obesity epidemic? Geneva, Switzerland: World Health Organization. Available from: http://www.who.int/dietphysicalactivity/childhood_what_can_be_done/en/.

42. Wang Y, Cai L, Wu Y, Wilson RF, Weston C, Fawole O, et al. (2015). What childhood obesity prevention programmes work? A systematic review and meta-analysis. Obes Rev. 16(7):547–65. http://dx.doi.org/10.1111/obr.12277 PMID:25893796

43. van Hoek E, Feskens EJM, Bouwman LI, Janse AJ (2014). Effective interventions in overweight or obese young children: systematic review and meta-analysis. Child Obes. 10(6):448–60. http://dx.doi.org/10.1089/chi.2013.0149 PMID:25333421

44. Wang Y, Wu Y, Wilson RF, Bleich S, Cheskin L, Weston C, et al. (2013). Childhood obesity prevention programs: comparative effectiveness review and meta-analysis. Comparative Effectiveness Review No. 115. AHRQ Publication No. 13-EHC081-EF. Rockville (MD), USA: Agency for Healthcare Research and Quality, United States Department of Health and Human Services. Available from: https://www.effectivehealthcare.ahrq.gov/ehc/products/330/1524/obesity-child-report-130610.pdf.

45. Bleich SN, Segal J, Wu Y, Wilson R, Wang Y (2013). Systematic review of community-based childhood obesity prevention studies. Pediatrics. 132(1):e201–10. http://dx.doi.org/10.1542/peds.2013-0886 PMID:23753099

46. Showell NN, Fawole O, Segal J, Wilson RF, Cheskin LJ, Bleich SN, et al. (2013). A systematic review of home-based childhood obesity prevention studies. Pediatrics. 132(1):e193–200. http://dx.doi.org/10.1542/peds.2013-0786 PMID:23753095

47. Cai L, Wu Y, Wilson RF, Segal JB, Kim MT, Wang Y (2014). Effect of childhood obesity prevention programs on blood pressure: a systematic review and meta-analysis. Circulation. 129(18):1832–9. http://dx.doi.org/10.1161/CIRCULATIONAHA.113.005666 PMID:24552832

48. Cai L, Wu Y, Cheskin LJ, Wilson RF, Wang Y (2014). Effect of childhood obesity prevention programmes on blood lipids: a systematic review and meta-analysis. Obes Rev. 15(12):933–44. http://dx.doi.org/10.1111/obr.12227 PMID:25263653

49. Barlow SE; Expert Committee (2007). Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. Pediatrics. 120(Suppl 4):S164–92. http://dx.doi.org/10.1542/peds.2007-2329C PMID:18055651

50. Davis MM, Gance-Cleveland B, Hassink S, Johnson R, Paradis G, Resnicow K (2007). Recommendations for prevention of childhood obesity. Pediatrics. 120(Suppl 4):S229–53. http://dx.doi.org/10.1542/peds.2007-2329E PMID:18055653

51. IOM (2011). Early childhood obesity prevention policies: goals, recommendations, and potential actions. Washington (DC), USA: Institute of Medicine of the National Academies. Available from: http://www.nationalacademies.org/hmd/~/media/Files/Report Files/2011/Early-Childhood-Obesity-Prevention-Policies/Young Child Obesity 2011 Recommendations.pdf.

CHAPTER 10.

The interplay of genes, lifestyle, and obesity

Paul W. Franks

This chapter reviews the evidence supporting a joint effect of genes and lifestyle factors in obesity, focusing mainly on evidence from epidemiological studies and clinical trials research.

Obesity is the scourge of most contemporary societies; about 40% of adults worldwide are overweight and 13% are obese (http://www.who.int/mediacentre/factsheets/fs311/en/). Much of the burden that obesity conveys arises from the life-threatening diseases it causes, although there are also direct consequences, because quality of life is often diminished in people with morbid obesity as a result of social stigma and other societal challenges.

Although intensive lifestyle modification leads to short-term weight loss in most people, weight regain typically begins within a year of intensive intervention, and only a small minority of the target populations are able to maintain reduced weight in the long term [1]. Success in pharmacotherapeutics for weight loss has also been meagre, and in some instances disastrous. A handful of anti-obesity medications have been approved by the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA). One of the most successful of these is the lipase inhibitor orlistat. However, because orlistat diminishes intestinal fat absorption, a frequent side-effect of the drug is fatty stool, which many patients cannot tolerate. Other weight-loss drugs, such as rimonabant, are approved for use in the European Union but are not widely prescribed because of safety concerns and limited effectiveness. Many other weight-loss drugs have been brought to market in the past few decades, only to be withdrawn because of serious side-effects, including death [2]. There are other drugs that do achieve safe weight loss, primarily those approved and marketed for treatment of diabetes: (i) metformin, which reduces hepatic gluconeogenesis (the production of glucose in the liver); (ii) sodium-glucose linked transporter 2 (SGLT2) inhibitors, such as empagliflozin, which reduce re-uptake of glucose in the kidneys and are diuretic; and (iii) glucagon-like peptide-1 (GLP-1) agonists, such as exenatide, which diminish appetite by delaying gastric emptying. However, because all of these drugs can cause side-effects and they are not all reimbursable by health insurance providers for treatment of obesity, they are rarely used primarily for weight reduction.

The third weapon in the anti-obesity arsenal is bariatric surgery. Unlike drugs and lifestyle intervention, which perturb the disease process, surgery can permanently alter the disease trajectory. Therefore, long-term weight loss through surgery is generally sustained to a much greater degree than weight loss from

lifestyle intervention or drug therapy. However, like drug therapies, bariatric surgery is expensive – although it is cost-effective for diabetes treatment compared with drug therapy [3] – and is not risk-free; serious adverse events [4] include about 4 in 1000 patients dying within 60 days of surgery [5]. Thus, although surgery is appropriate for a small minority of morbidly obese patients, it is no panacea for the obesity epidemic.

Of the three core prevention and treatment options for obesity, behavioural interventions that favourably affect chronic energy balance are by far the most compelling, not least because diet and exercise are generally safe, are relatively inexpensive, and convey numerous additional benefits to health and well-being that drugs and surgery do not. However, the considerable therapeutic idiosyncrasies of lifestyle therapy cause wide variability in its effectiveness at a population level. Some of this variability is due to the extent to which the participant adheres to the intervention, and some is due to differences in the participant's biology, which modulates the effects of lifestyle interventions on rates of weight loss and weight regain.

The common outcome variable in obesity research and clinical practice is weight change, because it can be assessed easily and inexpensively. Changes in the amount and deposition of adipose tissue and ectopic fat are probably more clinically important phenotypes, but they are more difficult to quantify. Beyond this, weight change should be more than merely aesthetic; thus, the many clinical sequelae of weight change should also be tracked. Nevertheless, whether the outcome of lifestyle intervention trials is weight or a related metabolic outcome, the response to the intervention is generally highly heterogeneous.

Therefore, quantifying and understanding the ways in which genetic factors modulate a person's response to weight-loss therapies might help to predict the response to different types of intervention, by guiding therapeutic choices in ways that are more precise and effective than conventional approaches, thereby avoiding unnecessary side-effects and reducing costs.

Why might gene–lifestyle interactions be relevant in obesity?

Germline DNA variants are especially appealing biomarkers for targeting obesity interventions, because they are randomly assigned at meiosis and are stable throughout a person's life, rendering their associations with phenotypes fairly robust to confounding and reverse causation. DNA variants are also the starting point of a process called the central dogma of molecular biology [6], downstream of which a complex molecular cascade ensues that translates the effects of extrinsic environmental exposures (of which diet and exercise are major components in obesity) to the clinical phenotypes that characterize health and disease. That molecular cascade is made up of gene transcripts and proteins, as well as epigenomic features (in the form of methylation marks, open chromatin, histone modifications, etc.), small circulating molecules (metabolites), and an array of peptide hormones and other biochemical components.

Studies in twins provided some of the earliest compelling evidence that obesity is under a high degree of genetic control. A study of children and adolescents showed that 82–90% of the phenotypic variance was explained by additive genetic factors [7]. The study used objective assessments of body composition (dual-energy X-ray absorptiometry [DEXA] and hydrostatic weighing), enabling the careful distillation of body corpulence into its constituent morphological features. Studies in adults have reported somewhat lower heritability estimates for obesity.

One of the most eloquent adult twin studies assessed the heritability of body mass index (BMI) in several hundred male and female Swedish twins; about half of them had been reared together, and the remainder had been reared apart, having been adopted into different families soon after birth [8]. The study showed that the concordance of BMI in monozygotic (identical) twins was about 70% regardless of whether the twins had been reared apart or together, whereas the concordance in dizygotic (fraternal) twins was substantially less, suggesting a strong genetic component to obesity. Importantly, however, as discussed later in this chapter, the genetic aberrations that cause obesity do so through a range of diverse mechanisms, including those that affect appetite, satiation, and energy expenditure.

However, knowing that obesity is highly heritable does not necessarily mean that it is the consequence of gene–lifestyle interactions. To determine this, one could test whether the obesogenic effects of lifestyle exposures (in epidemiological studies) or response to weight-perturbing interventions (in clinical trials) are heritable. In studies of twins in the USA exposed to long-term overfeeding [9] or exercise [10] interventions, the concordance in adaptive response to the interventions was significantly higher within twin pairs compared with the concordance between unrelated participants for a range of body composition measures, including waist circumference, body fat percentage, and fat-cell diameter (for exercise response).

Collectively, there is compelling evidence supporting the view that body corpulence in the free-living state and change in body corpulence with diet or exercise are governed to a considerable extent

by genetic factors. These are so-called *quantitative genetics* studies. Unlike the *molecular genetics* studies of the modern era, quantitative genetics provides a broad-strokes genome-wide overview of genetic influence on a phenotype but offers no insights into the specific molecular aberrations (e.g. single nucleotide polymorphisms [SNPs], insertions and deletions [indels], and copy number variations [CNVs]) that cause obesity or modify the effects of exposures and interventions on weight change.

Examples of gene–lifestyle interactions

Population-level molecular genetics studies of obesity, whether focused on associations or interactions, were once hopelessly unreliable. The evidence reported in most such studies before 2007 lacked any reasonable degree of replication. Sample sizes generally ranged from a few dozen to a few hundred participants, and most of the studies that focused on interactions lacked robust measures of lifestyle exposures. A recent systematic review [11] identified 212 studies published between 1995 and mid-2012 that tested gene–lifestyle interactions in obesity; the review found that only those studies that focused on gene–physical activity interactions at the *FTO* (rs9960939) locus and gene–diet interactions at the *PPARG* (Pro12Ala) locus had been independently replicated. As is explained later in this chapter, replication studies of gene–lifestyle interactions face many challenges that extend beyond those faced by association studies. Therefore, the absence of replication does not necessarily mean that the initial finding was false-positive. However, replication studies are a sentinel feature of science, and without replication results for interaction effects it would be difficult to justify major investments in expensive follow-up studies (such as clinical trials) to test whether a gene–lifestyle interaction has the potential for clinical translation.

The *FTO* example cited above was the first of several encouraging illustrations of gene–lifestyle interactions in obesity. The role of *FTO* variation in obesity was first described in three papers published in close proximity in 2007. Two of the studies made their discoveries using genome-wide association studies (GWAS) [12, 13], whereas the third [14] serendipitously identified the genetic association signal using a set of 48 intergenic SNPs intended for quality control, of which one was strongly associated with morbid obesity. Nevertheless, the three studies reached consistent conclusions and provided the first convincing evidence of an association of common genetic variation and obesity. The strongest signal for BMI emanated from the rs9960939 variant, which per copy conveys an odds ratio of 1.35 for obesity and amounted to a difference in body weight for a person 1.7 m tall of about 3 kg between the high-risk and low-risk homozygous genotype groups [12].

Soon after the publication of these papers, studies began to emerge reporting evidence of gene–lifestyle interactions at the *FTO* locus [12–17]. The first study to do so came from a Danish cohort study called Inter99 [15]. The authors used a cross-sectional subcohort of about 5500 Inter99 participants to show that the genetic effect of the rs9960939 *FTO* variant on BMI was about 2 kg/m^2 in people reporting little or no physical activity but was closer to 1 kg/m^2 in those reporting high levels of physical activity. Soon after this work was published, a second observational study and a clinical trial reported complementary results. The observational study was of a population isolate of Amish individuals living in Pennsylvania [17]. The authors undertook a comprehensive analysis of *FTO* variation and explored interactions with objectively assessed physical activity (via accelerometry). The trial tested for genotype–treatment interactions on changes in obesity-related traits in the Diabetes Prevention Program (DPP), a randomized controlled trial (RCT) of intensive lifestyle modification, metformin, and placebo control interventions [16]. Although there was no evidence of an interaction between the rs9960939 *FTO* variant and lifestyle intervention on weight change, there was nominal statistical evidence of an interaction on change in subcutaneous adipose mass (assessed using computed tomography). The interaction effect was consistent with the epidemiological data reported in the Danish and Amish studies.

Many studies were published in the following year, each addressing the *FTO* interaction hypothesis, but with mixed results. Given this state of equipoise, an analysis was undertaken involving about 220 000 adults and 20 000 children and adolescents, to seek replication of the original study's findings. To do this, a standardized analysis plan was executed in each of the 54 cohorts from which the 240 000 participants emanated. The meta-analysis of these data yielded a statistically significant interaction effect, one that was consistent in direction with the original reports, although of a much smaller magnitude (about one sixth of the magnitude of the original interaction effect) [19].

Replication studies: relevance and challenges

After the discovery of *FTO* in 2007, many subsequent GWAS analyses were performed, each larger than the last and each contributing to the burgeoning array of obesity-associated genetic variants [18]. With the emergence of these data came

studies modelling the combined effects of these loci (as genetic risk scores) and their interactions with lifestyle. Of the many that have now been published, three epidemiological studies stand out.

The first study examined the interaction of 12 obesity loci and physical activity in 20 000 adults in the United Kingdom [19a]. The study was a textbook analysis of gene–lifestyle interaction effects and yielded a highly statistically significant interaction effect, which showed that physical activity appeared to diminish the effect of the genetic loci on BMI.

These exciting results were published in one of the leading general medical journals, and the study was clearly well conducted, but without replication data the possibility that these findings might be population-specific or false-positive could not be ruled out. Therefore, a study attempted to replicate these findings in a combined sample of about 40 000 Swedish adults, but initially failed. For reasons outlined in detail by Ahmad et al. [11], a series of factors were identified that inhibited replication of gene–lifestyle interaction effects (listed in the "Key factors" box at the end of this chapter). It was subsequently determined that these factors are features that are likely to affect other replication studies of gene–lifestyle interactions, including the large study of interaction between *FTO* variation and physical activity discussed above [19]. Hence, although replication is the bulwark against false discovery, it is important to ensure that replication studies that fail to support the initial discoveries do so for the right reasons. In the replication study [11], it was shown that when inhibiting factors are considered, the sample size required to achieve sufficient power to test the hypothesis amounts to a cohort collection of more than about 100 000 adults, about 5 times as large as the original study. By testing this hypothesis in 111 000 adults, the authors were able to reproduce the original finding, albeit with an interaction effect of substantially smaller magnitude [11].

A third major study, performed in three epidemiological cohorts in the USA, focused on the interaction of a genetic risk score comprising 32 obesity-associated loci and consumption of sugar-sweetened beverages [20]. These analyses showed that the genetic predisposition to obesity tended to be stronger in people who consumed higher volumes of sugar-sweetened beverages. In a field that is plagued by a dearth of replication data, this study stands out as one of very few to report novel findings on gene–lifestyle interactions alongside robust replication data from independent cohorts.

Although replication is important, it provides no assurance of cause and effect in observational studies. There are many alternative explanations for why two variables might be associated with another that do not include causality, because the factors that might confound these relationships in one cohort could easily do so in others. Gene–lifestyle interaction studies are more prone to confounding and bias than studies that test the marginal associations of lifestyle or genetic exposures in disease. This is because interaction studies are prone to all of the major sources of bias and confounding that plague conventional association studies, as well as types of confounding and bias that are specific to interaction effects. For example, the way in which data are distributed can undermine the credibility of statistical interactions [21].

In the examples discussed above of gene–physical activity interactions in obesity (assessed using BMI, which is calculated as the weight in kilograms divided by the square of the height in metres), a further potential source of confounding exists. Although BMI is probably the most common estimate of adiposity in research studies and clinical practice, it is a proxy for the underlying degree of adiposity. In general, people with higher BMI scores are also fatter, but this is by no means always true. Consider, for example, muscular athletes such as major league basketball players, many of whom have BMI scores that classify them as "overweight" [22]. In population-based cohorts, one should expect there to be a subpopulation of people who are heavy and lean, in part because they are more physically active. One would expect few physically inactive people to be heavy and lean, and even fewer physically active people to be fat. Thus, if one were to model the association of obesogenic gene variants with BMI in the subpopulation of physically inactive people, one would anticipate a strong relationship, but if one were to model the same association in the physically active subpopulation, one should expect this relationship to be weaker, because BMI is a weaker proxy for total adiposity in physically active people compared with physically inactive people. Thus, because the interaction tests outlined in the studies discussed above compare the magnitude of the association between genotypes and BMI by strata of physical activity, statistically significant interaction tests could be driven entirely by confounding. Thus, when outcomes are assessed using imperfect proxies and the validity of that proxy varies across the distribution of the lifestyle exposure, this type of confounding, which is specific to interaction analyses, should be carefully considered.

Clinical trials

Epidemiology is a powerful tool for generating hypotheses about gene–lifestyle interactions, but it is prone to bias, confounding, and reverse

causality. RCTs of lifestyle interventions are more tightly controlled and monitored than epidemiological studies; they are prospective in design (most published epidemiological studies of gene–lifestyle interactions have been performed in cross-sectional data sets), thereby permitting the assessment of temporal relationships, and are less prone to confounding, because treatment (lifestyle vs control) is randomly assigned and hence should not be correlated with other factors that underlie an association between exposure and outcomes. However, because it is usually not possible to blind a participant to treatment allocation in a lifestyle trial (i.e. trials focused on changing diet and exercise behaviours), and because there is no placebo that can be given for exercise and most dietary factors, lifestyle trials are less robust to confounding than, say, placebo-controlled drug trials.

It is important to keep this in mind, because in lifestyle intervention studies behavioural compensation is known to occur, and this might lead participants assigned to treatment or control interventions to modify behaviours outside the hours of the intervention and thereby affect the trial's outcomes. Therefore, although much is made of the variability in treatment response in lifestyle intervention trials, perhaps most notably in the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) Family Study [23], it is reasonable to assume that some of the variability in response is due to behavioural compensation. The HERITAGE Family Study was an intervention-only exercise training (aerobic and resistance training) study administered over 20 weeks in about 1000 participants. The results from the study seem to suggest that there are "responders" and "non-responders" to exercise interventions, causing clinical phenotypes to improve dramatically in some participants (super-responders), whereas in other participants these same phenotypes do not improve (non-responders), or even worsen.

It is often the case that researchers interpret "phenotypic response" data from the HERITAGE Family Study and elsewhere as compelling evidence of biologically (genetically) encoded exercise-response potential [23]. However, genetic predisposition is only one of many plausible explanations for these results. For example, exercise intervention studies have shown that when people are encouraged to undertake structured exercise, non-exercise activity thermogenesis (the component of total physical activity that is not structured) decreases on average [24], a concept sometimes termed *behavioural compensation*. Importantly, because the time spent undergoing the lifestyle intervention in a trial (often about 150 minutes per week) is a very small proportion (< 2%) of the overall waking hours, a participant's behaviour during the hours when they are not participating in the intervention sessions will affect the extent to which their health phenotypes change during the trial, irrespective of the intervention's intensity or how faithfully the participant has adhered to it. Moreover, variability in measurement precision and accuracy (error), which are inherent features of all clinical trials and observational studies, causes a phenomenon called *regression dilution*, which contributes to the apparent variability in phenotypic response to interventions. Thus, measurement error is usually most abundant at the extremes of a trait's distribution, and this should be considered when using data from lifestyle intervention trials to understand human biology.

Nevertheless, some of the inter-individual variability in response to lifestyle interventions is likely to be under biological/genetic control, an assumption that is supported by heritability analyses undertaken in the HERITAGE Family Study and elsewhere, showing that the variability in trait response is larger between families than within families [25]. Studies of gene–treatment interactions performed in RCTs have the potential to identify specific genetic variants that underlie treatment response. Two of the largest and most comprehensive RCTs of lifestyle interventions were performed in the USA. The first, the DPP, was performed in about 3000 prediabetic overweight adults [26], whereas the second, the Action for Health in Diabetes (Look AHEAD) trial, focused on about 5000 people with clinically manifest type 2 diabetes [27]. The clinical interventions in both trials focused on inducing weight loss of about 7% of body weight through structured and personalized diet and exercise regimes, as well as comparison arms that provided standard of care; the DPP also included two drug arms (metformin and troglitazone). Extensive genetic analyses, including those relating to the *FTO* locus (discussed above for the DPP) have been performed in both trials, with several analyses focusing on weight change.

The first analysis of this nature in the DPP focused on the *PPARG* Pro12Ala locus [28]. These analyses in the DPP tested a hypothesis set forth by earlier epidemiological studies relating to the interaction of dietary fats. *PPARG* is a nuclear receptor that regulates many genes and pathways involved in energy metabolism, adipogenesis, and other metabolic processes. Long-chain unsaturated fatty acids bind with high affinity to *PPARG*, as do thiazolidinediones, a class of drugs used to improve peripheral insulin sensitivity. Therefore, the authors tested whether the Pro12Ala variant modified the weight-loss effects of (i) lifestyle intervention per se, (ii) dietary fatty acid consumption, and (iii) the

thiazolidinedione drug troglitazone. No statistical interaction was observed with lifestyle, but with both dietary fats and troglitazone, the hypothesized interaction effects were observed.

Many subsequent studies were conducted in the DPP; some involved detailed explorations of candidate genes, such as *MC4R* [29], *ADIPOQ* [30], *TCF7L2* [31], and *PPARGC1A* [32], and others focused on polygenic risk scores [33]. The most recent of these studies [34] assessed the effects of 92 variants that were recently reported for their associations with BMI by the Genetic Investigation of Anthropometric Traits (GIANT) consortium [18]. Joint analyses were conducted in the DPP and Look AHEAD trials to determine whether these variants, singly or in combination, modified the effects of lifestyle interventions focused on weight loss or prevention of weight regain. Overall, little evidence was found of interactions between lifestyle and these genetic variants, suggesting that GWAS-derived genetic loci for obesity have no clinically meaningful impact on response to lifestyle interventions. However, one variant (at *MTIF3*) yielded a statistically significant interaction effect on weight loss that was consistent in direction and magnitude in the DPP and Look AHEAD trials. The interaction manifested through a slightly elevated risk of weight gain in carriers of the G allele (the allele associated with higher BMI in the GIANT consortium meta-analysis [18]) who were assigned to the control intervention, which contrasted with the genetic effect in those assigned to the lifestyle interventions (where the G allele was associated with greater weight loss). The very similar results in the two trials represent some of the most robust evidence of a gene–lifestyle interaction in weight change published to date. Adding further credence to these findings is a large (N = 67 000), independent analysis of gene–diet interactions in BMI in a cross-sectional cohort collection [35]. This analysis of 32 of the 92 loci studied in the DPP and Look AHEAD trials found that the strongest evidence of interaction between a gene variant and diet was at the *MTIF3* locus. Obvious differences in study designs and outcomes make determining the comparability of the interaction effects across these studies challenging.

MTIF3 is involved in forming the initiation complex of the mitochondrial 55S ribosome [36, 37], which in turn synthesizes 13 of the inner mitochondrial membrane proteins. The regulation of *MTIF3* plays a key role in mitochondrial energy metabolism and reactive oxygen species production as part of the electron transport chain [37]. As was reported previously [34], although rs1885988 is an intronic variant, its close proximity (411 bp) to a triallelic missense SNP with a DNase peak indicates that the rs1885988 variant is a marker for a chromatin site involved in transcription factor binding regulation.

Functional implications

Notwithstanding the limitations of focusing on GWAS-derived (marginal-effect) loci for interaction analyses, the approach has the advantage that huge efforts have been invested in determining the functional basis of the genes to which the index maps. Importantly, locus mapping is still a fairly imprecise affair, and in many instances the region to which a variant with the strongest association signal in a GWAS maps spans several genes. Thus, leaping from an association signal to functional prognosis is fraught with caveats.

Nevertheless, in silico functional annotation performed by the GIANT consortium mapped BMI-associated loci to putative functional variants and transcription profiles across multiple human tissues [38], which indicated an overrepresentation of several of these loci across neural pathways involved in satiation and appetite. Those analyses were extended in the most recent GIANT publication on BMI-associated variants to include about 60 further variants [18]. Using the DEPICT software [39], the authors provided further evidence of enrichment across central nervous system pathways (i.e. synaptic function, long-term potentiation, and neurotransmitter signalling) but also found that some of the newly discovered loci mapped to pathways implicated in movement behaviour (physical activity and coordination) in mouse models. These intriguing functional implications add further support to the potential role of GWAS-derived loci in gene–lifestyle interactions. Although most common variants have roughly comparable effect sizes, *FTO* stands out given that the association and effect-modifying roles (of lifestyle exposures) in obesity are now well defined. However, despite huge efforts, the mechanisms through which *FTO* acts remain unclear. What is clear is that these mechanisms are complex, involving long-range interactions with other loci (e.g. *IRX3* [40]), and may be triggered by epigenomic factors (e.g. TRIM28 [41]).

Conclusions

There is an abundance of published evidence, predominantly from cross-sectional epidemiological studies, that supports the notion that lifestyle and genetic factors interact to cause obesity. However, few studies have been adequately replicated, and functional validation and specifically designed intervention studies are rarely undertaken; both of these are necessary to determine whether observations of gene–lifestyle interaction in obesity are causal and of clinical relevance.

Key points

- The patterns and distributions of obesity within and between ethnically diverse populations living in similar and contrasting environments suggest that some ethnic groups are more susceptible to obesity than others. Generally, when exposed to environments typical of industrialized countries, aboriginal peoples appear to be highly susceptible, whereas populations of European ancestry appear to be far less prone to obesity.
- More than 150 common loci have been robustly associated with measures of body composition.
- Evidence from several behavioural intervention studies suggests that response to caloric manipulation brought about by fasting, overfeeding, or exercise is heritable.
- There is now convincing epidemiological evidence of interactions between common variants at *FTO* and lifestyle on obesity. Almost all of these data are from cross-sectional studies, and temporal relationships are not clear. There are large studies supporting gene–lifestyle interactions at several other common loci, but the burden of evidence is far less for these loci than for *FTO*.
- The evidence from clinical trials supporting gene–lifestyle interactions at *FTO* or other loci is relatively weak compared with the epidemiological evidence.
- The magnitude of the interaction effects reported for *FTO* (or other common variants) is insufficient to warrant the use of those data for clinical translation.

Key factors

The following key factors affect the detection and replication of gene–lifestyle interaction effects.

- **Exposure variance.** When all else holds equal, statistical power is usually inversely related to the variance (usually expressed as standard deviation) of the exposure variable.
- **Outcome variance.** When all else holds equal, statistical power is usually positively related to the variance (usually expressed as standard deviation) of the outcome variable.
- **Categorization of variables.** For exposures (or outcomes) that are normally distributed and bear linear relationships with outcomes (or exposures), data stratification tends to reduce power [42]. Moreover, a variable that is stratified at the median point of its distribution will tend to yield higher statistical power than one that is stratified at other points in its distribution.
- **Measurement error.** Error in the assessment of exposure or outcome variables has a profound impact on statistical power, such that sample size requirements to detect interactions may differ by several orders of magnitude, depending on the quality of exposure and outcome measures [43].
- **Differential confounding.** Interaction effects detected in observational studies are prone to confounding. However, confounding variables often differ between populations. Thus, if an interaction effect that is detected in one population is driven by confounding, and the confounding variables are absent in a replication cohort, then the replication cohort is likely to fail to reproduce the results of the initial study. However, successful replication does not necessarily exclude the possibility that interaction effects are confounded, because confounding factors may be simultaneously present in the discovery and replication cohorts.
- **Publication bias.** Publishing negative findings, whether from studies of interaction or not, is generally more challenging than publishing results that appear statistically significant. Thus, the absence of negative-outcome replication studies in the literature may not mean that replication studies have not been performed.
- **Winner's curse.** The interaction effects featured in high-impact journals are often among the most striking. However, striking effects are sometimes overestimates of the true latent effect; thus, the results of subsequent studies are likely to be weaker, which in turn limits the statistical power of those later studies. This concept is often referred to as the "winner's curse".
- **Population-specific effects.** Although the logical conclusion when an adequately powered replication study fails is that the original discovery may be false-positive, one cannot exclude the possibility that the original finding was true-positive and population-specific. Further studies that explore three-way interactions (gene × lifestyle × population-specific parameters) would be needed to model these effects.

References

1. Delahanty LM, Pan Q, Jablonski KA, Aroda VR, Watson KE, Bray GA, et al.; Diabetes Prevention Program Research Group (2014). Effects of weight loss, weight cycling, and weight loss maintenance on diabetes incidence and change in cardiometabolic traits in the Diabetes Prevention Program. Diabetes Care. 37(10):2738–45. http://dx.doi.org/10.2337/dc14-0018 PMID:25024396

2. Colman E (2012). Food and Drug Administration's Obesity Drug Guidance Document: a short history. Circulation.125(17):2156–64. http://dx.doi.org/10.1161/CIRCULATIONAHA.111.028381 PMID:22547756

3. Colquitt JL, Pickett K, Loveman E, Frampton GK (2014). Surgery for weight loss in adults. Cochrane Database Syst Rev. 8:CD003641. PMID:25105982

4. Keating C, Neovius M, Sjöholm K, Peltonen M, Narbro K, Eriksson JK, et al. (2015). Health-care costs over 15 years after bariatric surgery for patients with different baseline glucose status: results from the Swedish Obese Subjects study. Lancet Diabetes Endocrinol. 3(11):855–65. http://dx.doi.org/10.1016/S2213-8587(15)00290-9 PMID:26386667

5. Morino M, Toppino M, Forestieri P, Angrisani L, Allaix ME, Scopinaro N (2007). Mortality after bariatric surgery: analysis of 13,871 morbidly obese patients from a national registry. Ann Surg. 246(6):1002–7, discussion 1007–9. http://dx.doi.org/10.1097/SLA.0b013e31815c404e PMID:18043102

6. Crick F (1970). Central dogma of molecular biology. Nature. 227(5258):561–3. http://dx.doi.org/10.1038/227561a0 PMID:4913914

7. Franks PW, Ravussin E, Hanson RL, Harper IT, Allison DB, Knowler WC, et al. (2005). Habitual physical activity in children: the role of genes and the environment. Am J Clin Nutr. 82(4):901–8. PMID:16210723

8. Stunkard AJ, Harris JR, Pedersen NL, McClearn GE (1990). The body-mass index of twins who have been reared apart. N Engl J Med. 322(21):1483–7. http://dx.doi.org/10.1056/NEJM199005243222102 PMID:2336075

9. Bouchard C, Tremblay A, Després JP, Nadeau A, Lupien PJ, Thériault G, et al. (1990). The response to long-term overfeeding in identical twins. N Engl J Med. 322(21):1477–82. http://dx.doi.org/10.1056/NEJM199005243222101 PMID:2336074

10. Bouchard C, Tremblay A, Després JP, Thériault G, Nadeau A, Lupien PJ, et al. (1994). The response to exercise with constant energy intake in identical twins. Obes Res. 2(5):400–10. http://dx.doi.org/10.1002/j.1550-8528.1994.tb00087.x PMID:16358397

11. Ahmad S, Varga TV, Franks PW (2013). Gene × environment interactions in obesity: the state of the evidence. Hum Hered. 75(2–4):106–15. http://dx.doi.org/10.1159/000351070 PMID:24081226

12. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, et al. (2007). A common variant in the *FTO* gene is associated with body mass index and predisposes to childhood and adult obesity. Science. 316(5826):889–94. http://dx.doi.org/10.1126/science.1141634 PMID:17434869

13. Scuteri A, Sanna S, Chen WM, Uda M, Albai G, Strait J, et al. (2007). Genome-wide association scan shows genetic variants in the *FTO* gene are associated with obesity-related traits. PLoS Genet. 3(7):e115. http://dx.doi.org/10.1371/journal.pgen.0030115 PMID:17658951

14. Dina C, Meyre D, Gallina S, Durand E, Körner A, Jacobson P, et al. (2007). Variation in *FTO* contributes to childhood obesity and severe adult obesity. Nat Genet. 39(6):724–6. http://dx.doi.org/10.1038/ng2048 PMID:17496892

15. Andreasen CH, Stender-Petersen KL, Mogensen MS, Torekov SS, Wegner L, Andersen G, et al. (2008). Low physical activity accentuates the effect of the *FTO* rs9939609 polymorphism on body fat accumulation. Diabetes. 57(1):95–101. http://dx.doi.org/10.2337/db07-0910 PMID:17942823

16. Franks PW, Jablonski KA, Delahanty LM, McAteer JB, Kahn SE, Knowler WC, et al.; Diabetes Prevention Program Research Group (2008). Assessing gene-treatment interactions at the *FTO* and *INSIG2* loci on obesity-related traits in the Diabetes Prevention Program. Diabetologia. 51(12):2214–23. http://dx.doi.org/10.1007/s00125-008-1158-x PMID:18839134

17. Rampersaud E, Mitchell BD, Pollin TI, Fu M, Shen H, O'Connell JR, et al. (2008). Physical activity and the association of common *FTO* gene variants with body mass index and obesity. Arch Intern Med. 168(16):1791–7. http://dx.doi.org/10.1001/archinte.168.16.1791 PMID:18779467

18. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al.; LifeLines Cohort Study; ADIPOGen Consortium; AGEN-BMI Working Group; CARDIOGRAMplusC4D Consortium; CKDGen Consortium; GLGC; ICBP; MAGIC Investigators; MuTHER Consortium; MIGen Consortium; PAGE Consortium; ReproGen Consortium; GENIE Consortium; International Endogene Consortium (2015). Genetic studies of body mass index yield new insights for obesity biology. Nature. 518(7538):197–206. http://dx.doi.org/10.1038/nature14177 PMID:25673413

19. Kilpeläinen TO, Qi L, Brage S, Sharp SJ, Sonestedt E, Demerath E, et al. (2011). Physical activity attenuates the influence of *FTO* variants on obesity risk: a meta-analysis of 218,166 adults and 19,268 children. PLoS Med. 8(11):e1001116. http://dx.doi.org/10.1371/journal.pmed.1001116 PMID:22069379

19a. Li S, Zhao JH, Luan J, Ekelund U, Luben RN, Khaw KT, et al. (2010). Physical activity attenuates the genetic predisposition to obesity in 20,000 men and women from EPIC-Norfolk prospective population study. PLoS Med. 7(8):e1000332. http://dx.doi.org/10.1371/journal.pmed.1000332 PMID:20824172

20. Qi Q, Chu AY, Kang JH, Jensen MK, Curhan GC, Pasquale LR, et al. (2012). Sugar-sweetened beverages and genetic risk of obesity. N Engl J Med. 367(15):1387–96. http://dx.doi.org/10.1056/NEJMoa1203039 PMID:22998338

21. Hunter DJ (2005). Gene-environment interactions in human diseases. Nat Rev Genet. 6(4):287–98. http://dx.doi.org/10.1038/nrg1578 PMID:15803198

22. McArdle WD, Katch FI, Katch VL (2014). Exercise physiology: nutrition, energy, and human performance. 8th ed. Baltimore (MD), USA: Wolters Kluwer Health, Lippincott Williams & Wilkins.

23. Roth SM (2008). Perspective on the future use of genomics in exercise prescription. J Appl Physiol (1985). 104(4):1243–5. PMID:18048588

24. Goran MI, Poehlman ET (1992). Endurance training does not enhance total energy expenditure in healthy elderly persons. Am J Physiol. 263(5 Pt 1):E950–7. PMID:1443128

25. Bouchard C, Rankinen T (2001). Individual differences in response to regular physical activity. Med Sci Sports Exerc. 33(6 Suppl):S446–51, discussion S452–3. http://dx.doi.org/10.1097/00005768-200106001-00013 PMID:11427769

26. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al.; Diabetes Prevention Program Research Group (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 346(6):393–403. http://dx.doi.org/10.1056/NEJMoa012512 PMID:11832527

27. Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, et al.; Look AHEAD Research Group (2013). Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med. 369(2):145–54. http://dx.doi.org/10.1056/NEJMoa1212914 PMID:23796131

28. Franks PW, Jablonski KA, Delahanty L, Hanson RL, Kahn SE, Altshuler D, et al.; Diabetes Prevention Program Research Group (2007). The Pro12Ala variant at the peroxisome proliferator-activated receptor gamma gene and change in obesity-related traits in the Diabetes Prevention Program. Diabetologia. 50(12):2451–60. http://dx.doi.org/10.1007/s00125-007-0826-6 PMID:17898990

29. Pan Q, Delahanty LM, Jablonski KA, Knowler WC, Kahn SE, Florez JC, et al.; Diabetes Prevention Program Research Group (2013). Variation at the melanocortin 4 receptor gene and response to weight-loss interventions in the Diabetes Prevention Program. Obesity (Silver Spring). 21(9):E520–6. PMID:23512951

30. Mather KJ, Christophi CA, Jablonski KA, Knowler WC, Goldberg RB, Kahn SE, et al.; Diabetes Prevention Program Research Group (2012). Common variants in genes encoding adiponectin (*ADIPOQ*) and its receptors (*ADIPOR1/2*), adiponectin concentrations, and diabetes incidence in the Diabetes Prevention Program. Diabet Med. 29(12):1579–88. http://dx.doi.org/10.1111/j.1464-5491.2012.03662.x PMID:22443353

31. McCaffery JM, Jablonski KA, Franks PW, Dagogo-Jack S, Wing RR, Knowler WC, et al.; Diabetes Prevention Program Research Group (2011). *TCF7L2* polymorphism, weight loss and proinsulin:insulin ratio in the Diabetes Prevention Program. PLoS One. 6(7):e21518. http://dx.doi.org/10.1371/journal.pone.0021518 PMID:21814547

32. Franks PW, Christophi CA, Jablonski KA, Billings LK, Delahanty LM, Horton ES, et al.; Diabetes Prevention Program Research Group (2014). Common variation at *PPARGC1A/B* and change in body composition and metabolic traits following preventive interventions: the Diabetes Prevention Program. Diabetologia. 57(3):485–90. http://dx.doi.org/10.1007/s00125-013-3133-4 PMID:24317794

33. Delahanty LM, Pan Q, Jablonski KA, Watson KE, McCaffery JM, Shuldiner A, et al.; Diabetes Prevention Program Research Group (2012). Genetic predictors of weight loss and weight regain after intensive lifestyle modification, metformin treatment, or standard care in the Diabetes Prevention Program. Diabetes Care. 35(2):363–6. http://dx.doi.org/10.2337/dc11-1328 PMID:22179955

34. Papandonatos GD, Pan Q, Pajewski NM, Delahanty LM, Peter I, Erar B, et al.; GIANT Consortium; Diabetes Prevention Program and the Look AHEAD Research Groups (2015). Genetic predisposition to weight loss & regain with lifestyle intervention: analyses from the Diabetes Prevention Program & the Look AHEAD randomized controlled trials. Diabetes. 64(12):4312–21. http://dx.doi.org/10.2337/db15-0441 PMID:26253612

35. Nettleton JA, Follis JL, Ngwa JS, Smith CE, Ahmad S, Tanaka T, et al. (2015). Gene × dietary pattern interactions in obesity: analysis of up to 68 317 adults of European ancestry. Hum Mol Genet. 24(16):4728–38. http://dx.doi.org/10.1093/hmg/ddv186 PMID:25994509

36. Christian BE, Spremulli LL (2009). Evidence for an active role of $IF3_{mt}$ in the initiation of translation in mammalian mitochondria. Biochemistry. 48(15):3269–78. http://dx.doi.org/10.1021/bi8023493 PMID:19239245

37. Behrouz B, Vilariño-Güell C, Heckman MG, Soto-Ortolaza AI, Aasly JO, Sando S, et al. (2010). Mitochondrial translation initiation factor 3 polymorphism and Parkinson's disease. Neurosci Lett. 486(3):228–30. http://dx.doi.org/10.1016/j.neulet.2010.09.059 PMID:20887776

38. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, et al.; MAGIC; Procardis Consortium (2010). Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet. 42(11):937–48. http://dx.doi.org/10.1038/ng.686 PMID:20935630

39. Pers TH, Karjalainen JM, Chan Y, Westra HJ, Wood AR, Yang J, et al.; Genetic Investigation of ANthropometric Traits (GIANT) Consortium (2015). Biological interpretation of genome-wide association studies using predicted gene functions. Nat Commun. 6:5890. http://dx.doi.org/10.1038/ncomms6890 PMID:25597830

40. Smemo S, Tena JJ, Kim KH, Gamazon ER, Sakabe NJ, Gómez-Marín C, et al. (2014). Obesity-associated variants within *FTO* form long-range functional connections with *IRX3*. Nature. 507(7492):371–5. http://dx.doi.org/10.1038/nature13138 PMID:24646999

41. Dalgaard K, Landgraf K, Heyne S, Lempradl A, Longinotto J, Gossens K, et al. (2016). Trim28 haploinsufficiency triggers bi-stable epigenetic obesity. Cell. 164(3):353–64. http://dx.doi.org/10.1016/j.cell.2015.12.025 PMID:26824653

42. Ragland DR (1992). Dichotomizing continuous outcome variables: dependence of the magnitude of association and statistical power on the cutpoint. Epidemiology. 3(5):434–40. http://dx.doi.org/10.1097/00001648-199209000-00009 PMID:1391136

43. Wong MY, Day NE, Luan JA, Chan KP, Wareham NJ (2003). The detection of gene-environment interaction for continuous traits: should we deal with measurement error by bigger studies or better measurement? Int J Epidemiol. 32(1):51–7. http://dx.doi.org/10.1093/ije/dyg002 PMID:12690008

CHAPTER 11.

The gut microbiota and obesity

Hervé M. Blottière

The human microbiota is composed of about as many microorganisms as there are cells in the human body. It is a very diverse ecosystem comprising more than 100 trillion microbes living in the intestines, the mouth, the skin, the vagina, and elsewhere in the body. Although it was previously called the gastrointestinal flora or microflora, the more pragmatic term "microbiota" is now preferred.

The microbiome, the "other genome" or "second genome" of the human body, is composed of about 10 million genes, compared with about 23 000 genes in the human genome, and thus provides a very rich functional potential. The colonic microbiome is the most diverse and also the best characterized microbial community. Although the human microbiome has fantastic potential, it has only been about 10 years since the scientific community first realized its importance outside the gut, especially after the pioneering work of Gordon and collaborators [1].

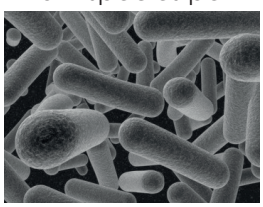
Recently, the development of molecular tools and subsequently of next-generation sequencing enabled the richness of the intestinal ecosystem to be revealed [2]. Each individual harbours hundreds of different species, most of which have not yet been cultured. Studies have revealed that 70–80% of the dominant species have no representative in culture collections. Only a few dozen species are conserved between individuals, representing a core that seems to be a stable community under healthy conditions. Although this view is controversial, some people consider the gut microbiota to be a true organ; as such, it could be transplanted. The recent success of faecal microbiota transplantation, especially in the context of *Clostridium difficile* infection, argues for such a definition [3]. In a healthy symbiotic state, the colonic microbiota is an important organ, interacting with food (in particular dietary fibre, enabling energy harvest from otherwise indigestible dietary compounds), interacting with cells (including immune cells, but also the metabolic and nervous systems), and protecting against pathogens by acting as a barrier to infection (Fig. 11.1).

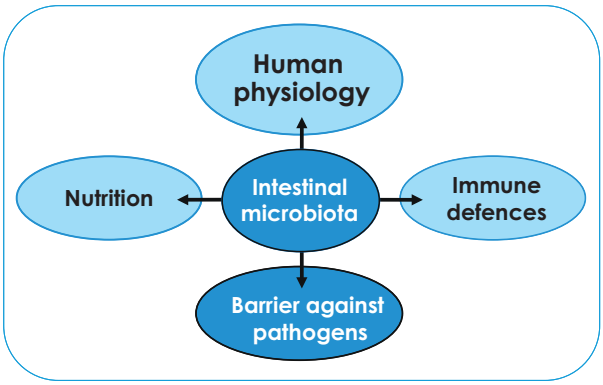
Gene catalogues of gut microbiota

The first draft of the human genome was published in 2000. In 2010, the Metagenomics of the Human Intestinal Tract (MetaHIT) consortium released the first catalogue of human gut microbial genes, obtained after sequencing whole faecal microbiota metagenomes from 124 European individuals [4]. Interestingly, the 3.3 million

Fig. 11.1. The gut microbiota.

- An average of 650 000 genes per microbiome
- About 25–30 times as many genes as the human genome
- About 500–1000 dominant species per individual
- A true organ





gut bacterial genes in the MetaHIT catalogue were also well represented in the other metagenomes that were available at the time, from faecal samples of individuals in the USA and Japan. In parallel, the Human Microbiome Project published a catalogue of 178 reference bacterial genomes distributed among different body sites and including 151 representative gastrointestinal species [5].

In 2014, the MetaHIT consortium published an integrated catalogue of 10 million bacterial genes derived from 1267 human gut metagenomes obtained from individuals on three continents, including 760 samples from Europe. As expected, the number of frequent genes stopped increasing, whereas the number of rare genes, present in not more than 1% of the cohort, continued to increase [6]. Analyses of this close-to-complete catalogue revealed country-specific signatures for xenobiotic metabolism and nutrient consumption for samples from individuals in China and Denmark.

More recently, a catalogue of the mouse gut metagenome was established, emphasizing the host specificity of the microbiota [7]. Only about 4.0% of the mouse gut microbial genes were shared with those of the human gut microbiome. It is important to take this into consideration when attempting to extrapolate results obtained in mouse models to the situation in humans.

Colonization

The colonization process starts at birth, and the delivery type is the first factor that has an impact. For infants that are vaginally delivered, the initial gut microbiota resembles the mother's vaginal microbiota, dominated by bacteria of the genera *Lactobacillus*, *Prevotella*, and *Sneathia*, whereas for infants delivered by caesarean section, the initial gut microbiota resembles the mother's skin microbial community, composed of *Staphylococcus*, *Corynebacterium*, and *Propionibacterium* [8]. Colonization is also strongly affected by the administration of antibiotics in early life [9]. During the first 3 years of life, the infant's gut microbiota is highly unstable and is largely influenced by feeding habits. Key factors are the type of feeding (breastfeeding or formula feeding), the weaning time and process, and food composition, as well as the hygiene of the environment.

By the time an individual reaches adulthood, the intestinal microbiota is composed of several hundreds of different species, belonging only to a few phyla, predominantly Firmicutes, Bacteroidetes, and Actinobacteria [10], although Proteobacteria, Verrucomicrobia, and Fusobacteria are present to a lesser extent. About 50% of individuals harbour Archaea in their microbiota, especially *Methanobrevibacter smithii*, which is responsible for methane excretion. A core of species has been identified as being present in most individuals, but with different relative abundances. The number of species identified in the core depends on the analytical method used: 66 from 16S rDNA sequencing [11] or 57 from whole-metagenome sequencing [5]. Under healthy conditions, the intestinal microbiota is considered to be a stable community, influenced by dietary habits as well as by the physiology of its host.

Enterotypes

Further analysis of several metagenomes led to the discovery of three balanced ecological arrangements, termed enterotypes; the three enterotypes are dominated by *Bacteroides*, *Prevotella*, and *Ruminococcus*, respectively [12]. The third enterotype is also linked to the presence of *M. smithii*. This description of community types is not limited to the gut [13]. These enterotypes or community types emerged as being independent of sex and country of origin but probably associated with

long-term dietary habits [14]. Wu et al. [14] were able to associate consumption of protein and animal fat with the *Bacteroides* enterotype and consumption of carbohydrates with the *Prevotella* enterotype. Interestingly, by analysing samples from volunteers randomized to a high-fat, low-fibre diet or a low-fat, high-fibre diet for 10 days, this study revealed rapid changes in microbiome composition; however, the enterotype of an individual did not seem to be affected by this relatively short-term dietary intervention. Transit time of food through the gut has also been correlated with enterotypes [15].

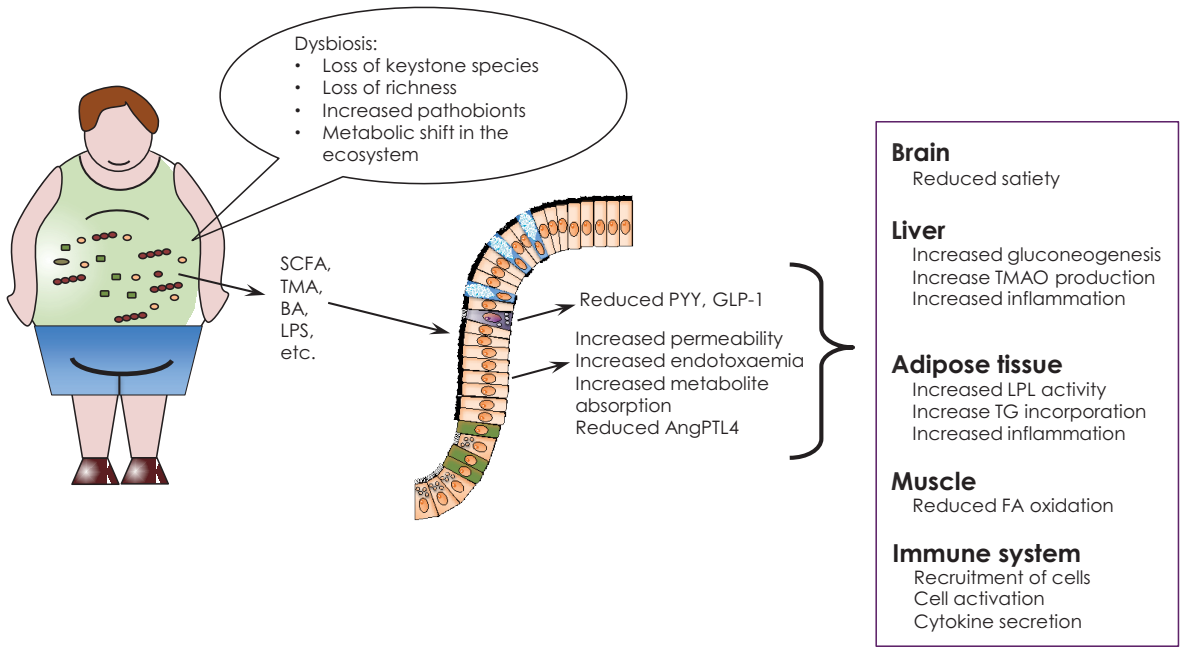
Dysbiosis

The human gut microbiota is very complex and diversified. The microbiome of an individual has more than 25 times as many genes as there are in the human genome. The fitness of this well-balanced symbiosis seems to be essential for the maintenance of a healthy state, and several reports have shown that a state of dysbiosis is often associated with diseases, including inflammatory bowel disease, allergies, colorectal cancer, and liver diseases, as well as obesity, diabetes, and cardiovascular diseases [2]. Dysbiosis may be defined as an imbalanced microbiota, including four types of imbalance: (i) loss of keystone species, (ii) reduced richness or diversity, (iii) increased pathogens or pathobionts, or (iv) modification or shift in metabolic capacities [9] (Fig. 11.2).

The link with obesity

The first link between gut microbiota and obesity came from studies in germ-free rodents. These animals eat more, move less, develop less fat content, and are resistant to diet-induced obesity. Conventionalization of germ-free mice resulted in a 60% increase in body fat mass, accompanied by increased leptin and insulin levels and linked to increased absorption of monosaccharides from the gut lumen, with resulting induction of hepatic de novo lipogenesis [16]. A comparison of the microbiota of lean and obese mice revealed that in obese mice (ob/ob animals), the relative abundance of Bacteroidetes was lower and that of Firmicutes was higher [17]. Moreover, transplanting microbiota from obese animal to germ-free mice resulted in a greater increase in total body fat compared with transplanting microbiota from lean animals, highlighting the contributory role of microbiota to obesity [18]. In a study comparing the microbiota from a dozen obese people with that of a few lean controls, the authors reported that the decreased proportion of Bacteroidetes and the increased proportion of Firmicutes observed in obese mice were also observed in obese people [19]. They

Fig. 11.2. Intestinal microbiota dysbiosis in obesity and physiological perturbation. AngPTL4, angiopoietin-like 4; BA, bile acids; FA, fatty acids; GLP-1, glucagon-like peptide 1; LPL, lipoprotein lipase; LPS, lipopolysaccharide; PYY, peptide YY; SCFA, short-chain fatty acids; TG, triglycerides; TMA, trimethylamine; TMAO, trimethylamine *N*-oxide.



also reported that obese people losing weight on a low-calorie diet had a more balanced microbiota, with an increased proportion of Bacteroidetes and a decreased proportion of Firmicutes, more similar to the microbiota of lean controls.

After this pioneering work, other researchers developed approaches to better understand the mechanisms by which the microbiota can contribute to metabolic syndrome and obesity [20]. Large cohorts of patients were studied.

The MetaHIT consortium investigated the composition of the human gut microbiota in a population sample of 123 non-obese and 169 obese individuals from a Danish cohort study called Inter99 [21]. A quantitative metagenomic pipeline was applied, and the study found two groups of individuals that differed by the number of genes in their metagenome, and thus the gut bacterial richness. About a quarter of the population had low bacterial richness. Individuals with a low gene count had higher adiposity, reduced insulin sensitivity, higher dyslipidaemia, and higher inflammatory status compared with those with a high gene count. The obese individuals in the group with a low gene count gained more weight during the 10 years of follow-up before stool sampling [21].

Similar observations were made in a cohort of obese individuals in France who were recruited to follow a hyper-low-calorie diet with increased intake of protein and fibre [22]. Although the microbial gene richness of the participants increased by 25% after the 6-week diet, the obese individuals with low bacterial richness benefited the least from the diet, whereas those with higher bacterial richness at the start of the diet lost more weight and had a larger improvement in metabolic status.

Interestingly, only a few bacterial species are sufficient to distinguish between individuals with a low gene count and those with high bacterial richness [21]. Among the species that are more prevalent in individuals with high bacterial richness, the analysis highlighted two species: *Faecalibacterium prausnitzii*, a bacterium that was previously described as lacking in patients with inflammatory bowel disease and that has anti-inflammatory properties [23], and *Akkermansia muciniphila*, a bacterium that was found to be associated with body fat mass and glucose intolerance in mice and that was further confirmed to be linked with a healthier metabolic phenotype and better clinical outcomes after a hyper-low-calorie diet in overweight or obese adults [24]. Among the species that are more prevalent in individuals with low bacterial richness are *Bacteroides* strains and *Ruminococcus gnavus*, which are considered to be pro-inflammatory and are often found in patients with inflammatory bowel disease.

Such a phylogenetic shift has also been confirmed at the functional level. Low bacterial richness is associated with a reduction in butyrate-producing bacteria, reduced production of hydrogen and methane, increased sulfate reduction and mucin degradation, increased endotoxaemia, and a higher capacity to manage exposure to oxygen/oxidative stress [21].

Dietary habits seem to be associated with microbiota richness [25]. A dietary pattern with high consumption of potatoes, confectionery, and sugary drinks and low intake of fruits and yogurt was correlated with low microbiota richness, whereas a dietary pattern with low consumption of confectionery and sugary drinks and high intake of fruits, vegetables, soups, and yogurt was correlated with higher microbiota richness.

Mechanisms

The proposed mechanisms by which gut microbiota dysbiosis and loss of richness can promote obesity and insulin resistance are diverse. They are often derived from mouse models and still require complete validation in humans. Dysbiosis is linked to increased energy harvest from food, altered fermentation of fibres, and increased endotoxaemia. These changes in microbiota functions have an impact on different tissues, including the intestine, muscles, adipose tissues, the liver, and the brain [26].

In the intestine, the changes result in increased permeability of the epithelium, allowing translocation of bacteria as well as bacterial products, such as lipopolysaccharides. Moreover, secretion by enteroendocrine cells of hormones, including peptide YY (PYY), glucagon-like peptide 1 (GLP-1), and neurotensin, is impaired, with effects on the brain, resulting in reduced satiety, as well as on the liver and on gut motility. The short-chain fatty acids acetate and propionate are taken up by hepatocytes and serve as substrates for lipogenesis and gluconeogenesis. Thus, increased triglyceride production by the liver, associated with reduced expression of angiopoietin-like 4 (AngPTL4), an inhibitor of lipoprotein lipase, by the small intestine, leads to increased triglyceride incorporation in adipose tissues [26]. Increased inflammation is also observed in different tissues, including gut, liver, and adipose tissues. A reduction of fatty acid oxidation by muscles is also observed.

Finally, the metabolism of bile acids and choline is affected. Perturbation of choline metabolism results in increased production by intestinal microbes of trimethylamine, which is further metabolized by hepatocytes to trimethylamine *N*-oxide, a compound that is associated with liver and cardiovascular diseases [27]. Primary bile acids are transformed by the intestinal microbiota to secondary bile acids, which are potent signalling molecules through

the activation of FXR, a nuclear receptor, and TGR5, a G protein-coupled receptor; these receptors are expressed in intestinal enteroendocrine cells, resulting in the modification of glucose homeostasis [26].

Conclusions

Dysbiosis in intestinal microbiota has been associated with obesity. A loss of bacterial gene richness is linked to more severe metabolic syndrome and lower sensitivity to weight loss after caloric restriction. The role of the gut microbiota in the development and chronicity of obesity still needs to be clarified, and the mechanisms of action in humans remain to be deciphered. Strategies to transiently modulate the human intestinal microbiota and to potentially increase its richness need to be explored [22, 25]. Specific nutrition, prebiotics, and probiotics may be efficient avenues for the prevention of obesity. The recent success of a diet rich in non-digestible carbohydrates in children with Prader–Willi syndrome, resulting in weight loss and reduction of inflammation as well as structural changes of the intestinal microbiota, highlights the feasibility of dietary modulation of the gut microbiome to manage metabolic diseases [28].

Key points

- The human microbiota is a dense and diverse microbiome.
- It includes 100 trillion microorganisms, as many as the number of cells in the human body.
- Each individual harbours hundreds of different species, most of which (70–80% of the dominant species) have not yet been cultured.
- A few dozen species are conserved between individuals (a core), representing a stable community.
- The gut microbiota is a true organ, protecting health and well-being throughout all life stages.
- The colonic microbiota is a key organ, interacting with food (fermentation), interacting with cells (the immune and nervous systems), and protecting against pathogens (barrier function).
- Dysbiosis has been observed in several chronic diseases.
- Dysbiosis is observed in obesity, and a loss of microbiota richness and diversity is associated with inflammatory status.

Research needs

- Standardization of analysis tools and processes is required.
- Longitudinal studies are needed.
- The impact of medication/drugs should be considered.
- Mechanisms of action remain to be deciphered.
- Holistic studies should be designed, associating excellent phenotyping of patients and deep characterization using metabolomics, immunomics, transcriptomics, and metagenomics.
- An ecological understanding of the intestinal ecosystem is needed.

References

1. Bäckhed F, Ley RE, Sonnenburg JL, Peterson DA, Gordon JI (2005). Host-bacterial mutualism in the human intestine. Science. 307(5717):1915–20. http://dx.doi.org/10.1126/science.1104816 PMID:15790844

2. Blottière HM, de Vos WM, Ehrlich SD, Doré J (2013). Human intestinal metagenomics: state of the art and future. Curr Opin Microbiol. 16(3):232–9. http://dx.doi.org/10.1016/j.mib.2013.06.006 PMID:23870802

3. van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, et al. (2013). Duodenal infusion of donor feces for recurrent *Clostridium difficile*. N Engl J Med. 368(5):407–15. http://dx.doi.org/10.1056/NEJMoa1205037 PMID:23323867

4. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, et al.; MetaHIT Consortium (2010). A human gut microbial gene catalogue established by metagenomic sequencing. Nature. 464(7285):59–65. http://dx.doi.org/10.1038/nature08821 PMID:20203603

5. Nelson KE, Weinstock GM, Highlander SK, Worley KC, Creasy HH, Wortman JR, et al.; Human Microbiome Jumpstart Reference Strains Consortium (2010). A catalog of reference genomes from the human microbiome. Science. 328(5981):994–9. http://dx.doi.org/10.1126/science.1183605 PMID:20489017

6. Li J, Jia H, Cai X, Zhong H, Feng Q, Sunagawa S, et al.; MetaHIT Consortium; MetaHIT Consortium (2014). An integrated catalog of reference genes in the human gut microbiome. Nat Biotechnol. 32(8):834–41. http://dx.doi.org/10.1038/nbt.2942 PMID:24997786

7. Xiao L, Feng Q, Liang S, Sonne SB, Xia Z, Qiu X, et al. (2015). A catalog of the mouse gut metagenome. Nat Biotechnol. 33(10):1103–8. http://dx.doi.org/10.1038/nbt.3353 PMID:26414350

8. Dominguez-Bello MG, Blaser MJ, Ley RE, Knight R (2011). Development of the human gastrointestinal microbiota and insights from high-throughput sequencing. Gastroenterology. 140(6):1713–9. http://dx.doi.org/10.1053/j.gastro.2011.02.011 PMID:21530737

9. Vangay P, Ward T, Gerber JS, Knights D (2015). Antibiotics, pediatric dysbiosis, and disease. Cell Host Microbe. 17(5):553–64. http://dx.doi.org/10.1016/j.chom.2015.04.006 PMID:25974298

10. Lepage P, Leclerc MC, Joossens M, Mondot S, Blottière HM, Raes J, et al. (2013). A metagenomic insight into our gut's microbiome. Gut. 62(1):146–58. http://dx.doi.org/10.1136/gutjnl-2011-301805 PMID:22525886

11. Tap J, Mondot S, Levenez F, Pelletier E, Caron C, Furet J-P, et al. (2009). Towards the human intestinal microbiota phylogenetic core. Environ Microbiol. 11(10):2574–84. http://dx.doi.org/10.1111/j.1462-2920.2009.01982.x PMID:19601958

12. Arumugam M, Raes J, Pelletier E, Le Paslier D, Yamada T, Mende DR, et al.; MetaHIT Consortium (2011). Enterotypes of the human gut microbiome. Nature. 473(7346):174–80. http://dx.doi.org/10.1038/nature09944 PMID:21508958

13. Ding T, Schloss PD (2014). Dynamics and associations of microbial community types across the human body. Nature. 509(7500):357–60. http://dx.doi.org/10.1038/nature13178 PMID:24739969

14. Wu GD, Chen J, Hoffmann C, Bittinger K, Chen Y-Y, Keilbaugh SA, et al. (2011). Linking long-term dietary patterns with gut microbial enterotypes. Science. 334(6052):105–8. http://dx.doi.org/10.1126/science.1208344 PMID:21885731

15. Vandeputte D, Falony G, Vieira-Silva S, Tito RY, Joossens M, Raes J (2016). Stool consistency is strongly associated with gut microbiota richness and composition, enterotypes and bacterial growth rates. Gut. 65(1):57–62 PMID:26069274

16. Bäckhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, et al. (2004). The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci U S A. 101(44):15718–23. http://dx.doi.org/10.1073/pnas.0407076101 PMID:15505215

17. Ley RE, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI (2005). Obesity alters gut microbial ecology. Proc Natl Acad Sci U S A. 102(31):11070–5. http://dx.doi.org/10.1073/pnas.0504978102 PMID:16033867

18. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI (2006). An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 444(7122):1027–31. http://dx.doi.org/10.1038/nature05414 PMID:17183312

19. Ley RE, Turnbaugh PJ, Klein S, Gordon JI (2006). Microbial ecology: human gut microbes associated with obesity. Nature. 444(7122):1022–3. http://dx.doi.org/10.1038/4441022a PMID:17183309

20. Cani PD, Delzenne NM (2009). The role of the gut microbiota in energy metabolism and metabolic disease. Curr Pharm Des. 15(13):1546–58. http://dx.doi.org/10.2174/138161209788168164 PMID:19442172

21. Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G, et al.; MetaHIT consortium (2013). Richness of human gut microbiome correlates with metabolic markers. Nature. 500(7464):541–6. http://dx.doi.org/10.1038/nature12506 PMID:23985870

22. Cotillard A, Kennedy SP, Kong LC, Prifti E, Pons N, Le Chatelier E, et al.; ANR MicroObes consortium (2013). Dietary intervention impact on gut microbial gene richness. Nature. 500(7464):585–8. http://dx.doi.org/10.1038/nature12480 PMID:23985875

23. Sokol H, Pigneur B, Watterlot L, Lakhdari O, Bermúdez-Humarán LG, Gratadoux J-J, et al. (2008). *Faecalibacterium prausnitzii* is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. Proc Natl Acad Sci U S A. 105(43):16731–6. http://dx.doi.org/10.1073/pnas.0804812105 PMID:18936492

24. Dao MC, Everard A, Aron-Wisnewsky J, Sokolovska N, Prifti E, Verger EO, et al.; MICRO-Obes Consortium (2016). *Akkermansia muciniphila* and improved metabolic health during a dietary intervention in obesity: relationship with gut microbiome richness and ecology. Gut. 65(3):426–36. PMID:26100928

25. Kong LC, Holmes BA, Cotillard A, Habi-Rachedi F, Brazeilles R, Gougis S, et al. (2014). Dietary patterns differently associate with inflammation and gut microbiota in overweight and obese subjects. PLoS One. 9(10):e109434. http://dx.doi.org/10.1371/journal.pone.0109434 PMID:25330000

26. Tremaroli V, Bäckhed F (2012). Functional interactions between the gut microbiota and host metabolism. Nature. 489(7415):242–9. http://dx.doi.org/10.1038/nature11552 PMID:22972297

27. Dumas ME, Kinross J, Nicholson JK (2014). Metabolic phenotyping and systems biology approaches to understanding metabolic syndrome and fatty liver disease. Gastroenterology. 146(1):46–62. http://dx.doi.org/10.1053/j.gastro.2013.11.001 PMID:24211299

28. Zhang C, Yin A, Li H, Wang R, Wu G, Shen J, et al. (2015). Dietary modulation of gut microbiota contributes to alleviation of both genetic and simple obesity in children. EBioMedicine. 2(8):966–82. http://dx.doi.org/10.1016/j.ebiom.2015.07.007 PMID:26425705

CHAPTER 12.

Molecular and metabolic mechanisms underlying the obesity–cancer link

Ciara H. O'Flanagan, Laura W. Bowers, Emma H. Allott, and Stephen D. Hursting

During the past 50 years in the USA, the prevalence of obesity, defined as having a body mass index (BMI) of 30 kg/m^2 or greater, has tripled. Today, nearly 40% of adults and 20% of children in the USA are obese [1]. Worldwide, more than 600 million adults are obese and 2.1 billion are overweight [2]. Obesity increases the risk of several chronic diseases and comorbidities [3], including type 2 diabetes, cardiovascular disease, hypertension, chronic inflammation, and, as discussed in this chapter, cancer.

In the USA, obesity has recently surpassed tobacco use as the leading preventable cause of cancer-related death [4]. As illustrated in Fig. 12.1, obese individuals are at a higher risk of developing several different cancer types, including breast (in postmenopausal women), ovarian, liver, kidney, colon, pancreatic, gastric, oesophageal, and endometrial cancers [5]. An estimated 13% of incident cancer cases worldwide, and approximately 20% of incident cases in Europe and North America, are attributable to obesity [6]. More than 40 000 new cancer diagnoses in the USA each year are attributed to obesity. In addition to having a higher risk of developing cancer, obese individuals are more likely to have reduced response to anticancer therapies [7], and obesity is implicated in about 20% of all cancer-related mortalities [8]. This includes prostate cancer, for which obesity is associated with progression but not incidence [9].

This chapter characterizes the many ways in which obesity can influence normal epithelial tissue homeostasis, cancer development, and/or cancer progression, including metabolic perturbations involving hormonal, growth factor, and inflammatory alterations as well as interactions with the stroma and vasculature.

Obesity affects each hallmark of cancer

Hanahan and Weinberg identified the essential biological capabilities acquired by all cancer cells during the multistep development of a tumour in their classic article "The hallmarks of cancer", published in 2000 [10], and updated these in their 2011 article "Hallmarks of cancer: the next generation" [11]. These essential aberrations of cancer cells, summarized in Fig. 12.2, include sustaining proliferative signalling, increased chronic inflammation, evading growth suppressors, resisting cell death, genome instability, enabling replicative immortality, inducing angiogenesis, and activating processes related to invasion and metastasis. Conceptual progress in the decade between

Fig. 12.1. Obesity-related cancers. Based on recent systematic reviews and meta-analyses (www.aicr.org/continuous-update-project/), obesity is associated with an increased risk of developing and dying from the following cancers: breast (in postmenopausal women), ovarian, endometrial, liver, pancreatic, kidney, colon, oesophageal (adenocarcinoma subtype), and gallbladder. In addition, obesity is associated with progression (but not incidence) of prostate cancer. Reprinted with permission from Hursting SD, O'Flanagan CH, Bowers LW (2015). Breaking the cancer-obesity link. The Scientist. 1 November 2015. Available from: http://www.the-scientist.com/?articles.view/articleNo/44280/title/Breaking-the-Cancer-Obesity-Link/.

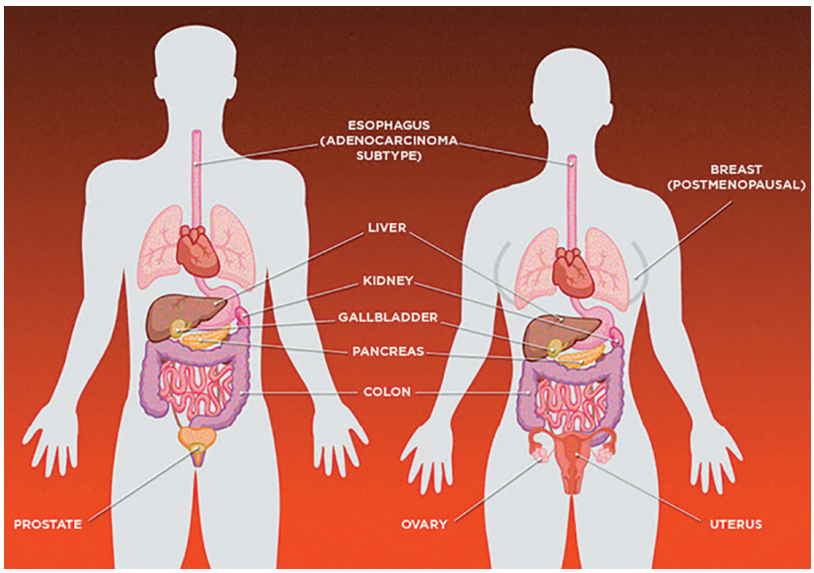
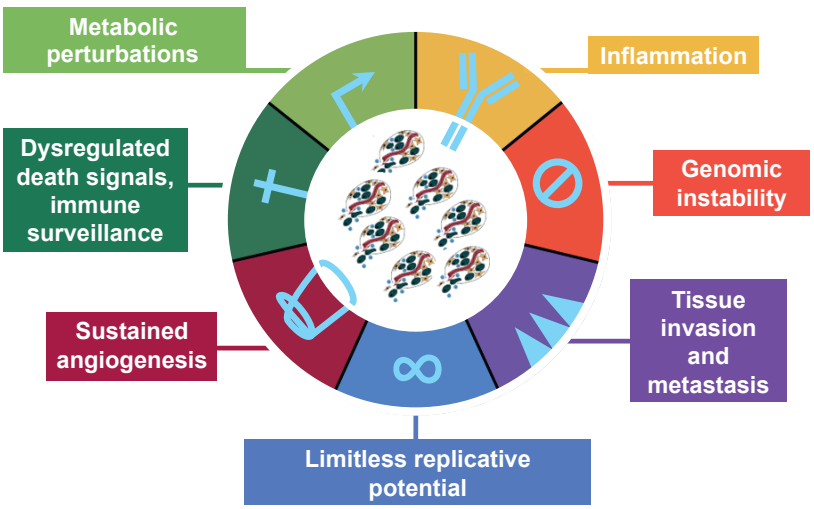


Fig. 12.2. Obesity affects each of the well-established hallmarks of cancer, including reprogrammed energy metabolism, sustained proliferative signalling, increased chronic inflammation, increased genome instability, enabled replicative immortality, enhanced angiogenesis, activated processes related to invasion and metastasis, and resistance to growth suppressors, cell death inducers, and immunoregulators. Reprinted from Hanahan and Weinberg (2011) [11], copyright 2011, with permission from Elsevier.



these two articles led to the identification of additional hallmarks, including reprogramming of energy metabolism, evading immune destruction, and the creation of the tumour microenvironment through the recruitment of various non-cancerous cells. Emerging evidence supports the concept that metabolic reprogramming, inflammation, and genome instability (including epigenetic changes) underlie many of the other hallmarks and foster multiple hallmark functions.

In the case of cancer-associated metabolic reprogramming, cancer cells preferentially metabolize glucose through glycolysis rather than oxidative phosphorylation, even in the presence of oxygen [11–13]. Thus, citric acid cycle intermediates are not used for adenosine triphosphate (ATP) production and are shuttled out of the mitochondria, providing precursors for nucleotide, amino acid, and lipid synthesis pathways for the dividing cell [13]. In this way, cancer cells readily take up and metabolize glucose to provide substrate for production of daughter cells, and levels of glucose uptake transporters (GLUT) and glycolytic enzymes (e.g. hexokinase II) are elevated in most cancers [14].

Metabolic syndrome and systemic metabolic perturbations

The interactions between cellular energetics in cancer cells and the systemic metabolic changes associated with obesity are emerging as critical drivers of obesity-related cancer. Intrinsically linked with obesity is metabolic syndrome, which is characterized by insulin resistance, hyperglycaemia, hypertension, and dyslipidaemia and is associated with alterations in several cancer-related host factors. In both obesity and metabolic syndrome, alterations occur in circulating levels of insulin and

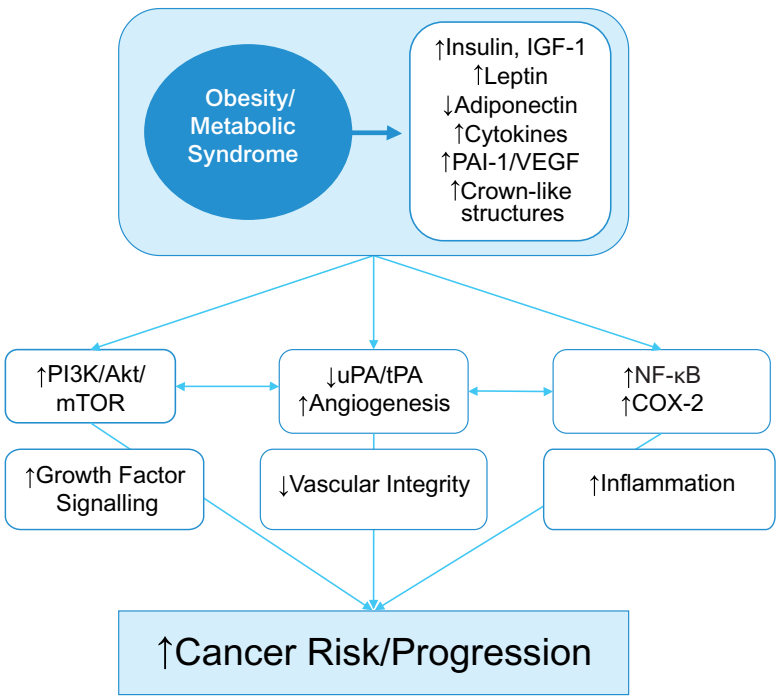
insulin-like growth factor-1 (IGF-1); adipokines, such as leptin, adiponectin, resistin, and monocyte chemotactic factors; inflammatory factors, such as interleukin-6 (IL-6), IL-10, and IL-17; interferon-γ and tumour necrosis factor-α (TNF-α); several chemokines; lipid mediators, such as prostaglandin E2 (PGE2); and vascular-associated factors, such as vascular endothelial growth factor (VEGF) and plasminogen activator inhibitor-1 (PAI-1) [15, 16]. Each of these factors has a putative role in the development and progression of cancer as well as several other chronic diseases [15, 16], including cardiovascular disease and type 2 diabetes. These factors are explored in more detail below.

Insulin, IGF-1, and growth factor signalling

As shown in Fig. 12.3, insulin, a peptide hormone produced by pancreatic β-cells, is released in response to elevated blood glucose. Hyperglycaemia is a hallmark of metabolic syndrome and is associated with insulin resistance, aberrant glucose metabolism, chronic inflammation, and the production of other metabolic hormones, such as IGF-1 [17]. IGF-1 is a peptide growth factor produced primarily by the liver after stimulation by growth hormone. IGF-1 regulates the growth and development of many tissues, particularly during embryonic development [18]. IGF-1 in circulation is typically bound to IGF-binding proteins (IGFBPs), which regulate the amount of free IGF-1 bioavailable to bind to the IGF-1 receptor (IGF-1R) to induce growth or survival signalling [19]. In metabolic syndrome, the amount of bioavailable IGF-1 is increased via hyperglycaemia-induced suppression of IGFBP synthesis and/or hyperinsulinaemia-induced promotion of hepatic growth hormone receptor expression and IGF-1 synthesis [17]. Elevated circulating IGF-1 is an established risk factor for many cancer types [19].

Downstream of both the insulin receptor and IGF-1R is the phosphatidylinositol-3 kinase (PI3K)/Akt pathway (Fig. 12.3), one of the most commonly altered pathways in epithelial cancers [20]. This pathway integrates intracellular and extracellular signals, such as growth factor concentrations and nutrient availability, to regulate cell survival and proliferation, protein translation, and metabolism. Activation of receptor tyrosine kinases, such as the insulin receptor or IGF-1R, stimulates PI3K to produce lipid messengers that facilitate activation of the Akt cascade [20]. Akt regulates the mammalian target of rapamycin (mTOR) [21], which controls cell growth, proliferation, and survival through downstream mediators. mTOR activation is inhibited by increased

Fig. 12.3. Obesity causes many metabolic disturbances (often characterized as metabolic syndrome), including insulin resistance, hyperinsulinaemia, and elevated bioavailable insulin-like growth factor-1 (IGF-1), which can activate receptor tyrosine kinase signalling through the phosphatidylinositol-3 kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway. An increase in steady-state signalling through this pathway can drive increases in cellular proliferation and protein translation, and reinforce cancer-associated metabolic reprogramming. Obesity is also associated with adipose remodelling, including the formation of crown-like structures and pro-inflammatory changes in the adipose secretome, including increased leptin and cytokines and decreased adiponectin. This typically results in increased inflammatory signalling through the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway and increased cyclooxygenase-2 (COX-2) activity. In addition, obesity often increases circulating levels of plasminogen activator inhibitor-1 (PAI-1) and vascular endothelial growth factor (VEGF), which can result in increased angiogenesis and decreased vascular integrity regulators, such as tissue plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA).



adenosine monophosphate (AMP)-activated protein kinase (AMPK) under low-nutrient conditions [22]. Increased activation of mTOR is common in tumours and many normal tissues from obese and/or diabetic mice [23], and specific mTOR inhibitors block the tumour-enhancing effects of obesity in mouse models [24–26]. Furthermore, both rapamycin (an mTOR inhibitor) and metformin (an AMPK activator) have been shown to block tumour formation in multiple animal models [27–31]. Interestingly, in some model systems rapamycin has also been shown to block inflammation associated with tumour formation [32].

Chronic inflammation: the role of adipose tissue

White adipose tissue (WAT) consists mainly of adipocytes, which serve to store neutralized triacylglycerides for use during periods of energy deficit. This is in contrast to brown adipose tissue, which generates body heat, particularly in neonate infants [33]. The secretome of white versus brown adipocytes differs markedly (Fig. 12.4). WAT is characterized by secretion of leptin, resistin, PAI-1, inflammatory cytokines, and free fatty acids, whereas brown adipose tissue is characterized by secretion of bone morphogenetic proteins, lactate (which induces uncoupling proteins), retinaldehyde, triiodothyronine (T3), and other factors associated with response to cold stress and/or increased energy expenditure [33]. Moreover, brown adipocytes produce adiponectin (but not leptin) and fibroblast growth factor-21, which can be anti-inflammatory and insulin-sensitizing [33]. Also contained in WAT are several types of stromal cells, including pre-adipocytes, vascular cells, fibroblasts, and a host of immune cells, such as adipose tissue macrophages [34].

The increase in adipose tissue mass associated with obesity drives chronic inflammation in at least three ways, depicted in Figs. 12.3 and 12.4 and summarized below.

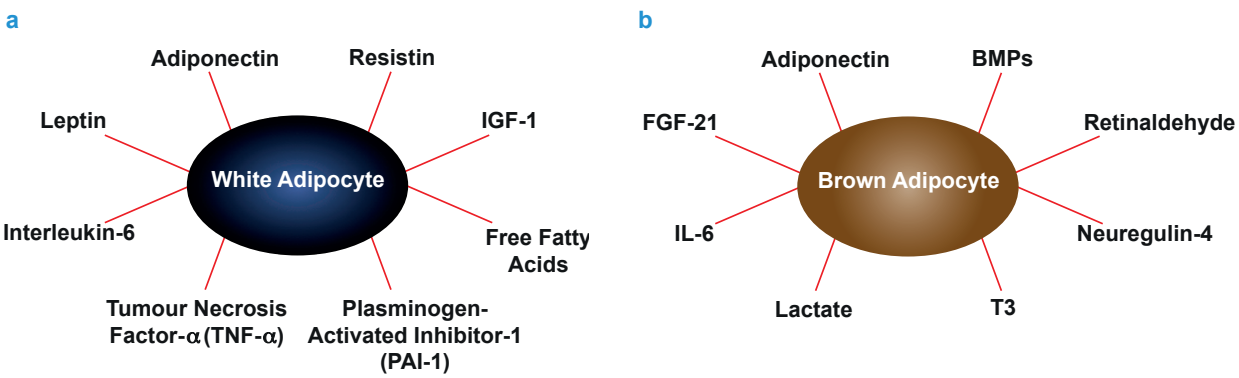
Altered adipose secretome

Leptin

Levels of leptin, a peptide hormone produced by adipocytes, are positively correlated with adipose storage and nutritional status, and leptin functions as an energy sensor. Leptin release from adipocytes signals to the brain to reduce appetite. In an obese state, WAT overproduces leptin and the brain becomes desensitized to the signal [35]. Leptin release is stimulated by several hormones and signalling factors, including insulin, glucocorticoids, TNF-α, and estrogen [36]. Leptin interacts directly with peripheral tissues, interacts indirectly with hypothalamic pathways, and modulates immune function, cytokine production, angiogenesis, carcinogenesis, and many other biological processes [36].

The leptin receptor is structurally and functionally similar to class I cytokine receptors, including in their ability to signal through the signal transducer and activator of transcription (STAT) family of transcription factors. STATs induce transcription programmes for several cellular processes, including cell growth, proliferation, survival, migration, and differentiation, and the activity of STATs is commonly deregulated in cancer [37].

Fig. 12.4. The secretomes of white versus brown adipocytes. (a) White adipocytes, when they accumulate triglyceride, produce more cancer-associated factors, such as leptin, resistin, insulin-like growth factor-1 (IGF-1), free fatty acids, tumour necrosis factor-α (TNF-α), and interleukin-6 (IL-6). They also decrease their production of adiponectin. (b) The secretome of brown adipocytes includes several factors involved in thermogenesis, decreased inflammation, normalized insulin sensitivity, and/or increased energy expenditure, such as adiponectin, bone morphogenetic proteins (BMPs), neuregulin-4, lactate, triiodothyronine (T3), retinaldehyde, and fibroblast growth factor-21 (FGF-21).



Adiponectin

Adiponectin is the most abundant hormone secreted from WAT. In contrast with leptin, levels of adiponectin are negatively correlated with adiposity. Adiponectin functions to counter the metabolic alterations associated with obesity and hyperleptinaemia by modulating glucose metabolism, increasing fatty acid oxidation and insulin sensitivity [38], and reducing IGF-1/mTOR signalling through AMPK activation. Adiponectin can also reduce pro-inflammatory cytokine expression and induce anti-inflammatory cytokine expression via inhibition of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [39]. Due to the anti-tumorigenic function of adiponectin, drugs mimicking its action are now coming to the fore as anticancer drugs and may pave the way in helping to treat obesity-related cancers [40]. Although leptin levels correlate with poor cancer prognosis and adiponectin levels correlate with favourable prognosis, it is the ratio of these two adipokines that may be important in cancer, rather than their absolute concentrations [41].

Sex hormones

Sex hormones have long been associated with obesity [42]. BMI is positively correlated with levels of estrone, estradiol, and free estradiol in postmenopausal women who are not taking hormone replacement therapy [43]. Increased estrogen levels are also observed in obese men [42, 44], whereas testosterone levels are significantly decreased [45]. Changes in sex hormones can have profound effects on the body, including menstrual disturbances, hirsutism, hypertension, erectile dysfunction, gynaecomastia, and increased adiposity [42]. Moreover, high estrogen levels are associated with a significantly increased risk of postmenopausal breast cancer [42, 43, 46], ovarian cancer [47], and endometrial cancer [48].

In premenopausal women, estrogen is synthesized mainly in the ovaries, whereas in postmenopausal women, endogenous estrogen is produced at peripheral sites. In obese postmenopausal women, adipose tissue is the main source of estrogen biosynthesis [43]. Circulating estrogens bind to either of the cytoplasmic estrogen receptors, ERα and ERβ, resulting in receptor dimerization and recruitment to the nucleus. ERα and ERβ can bind directly to DNA or to other transcription factors to induce expression of genes involved in a variety of cellular processes, including growth, proliferation, and differentiation [49]. The two receptors have opposite roles in cancer: ERα is mitogenic and ERβ is tumour-suppressive [50]. Obese postmenopausal cohorts are more consistently associated with increased risk of hormone receptor-positive than hormone receptor-negative breast cancers [51]. The increase in circulating estrogens and a greater risk of ER-positive breast cancer in obese women has led to several trials investigating the effectiveness of adjuvant therapy with aromatase inhibitors and ER antagonists (e.g. tamoxifen) in obese breast cancer patients [52]. Obesity may also play a role in development of male breast cancer, because aromatase in adipocytes converts androgens to estrogens. More than 90% of male breast cancer is ER-positive, and tamoxifen forms part of the standard of care [53].

Crown-like structures

Obesity further drives subclinical inflammation in visceral and subcutaneous WAT, characterized by rings of activated macrophages surrounding engorged or necrotic adipocytes and referred to as crown-like structures. This adipocyte–macrophage interaction results in a pro-inflammatory secretome from both cell types that activates the cellular transcription factor NF-κB, leading to increased levels of cytokines and other inflammatory factors, and triggers inflammation [54].

Adipose remodelling and lipid infiltration in other tissues

Stored triacylglycerides undergo lipolysis within the cytoplasm of adipocytes and are released into the bloodstream as free fatty acids during times of low substrate availability or heightened energy requirements [55]. Once in the circulation, free fatty acids can be used for β-oxidation by peripheral tissues to provide intermediates for both the citric acid cycle and oxidative phosphorylation to generate energy. In a diseased state such as metabolic syndrome or type 2 diabetes, WAT does not respond appropriately to changes in energy requirements, resulting in altered metabolic signalling characterized by elevated adipokine and cytokine production [56]. As stated above, cancer cells undergo a massive metabolic reprogramming to adapt to changing energy needs associated with the generation of daughter cells [11, 13]. In particular, there is a high demand for fatty acids for the formation of lipid bilayers in dividing cells. Excess WAT therefore promotes tumour cell proliferation through the provision of circulating fatty acids [57].

When lipid storage capacity in adipose tissue is exceeded, surplus lipids often accumulate within muscle, liver, and pancreatic tissue [58]. As a consequence, muscle dysfunction and hepatic and pancreatic steatosis can develop; each has been positively associated with insulin resistance and ultimately leads

to impairment of lipid processing and clearance within these tissues [58]. As a result of lipotoxic and inflammation-mediated adipocyte dysfunction, the liver and pancreas are unable to cope with the overflow of lipids and lipotoxic effects of free fatty acids [59]. Consequently, lipid intermediates impair the function of cellular organelles and cause further release of cytokines, which foster insulin resistance by activating intracellular kinases, thus impairing the cell's ability to respond to insulin.

Obesity is the most common cause of non-alcoholic fatty liver disease (NAFLD), a spectrum of diseases including variable degrees of simple steatosis, non-alcoholic steatohepatitis (NASH), and cirrhosis [60]. Simple steatosis is benign, whereas NASH is characterized by hepatocyte injury, inflammation, and/or fibrosis, which can lead to cirrhosis, liver failure, and hepatocellular carcinoma [61]. NAFLD is diagnosed when liver fat content is greater than 5–10% by weight in the absence of alcohol use or other liver disease [62]. About 80% of cases of cryptogenic cirrhosis present with NASH, and 0.5% of these patients will progress to hepatocellular carcinoma, a percentage that increases significantly with hepatitis C-associated cirrhosis [63].

NAFLD is one of the most common chronic diseases [64, 65], and the incidence in both adults and children is rising rapidly [65, 66]. Furthermore, the prevalence of fatty liver disease has increased concomitantly with the increase in childhood obesity during the past 30 years [66]. NAFLD is a multifactorial disorder linked to components of metabolic syndrome, including hypertriglyceridaemia, obesity, and insulin resistance [62]. Ultimately, hepatic steatosis leads to impairment of lipid processing and clearance in the liver. Lipotoxic and inflammation-mediated mechanisms have been suggested to be responsible for adipocyte dysfunction and remodelling of peripheral lipid storage capacities, resulting in release of free fatty acids and increased hepatic lipid burden [67]. In NAFLD, the liver is overwhelmed with excess lipids. The lipotoxic effects of free fatty acids and lipid intermediates impair the function of liver cell organelles by mechanisms that involve production of reactive oxygen species, endoplasmic reticular stress, activation of pro-inflammatory programmes, and eventually death of hepatic cells [68]. The accumulation of toxic lipids and the release of pro-inflammatory cytokines cause insulin resistance by activating JNK, PKC, and other kinases, thereby impairing insulin signalling [69]. Disturbed insulin signalling contributes to diminished fatty acid oxidation and assembly and secretion of very-low-density lipoprotein (VLDL) through inadequate regulation of peroxisome proliferator-activated receptor (PPARα and PPARγ) [70]. Activation of cellular defence programmes, specifically activation of NF-κB, is an important determinant for disease progression from steatosis to NASH [71]. Although those at risk of hepatocellular carcinoma currently make up a small proportion of the population, as the prevalence of obesity and type 2 diabetes continues to rise, this will become a more significant public health concern.

Pancreatic adipocyte infiltration and fat accumulation appears to be an early event in obesity-associated pancreatic endocrine dysfunction and can trigger pancreatic steatosis, non-alcoholic fatty pancreatic disease (NAFPD), and pancreatitis [72, 73]. In addition, "fatty pancreas" has been positively associated with visceral WAT mass and systemic insulin resistance [72, 73]. Together, pancreatic steatosis and NAFPD contribute to the already complex metabolic and inflammatory perturbations associated with obesity and metabolic syndrome.

Angiogenesis

As adipose tissue grows, so too does the need for new blood vessels. Angiogenesis is the outgrowth of new blood vessels from existing blood vessels and is mediated by factors such as VEGF, which can be produced and secreted by both adipocytes and tumour cells. VEGF is angiogenic, is mitogenic, and has vascular permeability-enhancing activities specific for endothelial cells [74]. Circulating levels of VEGF are increased in obese individuals, and expression of VEGF is associated with poor prognosis in several obesity-related cancer types [75]. Secretion of angiogenic factors induces local blood vessel development through interactions with proximal endothelial cells; release of VEGF into the circulation can interact with peripheral tissues and may also facilitate angiogenesis at tumour sites. In addition to providing adequate oxygen and nutrients to cells within the primary tumour mass, newly forming blood vessels presumably provide a route into the circulation for cells to metastasize to distal sites in the body. Excess VEGF may complicate treatment options for obese patients, because anti-VEGF therapies (e.g. bevacizumab) have reduced efficacy in obese colon cancer patients compared with non-obese individuals [76].

Another angiogenic factor, PAI-1, is a serine protease inhibitor produced by endothelial cells, stromal cells, and adipocytes in visceral WAT [77]. Increased circulating PAI-1 levels, frequently found in obese subjects, are associated with an increased risk of atherosclerosis and cardiovascular disease, diabetes, and several cancer types [77]. PAI-1, through its inhibition of plasminogen activators, regulates fibrinolysis and the integrity of the extracellular matrix [78]. Remodelling of the extracellular matrix is a key feature of invasive cancers

and is involved in the development of metastatic disease [79]. Therefore, PAI-1 is a potential anti-angiogenic target in some obese populations. However, caution should also be exercised when administering such treatments in obese patients, because the application of an anti-angiogenic therapy will induce hypoxia in the primary tumour and may encourage cells to metastasize, which is already a concern in obese patients.

Emerging mechanism linking obesity and cancer: the microbiome

An emerging field of research is the influence of the microbiome, the community of commensal, symbiotic, and pathogenic microorganisms that inhabit an individual, on obesity and related chronic diseases. In both humans and mice, two divisions of bacteria, the Bacteroidetes and Firmicutes, represent more than 90% of all phylogenetic types in the gut, although there are large differences between individuals at the species level [80]. The relative ratio of these two divisions is significantly altered with obesity, with a decrease in Bacteroidetes and a corresponding increase in Firmicutes, resulting in a microbiome with an enhanced ability to harvest dietary energy. This increased metabolic potential is transmissible between subjects: colonization of a germ-free mouse with the microbiota of an obese (versus lean) mouse leads to a significantly greater gain of fat mass, independent of energy intake [81].

Obesity is also associated with an overall reduction in gut bacterial diversity [82], and decreased bacterial richness has been linked to elevated systemic inflammation, measured by plasma C-reactive protein and white blood cell counts [83]. Furthermore, weight loss does not significantly improve C-reactive protein levels in obese subjects with low microbiome richness [84], suggesting that resistance to the inflammation-reducing effects of weight loss may be mediated by differences in microbiome richness. Other studies have demonstrated that high-fat feeding is accompanied by impairments in gut barrier function, including decreased gene expression for tight junction proteins and higher plasma levels of lipopolysaccharide, a component of the outer membrane of gram-negative bacteria [85]. Lipopolysaccharide has previously been shown to induce metabolic endotoxaemia, characterized in part by elevated infiltration of macrophages into adipose tissue and expression of pro-inflammatory cytokines [86]. Increased systemic inflammation is also apparent in mice fed high-fat diets, and these diet-related effects can be completely prevented by treatment with a broad-spectrum antibiotic [85]. Therefore, gut microbial dysbiosis and impaired barrier function associated with obesity can induce chronic systemic and adipose tissue inflammation. Given the known role of this type of inflammation in the progression of many cancer types [87], it is highly probable that obesity-induced perturbations of the gut microbiota are a contributing factor in the obesity–cancer link.

Key points

- Obesity is an established risk factor for many cancers.
- Obese cancer patients, relative to non-obese patients, often have poorer prognosis, are resistant to chemotherapies, and are more prone to developing distant metastases.
- Multiple mechanisms underlie the obesity–cancer link, and each hallmark of cancer is affected by obesity.
- Perturbations in systemic metabolism and inflammation, and the effects of these perturbations on cancer-prone cells, are a current research focus.
- Obesity-induced changes in the microbiome, and their impact on pro-tumorigenic metabolic and inflammatory signals, are an emerging research area.

Research needs

The association between obesity and many cancers is well established, but with the number of obese adults in the world rising towards 700 million, many important questions remain to be answered, including the following.

- Can the effects of chronic obesity on cancer risk or progression be reversed with weight loss? If so, what are the optimal weight-loss approaches to prevent obesity-related cancers? If not, can weight loss be combined with other interventions (anti-inflammatory agents or targeted interventions to normalize metabolism) to decrease the obesity-associated cancer burden?
- Can we eavesdrop on the cross-talk between adipocytes, macrophages, the microbiota, and epithelial cells to identify ways to disrupt the pro-tumorigenic signals coming from these interactions? This will require a transdisciplinary, systems approach to uncover new targets and intervention strategies.
- How does obesity increase cancer metastases, and what can be done about this?
- How does obesity impair the response to many cancer chemotherapeutic agents, and what can be done about this?

References

1. Flegal KM, Carroll MD, Kit BK, Ogden CL (2012). Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. JAMA. 307(5):491–7. http://dx.doi.org/10.1001/jama.2012.39 PMID:22253363

2. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. (2014). Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 384(9945):766–81. http://dx.doi.org/10.1016/S0140-6736(14)60460-8 PMID:24880830

3. Aronne LJ, Isoldi KK (2007). Overweight and obesity: key components of cardiometabolic risk. Clin Cornerstone. 8(3):29–37. http://dx.doi.org/10.1016/S1098-3597(07)80026-3 PMID:18452840

4. Ligibel JA, Alfano CM, Courneya KS, Demark-Wahnefried W, Burger RA, Chlebowski RT, et al. (2014). American Society of Clinical Oncology position statement on obesity and cancer. J Clin Oncol. 32(31):3568–74. http://dx.doi.org/10.1200/JCO.2014.58.4680 PMID:25273035

5. World Cancer Research Fund/American Institute for Cancer Research (2007). Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington (DC), USA: American Institute for Cancer Research. Available from: http://www.aicr.org/research/research_science_expert_report.html.

6. Arnold M, Pandeya N, Byrnes G, Renehan AG, Stevens GA, Ezzati M, et al. (2014). Global burden of cancer attributable to high body-mass index in 2012: a population-based study. Lancet Oncol. 16(1):36–46. http://dx.doi.org/10.1016/S1470-2045(14)71123-4 PMID:25467404

7. Lashinger LM, Rossi EL, Hursting SD (2014). Obesity and resistance to cancer chemotherapy: interacting roles of inflammation and metabolic dysregulation. Clin Pharmacol Ther. 96(4):458–63. http://dx.doi.org/10.1038/clpt.2014.136 PMID:24960521

8. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ (2003). Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 348(17):1625–38. http://dx.doi.org/10.1056/NEJMoa021423 PMID:12711737

9. Allott EH, Masko EM, Freedland SJ (2013). Obesity and prostate cancer: weighing the evidence. Eur Urol. 63(5):800–9. http://dx.doi.org/10.1016/j.eururo.2012.11.013 PMID:23219374

10. Hanahan D, Weinberg RA (2000). The hallmarks of cancer. Cell. 100(1):57–70. http://dx.doi.org/10.1016/S0092-8674(00)81683-9 PMID:10647931

11. Hanahan D, Weinberg RA (2011). Hallmarks of cancer: the next generation. Cell. 144(5):646–74. http://dx.doi.org/10.1016/j.cell.2011.02.013 PMID:21376230

12. Chen X, Qian Y, Wu S (2015). The Warburg effect: evolving interpretations of an established concept. Free Radic Biol Med. 79:253–63. http://dx.doi.org/10.1016/j.freeradbiomed.2014.08.027 PMID:25277420

13. Ward PS, Thompson CB (2012). Metabolic reprogramming: a cancer hallmark even Warburg did not anticipate. Cancer Cell. 21(3):297–308. http://dx.doi.org/10.1016/j.ccr.2012.02.014 PMID:22439925

14. Ganapathy-Kanniappan S, Geschwind JF (2013). Tumor glycolysis as a target for cancer therapy: progress and prospects. Mol Cancer. 12(1):152. http://dx.doi.org/10.1186/1476-4598-12-152 PMID:24298908

15. Hursting SD, Berger NA (2010). Energy balance, host-related factors, and cancer progression. J Clin Oncol. 28(26):4058–65. http://dx.doi.org/10.1200/JCO.2010.27.9935 PMID:20697088

16. Bonomini F, Rodella LF, Rezzani R (2015). Metabolic syndrome, aging and involvement of oxidative stress. Aging Dis. 6(2):109–20. http://dx.doi.org/10.14336/AD.2014.0305 PMID:25821639

17. Braun S, Bitton-Worms K, LeRoith D (2011). The link between the metabolic syndrome and cancer. Int J Biol Sci. 7(7):1003–15. http://dx.doi.org/10.7150/ijbs.7.1003 PMID:21912508

18. Agrogiannis GD, Sifakis S, Patsouris ES, Konstantinidou AE (2014). Insulin-like growth factors in embryonic and fetal growth and skeletal development (Review). Mol Med Rep. 10(2):579–84. http://dx.doi.org/10.3892/mmr.2014.2258 PMID:24859417

19. Pollak M (2012). The insulin and insulin-like growth factor receptor family in neoplasia: an update. Nat Rev Cancer. 12(3):159–69. http://dx.doi.org/10.1038/nrc3215 PMID:22337149

20. Wong KK, Engelman JA, Cantley LC (2010). Targeting the PI3K signaling pathway in cancer. Curr Opin Genet Dev. 20(1):87–90. http://dx.doi.org/10.1016/j.gde.2009.11.002 PMID:20006486

21. Memmott RM, Dennis PA (2009). Akt-dependent and -independent mechanisms of mTOR regulation in cancer. Cell Signal. 21(5):656–64. http://dx.doi.org/10.1016/j.cellsig.2009.01.004 PMID:19166931

22. Hardie DG, Ross FA, Hawley SA (2012). AMPK: a nutrient and energy sensor that maintains energy homeostasis. Nat Rev Mol Cell Biol. 13(4):251–62. http://dx.doi.org/10.1038/nrm3311 PMID:22436748

23. Moore T, Beltran L, Carbajal S, Strom S, Traag J, Hursting SD, et al. (2008). Dietary energy balance modulates signaling through the Akt/mammalian target of rapamycin pathways in multiple epithelial tissues. Cancer Prev Res (Phila). 1(1):65–76. http://dx.doi.org/10.1158/1940-6207.CAPR-08-0022 PMID:19138937

24. Cifarelli V, Lashinger LM, Devlin KL, Dunlap SM, Huang J, Kaaks R, et al. (2015). Metformin and rapamycin reduce pancreatic cancer growth in obese prediabetic mice by distinct microRNA-regulated mechanisms. Diabetes. 64(5):1632–42. http://dx.doi.org/10.2337/db14-1132 PMID:25576058

25. De Angel RE, Conti CJ, Wheatley KE, Brenner AJ, Otto G, Degraffenried LA, et al. (2013). The enhancing effects of obesity on mammary tumor growth and Akt/mTOR pathway activation persist after weight loss and are reversed by RAD001. Mol Carcinog. 52(6):446–58. http://dx.doi.org/10.1002/mc.21878 PMID:22290600

26. Nogueira LM, Dunlap SM, Ford NA, Hursting SD (2012). Calorie restriction and rapamycin inhibit MMTV-Wnt-1 mammary tumor growth in a mouse model of postmenopausal obesity. Endocr Relat Cancer. 19(1):57–68. http://dx.doi.org/10.1530/ERC-11-0213 PMID:22143497

27. Athar M, Kopelovich L (2011). Rapamycin and mTORC1 inhibition in the mouse: skin cancer prevention. Cancer Prev Res (Phila). 4(7):957–61. http://dx.doi.org/10.1158/1940-6207.CAPR-11-0266 PMID:21733819

28. Back JH, Rezvani HR, Zhu Y, Guyonnet-Duperat V, Athar M, Ratner D, et al. (2011). Cancer cell survival following DNA damage-mediated premature senescence is regulated by mammalian target of rapamycin (mTOR)-dependent inhibition of sirtuin 1. J Biol Chem. 286(21):19100–8. http://dx.doi.org/10.1074/jbc.M111.240598 PMID:21471201

29. Anisimov VN, Zabezhinski MA, Popovich IG, Piskunova TS, Semenchenko AV, Tyndyk ML, et al. (2010). Rapamycin extends maximal lifespan in cancer-prone mice. Am J Pathol. 176(5):2092–7. http://dx.doi.org/10.2353/ajpath.2010.091050 PMID:20363920

30. Tomimoto A, Endo H, Sugiyama M, Fujisawa T, Hosono K, Takahashi H, et al. (2008). Metformin suppresses intestinal polyp growth in *Apc*$^{Min/+}$ mice. Cancer Sci. 99(11):2136–41. http://dx.doi.org/10.1111/j.1349-7006.2008.00933.x PMID:18803638

31. Chaudhary SC, Kurundkar D, Elmets CA, Kopelovich L, Athar M (2012). Metformin, an antidiabetic agent reduces growth of cutaneous squamous cell carcinoma by targeting mTOR signaling pathway. Photochem Photobiol. 88(5):1149–56. http://dx.doi.org/10.1111/j.1751-1097.2012.01165.x PMID:22540890

32. Checkley LA, Rho O, Moore T, Hursting S, DiGiovanni J (2011). Rapamycin is a potent inhibitor of skin tumor promotion by 12-O-tetradecanoylphorbol-13-acetate. Cancer Prev Res (Phila). 4(7):1011–20. http://dx.doi.org/10.1158/1940-6207.CAPR-10-0375 PMID:21733825

33. Wang GX, Zhao XY, Lin JD (2015). The brown fat secretome: metabolic functions beyond thermogenesis. Trends Endocrinol Metab. 26(5):231–7. http://dx.doi.org/10.1016/j.tem.2015.03.002 PMID:25843910

34. Eto H, Suga H, Matsumoto D, Inoue K, Aoi N, Kato H, et al. (2009). Characterization of structure and cellular components of aspirated and excised adipose tissue. Plast Reconstr Surg. 124(4):1087–97. http://dx.doi.org/10.1097/PRS.0b013e3181b5a3f1 PMID:19935292

35. Friedman JM, Mantzoros CS (2015). 20 years of leptin: from the discovery of the leptin gene to leptin in our therapeutic armamentarium. Metabolism. 64(1):1–4. http://dx.doi.org/10.1016/j.metabol.2014.10.023 PMID:25497341

36. Gautron L, Elmquist JK (2011). Sixteen years and counting: an update on leptin in energy balance. J Clin Invest. 121(6):2087–93. http://dx.doi.org/10.1172/JCI45888 PMID:21633176

37. Yu H, Lee H, Herrmann A, Buettner R, Jove R (2014). Revisiting STAT3 signalling in cancer: new and unexpected biological functions. Nat Rev Cancer. 14(11):736–46. http://dx.doi.org/10.1038/nrc3818 PMID:25342631

38. Vaiopoulos AG, Marinou K, Christodoulides C, Koutsilieris M (2012). The role of adiponectin in human vascular physiology. Int J Cardiol. 155(2):188–93. http://dx.doi.org/10.1016/j.ijcard.2011.07.047 PMID:21907426

39. Fantuzzi G (2013). Adiponectin in inflammatory and immune-mediated diseases. Cytokine. 64(1):1–10. http://dx.doi.org/10.1016/j.cyto.2013.06.317 PMID:23850004

40. Otvos L Jr, Haspinger E, La Russa F, Maspero F, Graziano P, Kovalszky I, et al. (2011). Design and development of a peptide-based adiponectin receptor agonist for cancer treatment. BMC Biotechnol. 11(1):90. http://dx.doi.org/10.1186/1472-6750-11-90 PMID:21974986

41. Grossmann ME, Cleary MP (2012). The balance between leptin and adiponectin in the control of carcinogenesis – focus on mammary tumorigenesis. Biochimie. 94(10):2164–71. http://dx.doi.org/10.1016/j.biochi.2012.06.013 PMID:22728769

42. Kirschner MA, Schneider G, Ertel NH, Worton E (1982). Obesity, androgens, estrogens, and cancer risk. Cancer Res. 42(8 Suppl):3281s–5s. PMID:7083187

43. Cleary MP, Grossmann ME (2009). Minireview: Obesity and breast cancer: the estrogen connection. Endocrinology. 150(6):2537–42. http://dx.doi.org/10.1210/en.2009-0070 PMID:19372199

44. Meyer MR, Clegg DJ, Prossnitz ER, Barton M (2011). Obesity, insulin resistance and diabetes: sex differences and role of oestrogen receptors. Acta Physiol (Oxf). 203(1):259–69. http://dx.doi.org/10.1111/j.1748-1716.2010.02237.x PMID:21281456

45. Allan CA, McLachlan RI (2010). Androgens and obesity. Curr Opin Endocrinol Diabetes Obes. 17(3):224–32. http://dx.doi.org/10.1097/MED.0b013e3283398ee2 PMID:20418719

46. Bernstein L, Ross RK (1993). Endogenous hormones and breast cancer risk. Epidemiol Rev. 15(1):48–65. PMID:8405212

47. Ho SM (2003). Estrogen, progesterone and epithelial ovarian cancer. Reprod Biol Endocrinol. 1:73. http://dx.doi.org/10.1186/1477-7827-1-73 PMID:14577831

48. Rižner TL (2013). Estrogen biosynthesis, phase I and phase II metabolism, and action in endometrial cancer. Mol Cell Endocrinol. 381(1–2):124–39. http://dx.doi.org/10.1016/j.mce.2013.07.026 PMID:23911898

49. Heldring N, Pike A, Andersson S, Matthews J, Cheng G, Hartman J, et al. (2007). Estrogen receptors: how do they signal and what are their targets. Physiol Rev. 87(3):905–31. http://dx.doi.org/10.1152/physrev.00026.2006 PMID:17615392

50. Huang B, Warner M, Gustafsson JA (2014). Estrogen receptors in breast carcinogenesis and endocrine therapy. Mol Cell Endocrinol. 418(Pt 3):240–4. http://dx.doi.org/10.1016/j.mce.2014.11.015 PMID:25433206

51. Althuis MD, Fergenbaum JH, Garcia-Closas M, Brinton LA, Madigan MP, Sherman ME (2004). Etiology of hormone receptor-defined breast cancer: a systematic review of the literature. Cancer Epidemiol Biomarkers Prev. 13(10):1558–68. PMID:15466970

52. Goodwin PJ (2013). Obesity and endocrine therapy: host factors and breast cancer outcome. Breast. 22(Suppl 2):S44–7. http://dx.doi.org/10.1016/j.breast.2013.07.008 PMID:24074791

53. 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. http://dx.doi.org/10.1093/jnci/djt465 PMID:24552677

54. Subbaramaiah K, Howe LR, Bhardwaj P, Du B, Gravaghi C, Yantiss RK, et al. (2011). Obesity is associated with inflammation and elevated aromatase expression in the mouse mammary gland. Cancer Prev Res (Phila). 4(3):329–46. http://dx.doi.org/10.1158/1940-6207.CAPR-10-0381 PMID:21372033

55. Duncan RE, Ahmadian M, Jaworski K, Sarkadi-Nagy E, Sul HS (2007). Regulation of lipolysis in adipocytes. Annu Rev Nutr. 27(1):79–101. http://dx.doi.org/10.1146/annurev.nutr.27.061406.093734 PMID:17313320

56. Jung UJ, Choi MS (2014). Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. Int J Mol Sci. 15(4):6184–223. http://dx.doi.org/10.3390/ijms15046184 PMID:24733068

57. Balaban S, Lee LS, Schreuder M, Hoy AJ (2015). Obesity and cancer progression: is there a role of fatty acid metabolism? Biomed Res Int. 2015:274585. http://dx.doi.org/10.1155/2015/274585 PMID:25866768

58. Henry SL, Bensley JG, Wood-Bradley RJ, Cullen-McEwen LA, Bertram JF, Armitage JA (2012). White adipocytes: more than just fat depots. Int J Biochem Cell Biol. 44(3):435–40. http://dx.doi.org/10.1016/j.biocel.2011.12.011 PMID:22222895

59. Suganami T, Tanaka M, Ogawa Y (2012). Adipose tissue inflammation and ectopic lipid accumulation. Endocr J. 59(10):849–57. http://dx.doi.org/10.1507/endocrj.EJ12-0271 PMID:22878669

60. Papandreou D, Andreou E (2015). Role of diet on non-alcoholic fatty liver disease: an updated narrative review. World J Hepatol. 7(3):575–82. http://dx.doi.org/10.4254/wjh.v7.i3.575 PMID:25848481

61. Hui JM, Kench JG, Chitturi S, Sud A, Farrell GC, Byth K, et al. (2003). Long-term outcomes of cirrhosis in nonalcoholic steatohepatitis compared with hepatitis C. Hepatology. 38(2):420–7. http://dx.doi.org/10.1053/jhep.2003.50320 PMID:12883486

62. Vanni E, Bugianesi E, Kotronen A, De Minicis S, Yki-Järvinen H, Svegliati-Baroni G (2010). From the metabolic syndrome to NAFLD or vice versa? Dig Liver Dis. 42(5):320–30. http://dx.doi.org/10.1016/j.dld.2010.01.016 PMID:20207596

63. White DL, Kanwal F, El-Serag HB (2012). Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review. Clin Gastroenterol Hepatol. 10(12):1342–1359.e2. http://dx.doi.org/10.1016/j.cgh.2012.10.001 PMID:23041539

64. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, et al. (2004). Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology. 40(6):1387–95. http://dx.doi.org/10.1002/hep.20466 PMID:15565570

65. Bellentani S, Scaglioni F, Marino M, Bedogni G (2010). Epidemiology of non-alcoholic fatty liver disease. Dig Dis. 28(1):155–61. http://dx.doi.org/10.1159/000282080 PMID:20460905

66. Berardis S, Sokal E (2014). Pediatric non-alcoholic fatty liver disease: an increasing public health issue. Eur J Pediatr. 173(2):131–9. http://dx.doi.org/10.1007/s00431-013-2157-6 PMID:24068459

67. Anderson N, Borlak J (2008). Molecular mechanisms and therapeutic targets in steatosis and steatohepatitis. Pharmacol Rev. 60(3):311–57. http://dx.doi.org/10.1124/pr.108.00001 PMID:18922966

68. Tolman KG, Dalpiaz AS (2007). Treatment of non-alcoholic fatty liver disease. Ther Clin Risk Manag. 3(6):1153–63. PMID:18516264

69. Farese RV Jr, Zechner R, Newgard CB, Walther TC (2012). The problem of establishing relationships between hepatic steatosis and hepatic insulin resistance. Cell Metab. 15(5):570–3. http://dx.doi.org/10.1016/j.cmet.2012.03.004 PMID:22560209

70. Ahmadian M, Suh JM, Hah N, Liddle C, Atkins AR, Downes M, et al. (2013). PPARγ signaling and metabolism: the good, the bad and the future. Nat Med. 19(5):557–66. http://dx.doi.org/10.1038/nm.3159 PMID:23652116

71. Hijona E, Hijona L, Arenas JI, Bujanda L (2010). Inflammatory mediators of hepatic steatosis. Mediators Inflamm. 2010:837419. http://dx.doi.org/10.1155/2010/837419 PMID:20300479

72. Smits MM, van Geenen EJ (2011). The clinical significance of pancreatic steatosis. Nat Rev Gastroenterol Hepatol. 8(3):169–77. http://dx.doi.org/10.1038/nrgastro.2011.4 PMID:21304475

73. van Geenen EJ, Smits MM, Schreuder TC, van der Peet DL, Bloemena E, Mulder CJ (2010). Nonalcoholic fatty liver disease is related to nonalcoholic fatty pancreas disease. Pancreas. 39(8):1185–90. http://dx.doi.org/10.1097/MPA.0b013e3181f6fce2 PMID:20871475

74. Byrne AM, Bouchier-Hayes DJ, Harmey JH (2005). Angiogenic and cell survival functions of vascular endothelial growth factor (VEGF). J Cell Mol Med. 9(4):777–94. http://dx.doi.org/10.1111/j.1582-4934.2005.tb00379.x PMID:16364190

75. Cottam D, Fisher B, Ziemba A, Atkinson J, Grace B, Ward DC, et al. (2010). Tumor growth factor expression in obesity and changes in expression with weight loss: another cause of increased virulence and incidence of cancer in obesity. Surg Obes Relat Dis. 6(5):538–41. http://dx.doi.org/10.1016/j.soard.2010.04.011 PMID:20688580

76. Slaughter KN, Thai T, Penaroza S, Benbrook DM, Thavathiru E, Ding K, et al. (2014). Measurements of adiposity as clinical biomarkers for first-line bevacizumab-based chemotherapy in epithelial ovarian cancer. Gynecol Oncol. 133(1):11–5. http://dx.doi.org/10.1016/j.ygyno.2014.01.031 PMID:24680585

77. Iwaki T, Urano T, Umemura K (2012). PAI-1, progress in understanding the clinical problem and its aetiology. Br J Haematol. 157(3):291–8. http://dx.doi.org/10.1111/j.1365-2141.2012.09074.x PMID:22360729

78. Bauman KA, Wettlaufer SH, Okunishi K, Vannella KM, Stoolman JS, Huang SK, et al. (2010). The antifibrotic effects of plasminogen activation occur via prostaglandin E2 synthesis in humans and mice. J Clin Invest. 120(6):1950–60. http://dx.doi.org/10.1172/JCI38369 PMID:20501949

79. Malik R, Lelkes PI, Cukierman E (2015). Biomechanical and biochemical remodeling of stromal extracellular matrix in cancer. Trends Biotechnol. 33(4):230–6. http://dx.doi.org/10.1016/j.tibtech.2015.01.004 PMID:25708906

80. Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, et al. (2005). Diversity of the human intestinal microbial flora. Science. 308(5728):1635–8. http://dx.doi.org/10.1126/science.1110591 PMID:15831718

81. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI (2006). An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 444(7122):1027–31. http://dx.doi.org/10.1038/nature05414 PMID:17183312

82. Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, et al. (2009). A core gut microbiome in obese and lean twins. Nature. 457(7228):480–4. http://dx.doi.org/10.1038/nature07540 PMID:19043404

83. Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G, et al.; MetaHIT consortium (2013). Richness of human gut microbiome correlates with metabolic markers. Nature. 500(7464):541–6. http://dx.doi.org/10.1038/nature12506 PMID:23985870

84. Cotillard A, Kennedy SP, Kong LC, Prifti E, Pons N, Le Chatelier E, et al.; ANR MicroObes consortium (2013). Dietary intervention impact on gut microbial gene richness. Nature. 500(7464):585–8. http://dx.doi.org/10.1038/nature12480 PMID:23985875

85. Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM, et al. (2008). Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. Diabetes. 57(6):1470–81. http://dx.doi.org/10.2337/db07-1403 PMID:18305141

86. Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, et al. (2007). Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes. 56(7):1761–72. http://dx.doi.org/10.2337/db06-1491 PMID:17456850

87. Lashinger LM, Ford NA, Hursting SD (2014). Interacting inflammatory and growth factor signals underlie the obesity-cancer link. J Nutr. 144(2):109–13. http://dx.doi.org/10.3945/jn.113.178533 PMID:24285690

CHAPTER 13.

What steps should be recommended and implemented to prevent and control the obesity epidemic?

Simón Barquera and Jacob C. Seidell

Obesity as a major public health problem

Worldwide, currently an estimated 2.1 billion people are overweight or obese, and 3.4 million adult deaths per year are attributable to overweight and obesity [1, 2]. Obesity is a major public health problem, and no countries in the world have achieved significant decreases in the prevalence of obesity during the past 33 years [1]. Obesity is the most important risk factor for noncommunicable diseases (NCDs), which dominate the global burden of disease [3]. Most of the obese individuals live in developing countries, where nearly 80% of the deaths due to NCDs occur [4]. Obesity and NCDs occur disproportionately in low-income populations, creating a vicious cycle and contributing to social and economic inequalities [5]. Obesity and other malnutrition problems, such as micronutrient deficiencies and child stunting, tend to coexist in vulnerable subgroups in developing countries, making this health challenge even more complex [1, 4, 6–8].

Among the main causes of the alarming increase in the prevalence of obesity, researchers around the world have recognized important changes in food systems (including changes in supply, prices, distribution, energy density, and preparation of food) and a reduction in physical activity levels; these changes have not been adequately characterized and monitored [9–11]. The ecological model of obesity has been used to develop a conceptual framework for understanding the complexity of obesity, by identifying immediate, subjacent, and basic causes. This framework is useful to identify opportunities for action (Fig. 13.1) [12].

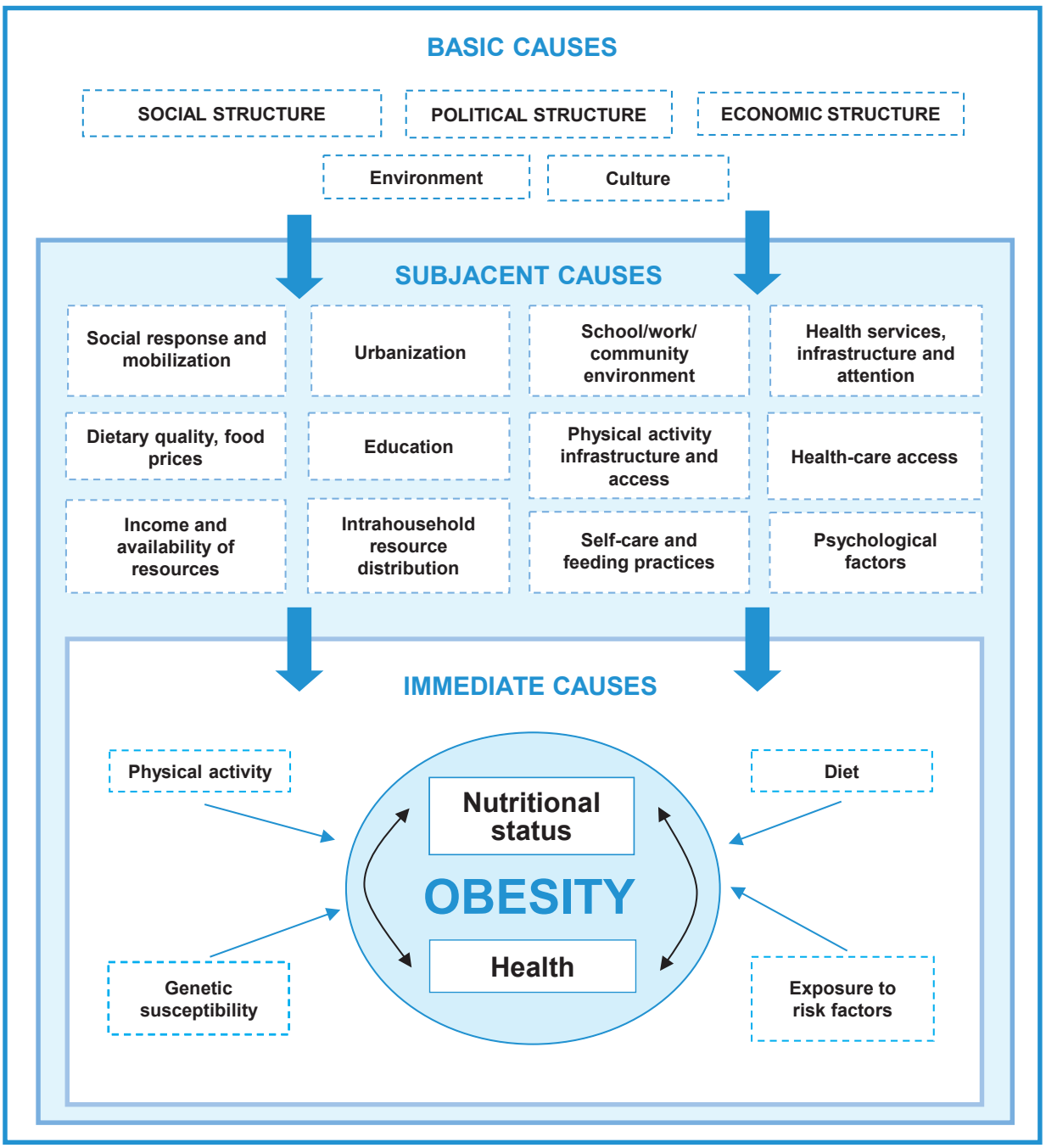
Given the rapid rise in the prevalence of obesity in most countries, health systems have not been able to adjust to the new epidemiological transition; therefore, in some cases resources have not been invested optimally to combat this epidemic, generating important deficiencies in prevention, early diagnosis, interdisciplinary treatment, adherence to treatment, and control and prevention of complications [13].

The purpose of this chapter is to review the main opportunities that have been identified in the literature for action to prevent and control the obesity epidemic *from the public health perspective* and to describe the steps needed to tackle the problem.

Main areas of opportunity to prevent and control obesity

Several reports from the World Health Organization (WHO) have recognized the importance of developing policies and actions to prevent NCDs. The reports have focused on

Fig. 13.1. Conceptual framework of obesity determinants based on the ecological model. Adapted with permission from Barquera et al. (2013) [12].



diet and physical activity through different preventive strategies, such as improving the knowledge and skills of the community, reducing the exposure of the population to obesogenic environments, and improving management strategies for at-risk individuals and groups, including early detection and screening systems, comprehensive health assessment, setting of appropriate targets, and monitoring of results [5, 13, 14]. A major recommendation in the 2008–2013 WHO action plan is "to raise the priority accorded to noncommunicable diseases in development work at global and national levels, and to integrate prevention and control of such diseases into policies across all government departments" [13]. However, a basic condition and

a major challenge for action is the availability of evidence-based research on the health effects and the cost–effectiveness of policy options [13, 15].

There are several policy options to prevent obesity that have been explored and for which enough evidence has been generated to conclude that they are cost-effective. Among these are (i) school-based interventions, (ii) worksite interventions, (iii) mass media campaigns, (iv) physician counselling, (v) physical activity interventions, (vi) fiscal measures, (vii) regulation of food advertising, and (viii) food labelling [16–44] (Table 13.1). Hawkes et al. have developed a framework to organize policy options, which comprises three domains: the food environment, the food system, and behaviour change communication. In addition, they have mapped interventions around the world in this framework by domain, policy area, and policy options/actions [26].

Given the multifactorial nature of obesity, as in other complex public health problems, a combination of interventions is more likely to generate good results than focusing on only a single measure [33].

Monitoring and benchmarking of obesity prevention efforts

The international Bellagio Conference on Program and Policy Options for Preventing Obesity in the Low- and Middle-Income Countries was held in 2013. The Bellagio Conference group identified the food and beverage industries (the Big Food and Big Beverage sectors) as a major impediment to the implementation of obesity prevention policies, and showed evidence of strong actions taken by Big Food to oppose food policies that benefit public health. In addition, the group documented the limitations of governments to protect public policy from such vested interests. The Bellagio Conference group developed the Bellagio Declaration, which identifies specific actions for sectors of society to counter the undermining influence of Big Food on healthy food policies [45, 46].

One of the most important recognized challenges to tackle obesity is adequate monitoring of the food environment and of policy efforts [13, 47]. This information is essential to analyse trends and to improve or adjust policies. Recently, the International Network for Food and Obesity/noncommunicable diseases Research, Monitoring and Action Support (INFORMAS) developed 11 different protocols to assess diverse aspects of the food environment. These protocols provide useful and sustainable low-cost tools to contribute to the information

Table 13.1. Policy options to prevent obesity

Domain	Type of intervention	Actions/policy options[a]
Behaviour change communication	School-based	School-based interventions have been demonstrated to be successful in preventing and controlling obesity in various studies, including several in middle-income countries. School healthy eating guidelines that forbid soda and unhealthy foods are in place in most Latin American countries [18, 27].
	Worksite	Worksite interventions are promising alternatives to increase physical activity and decrease energy intake. Governments could generate incentives to promote this policy option [16, 21].
	Mass media campaigns	Various countries, such as Brazil, Colombia, Mexico, and the USA, have published national nutrition guidelines and have developed diverse media campaigns to prevent and control obesity [28–31].
	Physician counselling	Physician counselling is an effective means of controlling obesity in adults. It also has independent benefits, such as improving glucose control and blood pressure. Although it is one of the most expensive interventions, it is cost-effective [20, 32, 33].
	Physical activity	Programmes to increase physical activity have many benefits in addition to the contribution to preventing and controlling excess weight. For example, a recent study in countries including Colombia, Mexico, and the USA concluded that Ciclovía programmes (community-based mass programmes in which streets are temporarily closed to motorized transportation, allowing exclusive access to individuals for recreational activities and physical activity) are cost-beneficial from the public health perspective [21, 34].
Food environment	Fiscal measures	In Mexico, a 10% excise tax on sugar-sweetened beverages and junk food was implemented in 2014. A recent evaluation has demonstrated that the policy decreased purchases of taxed beverages and increased purchases of untaxed beverages [25, 35, 36].
	Regulation of food advertising	Food marketing is recognized as an important driver of the consumption of unhealthy foods, in particular for children. Although it is not a direct driver of obesity, food marketing is associated with unhealthy diets [37–39].
	Food labelling	Food labelling is a powerful tool to help populations to easily make healthier choices. Various studies have modelled estimated potential improvements in diet with this type of intervention. However, these regulatory efforts face strong opposition from the food industry. In addition, the understanding of nutrition information from voluntary labelling of foods by manufacturers has proved to be poor among consumers in both developed and developing countries [40–44].

[a] Policy options are based on the NOURISHING framework of Hawkes et al. (2013) [26].

challenge and have the additional advantage of allowing cross-sectional multicountry comparisons, which could facilitate insights into national efforts in the absence of trends [48].

Cost–effectiveness of obesity interventions

Many approaches to policies have been tried, including community-based interventions and policy interventions that target either children only or the general population. The effectiveness and reach of these interventions vary widely, as do the costs of implementing them. Only a few attempts have been made to compare the cost–effectiveness of these interventions.

Gortmaker et al. [49] estimated the cost–effectiveness of seven interventions that are generally considered to be the most promising. They modelled the reach, costs, and returns for the population of the USA in 2015–2025. The seven interventions were: (i) an excise tax on sugar-sweetened beverages, (ii) restaurant menu calorie labelling, (iii) elimination of the tax subsidy for advertising unhealthy food to children, (iv) nutrition standards for school meals, (v) nutrition standards for all other food and beverages sold in schools, (vi) improved early care and education policies and practices, and (vii) increased access to adolescent bariatric surgery. The authors found that most of these interventions not only could prevent many cases of childhood obesity but also would potentially cost less to implement than they would save for society. For example, the estimated health-care cost saved per dollar spent was US$ 30.78 for the excise tax on sugar-sweetened beverages and US$ 32.53 for the elimination of the tax subsidy for advertising unhealthy food to children [49].

The McKinsey Global Institute performed an economic analysis of 44 interventions [50]. Its report concluded that although no single solution creates sufficient impact to reverse obesity, almost all of the interventions are highly cost-effective from the viewpoint of society. This means that the health-care costs and productivity savings that accrue from reducing obesity outweigh the direct investment required to deliver the intervention [50].

Integrating prevention and management of obesity

Although considerable benefit is to be expected from preventive actions (top–down corporate and government interventions and bottom–up community-based interventions), it is unavoidable that a considerable proportion of the population will become or remain overweight or obese. An integrated approach is necessary using the principles of NCD management. For example, these principles have been translated into an integrated health-care standard [51].

The integrated health-care standard for obesity involves strategies for diagnosis and early detection of high-risk individuals as well as appropriate combined lifestyle interventions for those who are overweight and obese and, when appropriate, additional medical therapies. This standard transcends traditional boundaries of conventional health-care systems and health-care professions; instead, it focuses on competences of groups of health professionals who organize care from a patient-oriented perspective. This approach also implements the elements of matched and stepped care (increasing levels of care are matched to the individual's needs based on weight-related health risk, so that interventions are not more intensive than needed but not less intensive than needed). Integrating and implementing such integrated care will require many steps, including training of health-care professionals [52].

Example of a successful obesity-related policy in Latin America

As an example of a successful obesity-related policy in Latin America, the case of a tax on sugar-sweetened beverages in Mexico is discussed.

During the past decades, various studies suggested that the consumption of sugar-sweetened beverages was associated with the alarming epidemic of obesity and diabetes in Mexico and that there was a pressing need to reduce consumption of these products as part of the policies to prevent and control nutrition-related NCDs [53–58]. At the same time, important intervention studies and meta-analyses conducted around the world confirmed the unhealthy effects of consumption of sugar-sweetened beverages [59–66].

In 2010, the Ministry of Health of Mexico, with support from the National Institute of Public Health, developed the National Agreement for Nutritional Health – Strategy to Control Overweight and Obesity [67] and launched several efforts to reduce consumption of sugar-sweetened beverages and junk food. The recommendations included healthy hydration, taxation, restrictions on the marketing of unhealthy products, labelling, and strategies to improve nutrition in the work and school environments, among others. This document faced strong opposition from the beverage and food industry [68].

In 2012, the National Academy of Medicine of Mexico published a position book on policies to prevent and control obesity, endorsing the previously recommended policy actions, including taxation of sugar-sweetened beverages [69]. During 2013, in the context of a world economic recession and a fall in oil prices, the government approved an initiative for an excise tax on

sugar-sweetened beverages and junk food, with strong support from civil society, including health and consumer associations, academia, and opposition parties. This policy was implemented in 2014 and has been under evaluation since then. Various analyses have observed a reduction in consumption of these products after taxation, after adjusting for seasonality (change in temperature; holidays and festivities) and population growth [35, 70–73], despite major efforts from industry to maintain sales with aggressive marketing campaigns. The results and experience in Mexico are now being used by other Latin American countries as a background to promote similar initiatives.

Conclusions

Obesity and its consequences are among the greatest global health burdens, leading to impairment of health-related quality of life and considerable costs to society. Although there are individual differences in susceptibility, obesity is by and large a societal problem, resulting from health-related behaviours that are driven largely by upstream environmental factors. Many options for policies to prevent obesity are available, and many of these are effective and cost-effective. Integrated management of the obesity epidemic requires top–down government policies, bottom–up community-based approaches, and the involvement of many sectors of society. Integrating evidence-based prevention and management of obesity is essential.

Key points

- Obesity is mostly a societal problem, resulting from behaviours that are driven largely by upstream environmental factors.
- There are several cost-effective policy options to prevent obesity, including taxation, regulation of marketing of unhealthy foods/beverages, and adequate front-of-package labelling systems.
- Monitoring and benchmarking of the food system and of obesity prevention and control policies are essential to compare national efforts across countries, analyse trends, and achieve better results.

Research needs

- Behavioural and environmental determinants of food choice and physical activity practices should be studied.
- Cost-effective top–down policy interventions and bottom–up community-based approaches are needed to prevent and control obesity.
- Benchmarking of the food policy environment across countries is needed to identify best practices.

References

1. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. (2014). Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 384(9945):766–81. http://dx.doi.org/10.1016/S0140-6736(14)60460-8 PMID:24880830

2. WHO (2011). Global atlas on cardiovascular disease prevention and control. Geneva, Switzerland: World Health Organization. Available from: http://www.who.int/cardiovascular_diseases/publications/atlas_cvd/en/.

3. Swinburn B, Sacks G, Vandevijvere S, Kumanyika S, Lobstein T, Neal B, et al.; INFORMAS (2013). INFORMAS (International Network for Food and Obesity/non-communicable diseases Research, Monitoring and Action Support): overview and key principles. Obes Rev. 14(Suppl 1):1–12. http://dx.doi.org/10.1111/obr.12087 PMID:24074206

4. WHO (2011). A prioritized research agenda for prevention and control of noncommunicable diseases. Geneva, Switzerland: World Health Organization. Available from: http://whqlibdoc.who.int/publications/2011/9789241564205_eng.pdf.

5. WHO (2004). Global strategy on diet, physical activity and health, Resolution of the Fifty-Seventh World Health Assembly. Geneva, Switzerland: World Health Organization. Available from: http://apps.who.int/gb/ebwha/pdf_files/WHA57/A57_R17-en.pdf.

6. Popkin BM, Doak CM (1998). The obesity epidemic is a worldwide phenomenon. Nutr Rev. 56(4 Pt 1):106–14. PMID:9584495

7. Popkin BM (1998). The nutrition transition and its health implications in lower-income countries. Public Health Nutr. 1(1):5–21. http://dx.doi.org/10.1079/PHN19980004 PMID:10555527

8. Popkin BM, Slining MM (2013). New dynamics in global obesity facing low- and middle-income countries. Obes Rev. 14(Suppl 2):11–20. http://dx.doi.org/10.1111/obr.12102 PMID:24102717

9. Swinburn B, Wood A (2013). Progress on obesity prevention over 20 years in Australia and New Zealand. Obes Rev. 14(Suppl 2):60–8. http://dx.doi.org/10.1111/obr.12103 PMID:24102746

10. Seidell JC, Halberstadt J (2015). The global burden of obesity and the challenges of prevention. Ann Nutr Metab. 66(Suppl 2):7–12. http://dx.doi.org/10.1159/000375143 PMID:26045323

11. Vandevijvere S, Tseng M (2013). Towards comprehensive global monitoring of food environments and policies to reduce diet-related non-communicable diseases. Public Health Nutr. 16(12):2101–4. http://dx.doi.org/10.1017/S1368980013002887 PMID:24182451

12. Barquera S, Campirano F, Campos I, Hernández-Barrera L, Flores M, Rivera JA (2013). Nutrición y salud pública: el principio de la prevención. In: Hernández Ávila M, Lazcano Ponce E, editors. Salud pública. Teoría y práctica. Mexico City: Instituto Nacional de Salud Pública: Editorial El Manual Moderno; pp. 209–230.

13. WHO (2009). 2008-2013 Action plan for the global strategy for the prevention and control of noncommunicable diseases. Geneva, Switzerland: World Health Organization. Available from: http://www.who.int/nmh/publications/9789241597418/en/.

14. WHO (2000). Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. Geneva, Switzerland: World Health Organization (WHO Technical Report Series, No. 894). Available from: http://www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/.

15. Swinburn B, Vandevijvere S, Kraak V, Sacks G, Snowdon W, Hawkes C, et al.; INFORMAS (2013). Monitoring and benchmarking government policies and actions to improve the healthiness of food environments: a proposed Government Healthy Food Environment Policy Index. Obes Rev. 14(Suppl 1):24–37. http://dx.doi.org/10.1111/obr.12073 PMID:24074208

16. Mehta S, Dimsdale J, Nagle B, Holub CK, Woods C, Barquera S, et al. (2013). Worksite interventions: improving lifestyle habits among Latin American adults. Am J Prev Med. 44(5):538–42. http://dx.doi.org/10.1016/j.amepre.2013.01.015 PMID:23597820

17. Marshall SJ, Simoes EJ, Eisenberg CM, Holub CK, Arredondo EM, Barquera S, et al. (2013). Weight-related child behavioral interventions in Brazil: a systematic review. Am J Prev Med. 44(5):543–9. http://dx.doi.org/10.1016/j.amepre.2013.01.017 PMID:23597821

18. Lobelo F, Garcia de Quevedo I, Holub CK, Nagle BJ, Arredondo EM, Barquera S, et al. (2013). School-based programs aimed at the prevention and treatment of obesity: evidence-based interventions for youth in Latin America. J Sch Health. 83(9):668–77. http://dx.doi.org/10.1111/josh.12080 PMID:23879787

19. Martinez SM, Ainsworth BE, Elder JP (2008). A review of physical activity measures used among US Latinos: guidelines for developing culturally appropriate measures. Ann Behav Med. 36(2):195–207. http://dx.doi.org/10.1007/s12160-008-9063-6 PMID:18855091

20. Holub CK, Elder JP, Arredondo EM, Barquera S, Eisenberg CM, Sánchez Romero LM, et al. (2013). Obesity control in Latin American and U.S. Latinos: a systematic review. Am J Prev Med. 44(5):529–37. http://dx.doi.org/10.1016/j.amepre.2013.01.023 PMID:23597819

21. Heath GW, Parra DC, Sarmiento OL, Andersen LB, Owen N, Goenka S, et al.; Lancet Physical Activity Series Working Group (2012). Evidence-based intervention in physical activity: lessons from around the world. Lancet. 380(9838):272–81. http://dx.doi.org/10.1016/S0140-6736(12)60816-2 PMID:22818939

22. Taber DR, Chriqui JF, Vuillaume R, Chaloupka FJ (2014). How state taxes and policies targeting soda consumption modify the association between school vending machines and student dietary behaviors: a cross-sectional analysis. PLoS One. 9(8):e98249. http://dx.doi.org/10.1371/journal.pone.0098249 PMID:25083906

23. Fletcher JM, Frisvold DE, Tefft N (2015). Non-linear effects of soda taxes on consumption and weight outcomes. Health Econ. 24(5):566–82. http://dx.doi.org/10.1002/hec.3045 PMID:24615758

24. Powell LM, Chriqui J, Chaloupka FJ (2009). Associations between state-level soda taxes and adolescent body mass index. J Adolesc Health. 45(3 Suppl):S57–63. http://dx.doi.org/10.1016/j.jadohealth.2009.03.003 PMID:19699437

25. Powell LM, Chriqui JF, Khan T, Wada R, Chaloupka FJ (2013). Assessing the potential effectiveness of food and beverage taxes and subsidies for improving public health: a systematic review of prices, demand and body weight outcomes. Obes Rev. 14(2):110–28. http://dx.doi.org/10.1111/obr.12002 PMID:23174017

26. Hawkes C, Jewell J, Allen K (2013). A food policy package for healthy diets and the prevention of obesity and diet-related non-communicable diseases: the NOURISHING framework. Obes Rev. 14(Suppl 2):159–68. http://dx.doi.org/10.1111/obr.12098 PMID:24103073

27. Story M, Nanney MS, Schwartz MB (2009). Schools and obesity prevention: creating school environments and policies to promote healthy eating and physical activity. Milbank Q. 87(1):71–100. http://dx.doi.org/10.1111/j.1468-0009.2009.00548.x PMID:19298416

28. ICBF (2015). Guías alimentarias basadas en alimentos para la población colombiana mayor de 2 años. Bogotá, Colombia: Instituto Colombiano de Bienestar Familiar. Available from: https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/VS/PP/SNA/guias-alimentarias-basadas-en-alimentos.pdf.

29. Ministerio de Salud de Brasil (2015). Guía alimentaria para la población Brasileña. Brasília, Brazil: Ministerio de Salud de Brasil. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/guia_alimentaria_poblacion_brasilena.pdf.

30. Bonvecchio Arenas A, Fernández-Gaxiola AC, Plazas Belausteguigoitia M, Kaufer-Horwitz M, Pérez Lizaur AB, Rivera Dommarco JA (2015). Guías alimentarias y de actividad física en contexto de sobrepeso y obesidad en la población mexicana. Documento de postura. Mexico City: Academia Nacional de Medicina de México. Available from: http://guiasalimentacionyactividadfisica.org.mx/pg/.

31. USDHHS/USDA (2015). 2015–2020 Dietary guidelines for Americans. 8th ed. Washington (DC), USA: United States Department of Health and Human Services/United States Department of Agriculture. Available from: http://health.gov/dietaryguidelines/2015/guidelines/.

32. Jaime PC, da Silva AC, Gentil PC, Claro RM, Monteiro CA (2013). Brazilian obesity prevention and control initiatives. Obesity Rev. 14(Suppl 2):88–95. http://dx.doi.org/10.1111/obr.12101 PMID:24102701

33. Cecchini M, Sassi F, Lauer JA, Lee YY, Guajardo-Barron V, Chisholm D (2010). Tackling of unhealthy diets, physical inactivity, and obesity: health effects and cost-effectiveness. Lancet. 376(9754):1775–84. http://dx.doi.org/10.1016/S0140-6736(10)61514-0 PMID:21074255

34. Montes F, Sarmiento OL, Zarama R, Pratt M, Wang G, Jacoby E, et al. (2012). Do health benefits outweigh the costs of mass recreational programs? An economic analysis of four Ciclovía programs. J Urban Health. 89(1):153–70. http://dx.doi.org/10.1007/s11524-011-9628-8 PMID:22170324

35. Colchero MA, Popkin BM, Rivera JA, Ng SW (2016). Beverage purchases from stores in Mexico under the excise tax on sugar sweetened beverages: observational study. BMJ. 352:h6704. http://dx.doi.org/10.1136/bmj.h6704 PMID:26738745

36. Sturm R, Powell LM, Chriqui JF, Chaloupka FJ (2010). Soda taxes, soft drink consumption, and children's body mass index. Health Aff (Millwood). 29(5):1052–8. http://dx.doi.org/10.1377/hlthaff.2009.0061 PMID:20360173

37. PAHO (2011). Recommendations from a Pan American Health Organization Expert Consultation on the marketing of food and non-alcoholic beverages to children in the Americas. Washington (DC), USA: Pan American Health Organization. Available from: http://iris.paho.org/xmlui/handle/123456789/3594.

38. No E, Kelly B, Devi A, Swinburn B, Vandevijvere S (2014). Food references and marketing in popular magazines for children and adolescents in New Zealand: a content analysis. Appetite. 83:75–81. http://dx.doi.org/10.1016/j.appet.2014.08.013 PMID:25128834

39. Swinburn B, Sacks G, Lobstein T, Rigby N, Baur LA, Brownell KD, et al.; International Obesity Taskforce Working Group on Marketing to Children (2008). The 'Sydney Principles' for reducing the commercial promotion of foods and beverages to children. Public Health Nutr. 11(9):881–6. http://dx.doi.org/10.1017/S136898000800284X PMID:18510788

40. Corvalán C, Reyes M, Garmendia ML, Uauy R (2013). Structural responses to the obesity and non-communicable diseases epidemic: the Chilean Law of Food Labeling and Advertising. Obes Rev. 14(Suppl 2):79–87. http://dx.doi.org/10.1111/obr.12099 PMID:24102671

41. Feunekes GI, Gortemaker IA, Willems AA, Lion R, van den Kommer M (2008). Front-of-pack nutrition labelling: testing effectiveness of different nutrition labelling formats front-of-pack in four European countries. Appetite. 50(1):57–70. http://dx.doi.org/10.1016/j.appet.2007.05.009 PMID:17629351

42. Grunert KG, Wills JM (2007). A review of European research on consumer response to nutrition information on food labels. J Public Health. 15(5):385–99. http://dx.doi.org/10.1007/s10389-007-0101-9

43. Grunert KG, Wills JM, Fernández-Celemín L (2010). Nutrition knowledge, and use and understanding of nutrition information on food labels among consumers in the UK. Appetite. 55(2):177–89. http://dx.doi.org/10.1016/j.appet.2010.05.045 PMID:20546813

44. Vyth EL, Steenhuis IH, Mallant SF, Mol ZL, Brug J, Temminghoff M, et al. (2009). A front-of-pack nutrition logo: a quantitative and qualitative process evaluation in the Netherlands. J Health Commun. 14(7):631–45. http://dx.doi.org/10.1080/10810730903204247 PMID:19851915

45. Popkin B, Monteiro C, Swinburn B (2013). Overview: Bellagio Conference on Program and Policy Options for Preventing Obesity in the Low- and Middle-Income Countries. Obes Rev. 14(Suppl 2):1–8. http://dx.doi.org/10.1111/obr.12108 PMID:24102826

46. Popkin BM; Bellagio Meeting group (2013). Bellagio Declaration 2013: countering Big Food's undermining of healthy food policies. Obes Rev. 14(Suppl 2):9–10. http://dx.doi.org/10.1111/obr.12104 PMID:24102762

47. Vandevijvere S, Swinburn B; International Network for Food and Obesity/non-communicable diseases (NCDs) Research, Monitoring and Action Support (INFORMAS) (2014). Towards global benchmarking of food environments and policies to reduce obesity and diet-related non-communicable diseases: design and methods for nation-wide surveys. BMJ Open. 4(5):e005339. http://dx.doi.org/10.1136/bmjopen-2014-005339 PMID:24833697

48. Kumanyika S (2013). INFORMAS (International Network for Food and Obesity/non-communicable diseases Research, Monitoring and Action Support): summary and future directions. Obes Rev. 14(Suppl 1):157–64. http://dx.doi.org/10.1111/obr.12084 PMID:24074219

49. Gortmaker SL, Wang YC, Long MW, Giles CM, Ward ZJ, Barrett JL, et al. (2015). Three interventions that reduce childhood obesity are projected to save more than they cost to implement. Health Aff (Millwood). 34(11):1932–9. http://dx.doi.org/10.1377/hlthaff.2015.0631 PMID:26526252

50. McKinsey Global Institute (2014). Overcoming obesity: an initial economic analysis. London, UK: McKinsey & Company. Available from: http://www.mckinsey.com/~/media/McKinsey/Business Functions/Economic Studies TEMP/Our Insights/How the world could better fight obesity/MGI_Overcoming_obesity_Full_report.ashx.

51. Seidell JC, Halberstadt J, Noordam H, Niemer S (2012). An integrated health care standard for the management and prevention of obesity in The Netherlands. Fam Pract. 29(Suppl 1):i153–6. http://dx.doi.org/10.1093/fampra/cmr057 PMID:22399546

52. Dietz WH, Baur LA, Hall K, Puhl RM, Taveras EM, Uauy R, et al. (2015). Management of obesity: improvement of health-care training and systems for prevention and care. Lancet. 385(9986):2521–33. http://dx.doi.org/10.1016/S0140-6736(14)61748-7 PMID:25703112

53. Rivera JA, Barquera S, Campirano F, Campos I, Safdie M, Tovar V (2002). Epidemiological and nutritional transition in Mexico: rapid increase of non-communicable chronic diseases and obesity. Public Health Nutr. 5(1A):113–22. http://dx.doi.org/10.1079/PHN2001282 PMID:12027273

54. Barquera S, Hotz C, Rivera J, Tolentino L, Espinosa J, Campos I, et al. (2006). Food consumption, food expenditure, anthropometric status and nutrition-related diseases in Mexico. In: Kennedy G, Nantel G, Shetty P, editors. The double burden of malnutrition: case studies from six developing countries. Rome, Italy: Food and Agriculture Organization of the United Nations (FAO Food and Nutrition Paper No. 84); pp. 161–204.

55. Barquera S, Campirano F, Bonvecchio A, Hernández-Barrera L, Rivera JA, Popkin BM (2010). Caloric beverage consumption patterns in Mexican children. Nutr J. 9(1):47. http://dx.doi.org/10.1186/1475-2891-9-47 PMID:20964842

56. Barquera S, Hernandez-Barrera L, Tolentino ML, Espinosa J, Ng SW, Rivera JA, et al. (2008). Energy intake from beverages is increasing among Mexican adolescents and adults. J Nutr. 138(12):2454–61. http://dx.doi.org/10.3945/jn.108.092163 PMID:19022972

57. Stern D, Piernas C, Barquera S, Rivera JA, Popkin BM (2014). Caloric beverages were major sources of energy among children and adults in Mexico, 1999-2012. J Nutr. 144(6):949–56. http://dx.doi.org/10.3945/jn.114.190652 PMID:24744311

58. Piernas C, Barquera S, Popkin BM (2014). Current patterns of water and beverage consumption among Mexican children and adolescents aged 1-18 years: analysis of the Mexican National Health and Nutrition Survey 2012. Public Health Nutr. 17(10):2166–75. http://dx.doi.org/10.1017/S1368980014000998 PMID:24866372

59. Huang C, Huang J, Tian Y, Yang X, Gu D (2014). Sugar sweetened beverages consumption and risk of coronary heart disease: a meta-analysis of prospective studies. Atherosclerosis. 234(1):11–6. http://dx.doi.org/10.1016/j.atherosclerosis.2014.01.037 PMID:24583500

60. Te Morenga L, Mallard S, Mann J (2012). Dietary sugars and body weight: systematic review and meta-analyses of randomised controlled trials and cohort studies. BMJ. 346:e7492. http://dx.doi.org/10.1136/bmj.e7492 PMID:23321486

61. Niknam M, Saadatnia M, Shakeri F, Keshteli AH, Esmaillzadeh A (2013). Consumption of sugar-sweetened beverages in relation to stroke: a case-control study. Int J Food Sci Nutr. 64(1):1–6. http://dx.doi.org/10.3109/09637486.2012.694850 PMID:22694119

62. Romaguera D, Norat T, Wark PA, Vergnaud AC, Schulze MB, van Woudenbergh GJ, et al.; InterAct Consortium (2013). Consumption of sweet beverages and type 2 diabetes incidence in European adults: results from EPIC-InterAct. Diabetologia. 56(7):1520–30. http://dx.doi.org/10.1007/s00125-013-2899-8 PMID:23620057

63. Malik VS, Popkin BM, Bray GA, Després JP, Willett WC, Hu FB (2010). Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. Diabetes Care. 33(11):2477–83. http://dx.doi.org/10.2337/dc10-1079 PMID:20693348

64. Malik VS, Popkin BM, Bray GA, Després JP, Hu FB (2010). Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. Circulation. 121(11):1356–64. http://dx.doi.org/10.1161/CIRCULATIONAHA.109.876185 PMID:20308626

65. Hu FB, Malik VS (2010). Sugar-sweetened beverages and risk of obesity and type 2 diabetes: epidemiologic evidence. Physiol Behav. 100(1):47–54. http://dx.doi.org/10.1016/j.physbeh.2010.01.036 PMID:20138901

66. Malik VS, Willett WC, Hu FB (2009). Sugar-sweetened beverages and BMI in children and adolescents: reanalyses of a meta-analysis. Am J Clin Nutr. 89(1):438–9, author reply 439–40. http://dx.doi.org/10.3945/ajcn.2008.26980 PMID:19056589

67. Secretaría de Salud (2010). Acuerdo Nacional para la Salud Alimentaria: estrategia contra el sobrepeso y la obesidad. Mexico City: Sub-Secretaría de Prevención y Promoción de la Salud de la Secretaría de Salud. Available from: http://activate.gob.mx/documentos/acuerdo%20nacional%20por%20la%20salud%20alimentaria.pdf.

68. Barquera S, Campos I, Rivera JA (2013). Mexico attempts to tackle obesity: the process, results, push backs and future challenges. Obes Rev. 14(Suppl 2):69–78. http://dx.doi.org/10.1111/obr.12096 PMID:24103026

69. Academia Nacional de Medicina (2012). Obesidad en México: recomendaciones para una política de estado. Mexico City: Universidad Nacional Autónoma de México. Available from: www.anmm.org.mx/publicaciones/Obesidad/obesidad.pdf.

70. Batis C, Rivera JA, Popkin BM, Taillie LS (2016). First-year evaluation of Mexico's tax on nonessential energy-dense foods: an observational study. PLoS Med. 13(7):e1002057. http://dx.doi.org/10.1371/journal.pmed.1002057 PMID:27379797

71. Colchero MA, Salgado JC, Unar-Munguía M, Molina M, Ng S, Rivera-Dommarco JA (2015). Changes in prices after an excise tax to sweetened sugar beverages was implemented in Mexico: evidence from urban areas. PLoS One. 10(12):e0144408. http://dx.doi.org/10.1371/journal.pone.0144408 PMID:26675166

72. Colchero MA, Salgado JC, Unar-Munguía M, Hernández-Ávila M, Rivera-Dommarco JA (2015). Price elasticity of the demand for sugar sweetened beverages and soft drinks in Mexico. Econ Hum Biol. 19:129–37. http://dx.doi.org/10.1016/j.ehb.2015.08.007 PMID:26386463

73. Colchero MA, Guerrero-López CM, Molina M, Rivera JA (2016). Beverages sales in Mexico before and after implementation of a sugar sweetened beverage tax. PLoS One. 11(9):e0163463. http://dx.doi.org/10.1371/journal.pone.0163463 PMID:27668875

CHAPTER 14.

Which new data are needed to explore the relationships of diet and dietary patterns to obesity and weight gain?

Nancy Potischman

There is an abundance of evidence that obesity and/or weight gain are related to a variety of types of cancer [1], for several of which the incidence is rising in low- and middle-income countries (LMICs) [2]. Obesity-related cancers of particular concern in LMICs include colorectal and oesophageal cancers [1] and breast cancer, which is related to weight gain in postmenopausal women [3]. Convincing evidence is available that other cancers are associated with obesity, including pancreatic, endometrial, and kidney cancers, and possibly gallbladder cancer [4].

Although weight gain and obesity may have been studied extensively in high-income countries (HICs), the cofactors and etiologies may be slightly different in LMICs. An example is oesophageal cancer, a serious malignancy in terms of prognosis and mortality, for which the incidence is expected to increase over the next 10 years [5]. The most common histological type of oesophageal cancer worldwide is squamous cell carcinoma, which has a higher incidence in developing countries than in developed countries [5]. Identified risk factors for oesophageal squamous cell carcinoma include smoking, alcohol consumption, drinking hot tea, consumption of red meat, poor oral health, low intake of fresh fruits and vegetables, and low socioeconomic status [6, 7], whereas risk factors for oesophageal adenocarcinomas include chronic heartburn, tobacco use, white race, and obesity [8]. If the rise in the prevalence of obesity continues in LMICs, there may be an increase in the incidence of oesophageal adenocarcinoma, colorectal cancer, and other cancers, as well as a continued high incidence of stomach cancer, liver cancer, and oesophageal squamous cell carcinoma. It will be important to monitor trends in the incidence and the epidemiology of these cancers in LMICs in the coming years.

Cultural diversity

Most research on obesity and cancer has focused on Caucasians in HICs. Although many of the identified risk factors in HICs will have the same physiological effects in LMICs, the determinants may be different, in addition to other environmental and genetic differences across populations. Novel risk factors may be identified in newly studied populations and regions.

Diet is shaped by many factors, such as knowledge about diet, food availability, budgetary constraints, and health conditions. Similarly, a

variety of factors influence daily physical activity, including dwellings, urbanization, employment constraints, and health conditions. A broad review of cultural determinants of obesity in LMICs is presented in Chapter 2. To the extent possible, evaluation of these factors that influence weight gain and obesity will inform efforts to mitigate the rising prevalence of obesity in the study populations.

Reporting and analyses of dietary intakes

Evaluation of biases in reported intake of macronutrients in HICs has shown underreporting of intake of carbohydrates and fat, but less underreporting of protein intake [9]. However, obese subjects are more likely to underreport intake of all macronutrients [9], and the lack of accuracy is dependent on the specific dietary assessment instrument used [10]. Such associations may be similar in research conducted in LMICs [11].

Whereas lack of food composition tables may be a current limitation in many regions, use of food patterns may be helpful, and may be more pertinent and more applicable for comparing results across populations in LMICs. If nutrient data are preferred, regional food composition tables from neighbouring countries could be used, or Food and Agriculture Organization of the United Nations (FAO) food composition data by continent (http://www.fao.org/infoods/en/) could be used. Significant efforts and funding are needed to develop country-specific and continent-specific food composition tables.

Foods and nutrients are eaten in a variety of combinations and can have interactive or cumulative effects when consumed together. Dietary patterns are defined as the quantities, proportions, variety, and combinations of different foods, drinks, and nutrients, and the frequency with which they are routinely consumed [12]. It will be important to identify dietary patterns related to weight gain and obesity in a variety of settings to evaluate the major lifestyle, behavioural, and policy influences, in an effort to plan public health interventions appropriately.

Recent research exploring the effect of dietary patterns on mortality suggests that overall nutritional quality may be more predictive than individual dietary components. Defining dietary quality usually involves comparison of the dietary intakes with guidance provided for that region.

In 2014, the United States Department of Agriculture (USDA) Nutrition Evidence Library summarized the literature on dietary patterns and obesity as part of a larger review of dietary patterns and several outcomes [12]. Dietary patterns can be assessed in various ways, including numerical indices designed to gauge adherence to a particular recommended pattern (e.g. the Healthy Eating Index in the USA) or data-driven approaches that use mathematics to empirically derive food intake patterns inherent in a study population.

The USDA review concluded that "there is moderate evidence that, in adults, increased adherence to dietary patterns scoring high in fruits, vegetables, whole grains, legumes, unsaturated oils, and fish; low in total meat, saturated fat, cholesterol, sugar-sweetened foods and beverages, and sodium; and moderate in dairy products and alcohol is associated with more favorable outcomes related to body weight or risk of obesity", with some variation by sex, race, or body weight status [12]. Adherence to a Mediterranean diet score or a dietary guidelines-related score was associated with decreased risk of obesity and with decreased body weight, body mass index (BMI), waist circumference, or body fat percentage. Mediterranean or dietary guidelines-related dietary patterns generally reflect a plant-based, minimally processed, nutrient-dense diet.

A variety of scores were included in the USDA review, including the Mediterranean Diet Score (MDS), the relative Mediterranean Diet Score (rMED), the Healthy Eating Index (HEI-1995 and HEI-2005), the Diet Quality Index-International (DQI-I), the Dietary Guidelines Adherence Index (DGAI), and the French Programme National Nutrition Santé Guideline Score (PNNS-GS). Overall, common dietary components related to decreased risk of obesity were fruits, vegetables, whole grains, legumes, and fish. Sugar-sweetened food and drink components were included and scored negatively in most of the dietary guidelines indices. Data-driven studies that used factor or cluster analyses or reduced rank regression provided limited or insufficient evidence for the association of dietary patterns with favourable body weight status [12].

Future efforts in LMICs should have regional similarities in the approaches and methods used, and use of guidance-based indices may prove more effective. Once dietary patterns in various countries/cultures are identified, a culturally appropriate set of dietary guidance recommendations may be used to calculate indices of nutritional quality for analyses in relation to outcomes, such as obesity.

Much attention has been focused on the association of childhood and adolescent obesity with higher risk of obesity in adulthood [13]. A systematic review on childhood nutrition and obesity later in life showed that diets high in energy-dense, high-fat, low-dietary-fibre foods were associated with later obesity [14]. This review of the evidence highlighted that food patterns better explained the link with later obesity than individual foods or nutrients.

Given that metabolic syndrome is likely to be a comorbid condition with the rising prevalence of obesity in LMICs, an evaluation of dietary patterns related to ameliorating the components of metabolic syndrome shows promise. Three dietary patterns were shown to improve components of metabolic syndrome (a Mediterranean dietary pattern, the Dietary Approaches to Stop Hypertension [DASH] diet, and the Nordic diet), and they were characterized by increases in intake of fruits, vegetables, whole grains, dairy products, whey protein, calcium, vitamin D, monounsaturated fatty acids, and omega-3 fatty acids [15]. Future studies in LMICs may benefit from a similar approach evaluating dietary patterns associated with components of metabolic syndrome.

There have been many intervention studies in children to prevent obesity later in life. A particularly interesting recent study in Finland shows promise. This longitudinal trial provided repeated dietary counselling aimed at reducing saturated fat intake beginning in infancy. The long-term risk, up to age 20 years, of metabolic syndrome was 40% lower in the intervention group [16]. Knowing the variety of region-specific dietary patterns and their associations with obesity and other morbidities will enable the implementation of interventions to improve nutritional status and general health.

Although they are not included in specific dietary pattern analyses, sugar-sweetened beverages have been shown to increase the risk of a variety of conditions in HICs. Literature reviews have found a strong association of high intakes of sugar-sweetened beverages with weight gain [17, 18], and evidence exists that decreasing the intake of sugar-sweetened beverages reduces the prevalence of obesity and obesity-related diseases [19]. New efforts in LMICs should monitor the intakes of sugar-sweetened beverages as part of dietary surveillance programmes in the diverse regions.

Surveillance to assess current intakes and trends

Surveillance efforts provide information on the population's weight and nutritional status as well as on food system variables at one time point and across time points. A food system encompasses foods, nutrition, health, community economic development, agriculture, and the social, political, economic, and environmental contexts of these processes.

For assessing baseline nutritional status and dietary changes over time, it will be important that suitable methods for measuring diet and nutrition-related behaviours are used in various LMICs. There is a need to evaluate the use of available methods in LMICs, their potential for standardization, and the capacity to develop new methods to enhance assessment, comparisons, and pooling of data.

For surveillance, it is desirable to use 24-hour recalls with standardized methodologies that will permit comparisons across populations at both the food and nutrient levels. Repeated surveys of diet, anthropometric measures, and physical activity will generate baseline information and enable assessment of changes over time at the population level. Such data are needed in low-resource countries to evaluate the current status of the population and to address adverse trends with a variety of prevention and control programmes.

Intervention studies in countries/regions are needed to learn about physiological changes and the sustainability of the changes. For example, a 2-year worksite intervention study in Israel showed favourable effects in weight loss and lipid profiles, with the largest effects in the Mediterranean-diet and low-carbohydrate-diet groups compared with the low-fat-diet group [20]. There was high compliance during the study (85%), and a 6-year follow-up showed long-lasting post-intervention effects on dietary intakes, weight, and lipid parameters [21]. The participants were invited to the clinic for a regular check-up, anthropometry, and a blood sample once a year during the follow-up period. Although the special labels were not available in the cafeteria after the intervention study ended, most participants continued to consume their specific dishes from the intervention study. At 6 years, 67% of the participants were complying with the original diet, demonstrating that appropriate, sustainable diets and intervention methods hold promise for future intervention research.

Short-term intervention studies can also be revealing. In a 2-week food exchange programme, African Americans were fed a high-fibre, low-fat African diet and rural Africans were fed a high-fat, low-fibre diet typical of high-income countries [22]. The food interventions resulted in the acquisition of microbiota and other biological parameters consistent with those found in the original diet group. There were changes in colonic mucosal proliferation rates and inflammation, and in characteristics of the microbiota and the metabolome that are associated with cancer risk. Given that the microbiota and inflammation have been related to obesity [23–25], further work in this area is worthwhile. Similar targeted intervention studies in LMICs may reveal dramatic effects from changes in dietary composition, with implications for improved health.

Influence of early life and life-cycle

Increasing attention is being paid to the role of factors across the life-course in relation to weight and

health outcomes in adulthood. More specifically, the role of nutrition in early development has been suggested to influence metabolic parameters and disease outcomes later in life [26]. It has been shown that a mother's own birth weight influenced her adult BMI, and that the risk of large-for-gestational-age offspring was increased among women with a high adult BMI who also had a high birth weight [27]. A variety of studies have shown independent effects of maternal BMI and offspring BMI, adiposity, abdominal obesity, and insulin resistance [28, 29]. Such observations suggest a vicious cycle of overweight across generations.

In 2011, the United Kingdom Scientific Advisory Committee on Nutrition (https://www.gov.uk/government/groups/scientific-advisory-committee-on-nutrition) published a review entitled "The influence of maternal, fetal and child nutrition on development of chronic disease in later life" [30]. The review warned against the later health consequences of excessive nutrient supply during early fetal and infant life, and emphasized that current dietary patterns of girls and women of reproductive age are a particular concern. The review suggested that improving the nutritional status of these women and of infants and young children has the potential to improve the health of future generations.

Further work on birth cohorts or other prospective studies in LMICs is likely to provide additional insights into developmental causes of obesity and noncommunicable diseases. Early-life factors operate together with exposures that accumulate over the life-course [31], but fundamental information on key time periods is still lacking. Although prospective studies are an important area of research, as are surveillance, intervention, and implementation research, resources and expanded research capacity are of the highest priority.

Discussion

Diet and physical activity are shaped by many physical, social, and cultural determinants, which need to be investigated in each population. New efforts should take into account factors that may modify energy requirements and response to dietary intakes, such as ageing, sex, body composition, activity level, environmental exposures, smoking, genetics, and disease status. The prevalence and etiologies of obesity in different populations need to be evaluated, addressing many of these factors and with culturally adapted methods.

To effectively advance the role of nutrition in improving and maintaining optimal weight status in populations, efforts need to be made to develop capacity and coordinate training efforts to support nutrition research. A key priority is nutrition surveillance; intervention research and implementation sciences are also important. Efforts should begin with evaluation of the available dietary methods in LMICs, their potential for standardization, and the capacity to develop new methods to enhance assessment, comparisons, and pooling of data. The potential of using 24-hour recalls with standardized methods should be evaluated, because they have been used successfully in many populations.

Given the evidence suggesting that physical activity and nutrition may interact in their influence on metabolic programming, research should include examination of the role of physical activity and its interaction with nutrition. These observations are of paramount importance in some LMIC settings, where emerging evidence suggests that physical activity patterns are changing and that nutrient supply early in life may vary with time and often moves towards food patterns that are less nutrient-rich. The prime importance of addressing physical activity in energy balance is discussed in Chapter 6, and these efforts could incorporate parallel capacity-building approaches to those for dietary assessment.

Further research focused on food patterns in LMICs may be beneficial in identifying helpful interventions for specific populations and subgroups. In some regions, lack of food composition tables may be a current limitation. It may be useful to conduct evaluations at the food level now, which may be followed by nutrient-level evaluations when food composition tables become available. Food pattern analyses in populations have many advantages. They can be used to develop dietary guidance, evaluate the nutritional quality of diets, evaluate associations with weight gain and obesity, and enable informed interventions to improve nutritional status. It will be important to identify dietary patterns related to weight gain and obesity in a variety of settings to evaluate the major lifestyle, behavioural, and policy influences, in an effort to plan public health interventions and research efforts appropriately. In addition, given the evidence from other countries, new efforts in LMICs should monitor the intake of sugar-sweetened beverages as part of dietary surveillance programmes.

Conclusions

There is clearly a need for capacity-building and resources devoted to nutrition research in LMICs. The first step would be a comprehensive assessment of resources already in place, and the identification of gaps and priorities for moving forward. Repeated surveillance surveys are essential in LMICs, to evaluate the current and future status of the population and to address undesirable

trends with prevention and control programmes. It is recognized that few prospective studies are currently under way in LMICs, and resources will be needed to pursue this important area of research. Input from local research communities, health ministries, and policy-makers is critical for the success of new efforts in LMICs.

Key points

- The prevalence of obesity is increasing in LMICs.
- Cultural and environmental aspects of the context are drivers of the obesity epidemic and require evaluation in each setting.
- Dietary quality is a main driver of weight gain and maintenance of optimal body weight.
- Evaluation of dietary patterns may be helpful in identifying region-specific patterns related to weight gain and obesity.
- Evaluation of dietary patterns will inform intervention strategies.
- Physical activity influences body weight, and the interaction of physical activity with dietary intakes affects weight status.
- Surveillance efforts provide information on current status and trends over time, and enable pooling of data across regions.
- Early-life time periods are important, and childhood obesity is particularly problematic.

Research needs

The following are needed in LMICs.

- Develop capacity and coordinate training efforts for nutrition research.
- Evaluate current methods and plan for standardized methods within and across regions.
- Build capacity to monitor and conduct research on physical activity.
- Develop methods to evaluate dietary patterns related to body weight status.
- Develop interventions related to foods and dietary patterns to improve nutritional status and modify negative trends in weight status in the populations.
- Prospective studies are needed to evaluate influences over the life-course, and resources are needed to support such studies.

References

1. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M (2008). Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 371(9612):569–78. http://dx.doi.org/10.1016/S0140-6736(08)60269-X PMID:18280327

2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. (2015). Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 136(5):E359–86. http://dx.doi.org/10.1002/ijc.29210 PMID:25220842

3. Keum N, Greenwood DC, Lee DH, Kim R, Aune D, Ju W, et al. (2015). Adult weight gain and adiposity-related cancers: a dose-response meta-analysis of prospective observational studies. J Natl Cancer Inst. 107(2):djv088. http://dx.doi.org/10.1093/jnci/djv088 PMID:25757865

4. WCRF/AICR (2007). Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington (DC), USA: World Cancer Research Fund/American Institute for Cancer Research. Available from: www.aicr.org/assets/docs/pdf/reports/Second_Expert_Report.pdf.

5. Napier KJ, Scheerer M, Misra S (2014). Esophageal cancer: a review of epidemiology, pathogenesis, staging workup and treatment modalities. World J Gastrointest Oncol. 6(5):112–20. http://dx.doi.org/10.4251/wjgo.v6.i5.112 PMID:24834141

6. Prabhu A, Obi KO, Rubenstein JH (2014). The synergistic effects of alcohol and tobacco consumption on the risk of esophageal squamous cell carcinoma: a meta-analysis. Am J Gastroenterol. 109(6):822–7. http://dx.doi.org/10.1038/ajg.2014.71 PMID:24751582

7. Zhang Y (2013). Epidemiology of esophageal cancer. World J Gastroenterol. 19(34):5598–606. http://dx.doi.org/10.3748/wjg.v19.i34.5598 PMID:24039351

8. Runge TM, Abrams JA, Shaheen NJ (2015). Epidemiology of Barrett's esophagus and esophageal adenocarcinoma. Gastroenterol Clin North Am. 44(2):203–31. http://dx.doi.org/10.1016/j.gtc.2015.02.001 PMID:26021191

9. Lissner L, Heitmann BL, Bengtsson C (2000). Population studies of diet and obesity. Br J Nutr. 83(Suppl 1):S21–4. http://dx.doi.org/10.1017/S000711450000091X PMID:10889788

10. Lissner L, Troiano RP, Midthune D, Heitmann BL, Kipnis V, Subar AF, et al. (2007). OPEN about obesity: recovery biomarkers, dietary reporting errors and BMI. Int J Obes. 31(6):956–61. http://dx.doi.org/10.1038/sj.ijo.0803527 PMID:17299385

11. Scagliusi FB, Ferriolli E, Pfrimer K, Laureano C, Cunha CS, Gualano B, et al. (2008). Underreporting of energy intake in Brazilian women varies according to dietary assessment: a cross-sectional study using doubly labeled water. J Am Diet Assoc. 108(12):2031–40. http://dx.doi.org/10.1016/j.jada.2008.09.012 PMID:19027406

12. USDA Nutrition Evidence Library (2014). A series of systematic reviews on the relationship between dietary patterns and health outcomes. Alexandria (VA), USA: United States Department of Agriculture. Available from: https://www.cnpp.usda.gov/sites/default/files/usda_nutrition_evidence_flbrary/DietaryPatternsReport-FullFinal.pdf.

13. Simmonds M, Burch J, Llewellyn A, Griffiths C, Yang H, Owen C, et al. (2015). The use of measures of obesity in childhood for predicting obesity and the development of obesity-related diseases in adulthood: a systematic review and meta-analysis. Health Technol Assess. 19(43):1–336. http://dx.doi.org/10.3310/hta19430 PMID:26108433

14. Ambrosini GL (2014). Childhood dietary patterns and later obesity: a review of the evidence. Proc Nutr Soc. 73(1):137–46. http://dx.doi.org/10.1017/S0029665113003765 PMID:24280165

15. Calton EK, James AP, Pannu PK, Soares MJ (2014). Certain dietary patterns are beneficial for the metabolic syndrome: reviewing the evidence. Nutr Res. 34(7):559–68. http://dx.doi.org/10.1016/j.nutres.2014.06.012 PMID:25150114

16. Nupponen M, Pahkala K, Juonala M, Magnussen CG, Niinikoski H, Rönnemaa T, et al. (2015). Metabolic syndrome from adolescence to early adulthood: effect of infancy-onset dietary counseling of low saturated fat: the Special Turku Coronary Risk Factor Intervention Project (STRIP). Circulation. 131(7):605–13. http://dx.doi.org/10.1161/CIRCULATIONAHA.114.010532 PMID:25605660

17. Malik VS, Schulze MB, Hu FB (2006). Intake of sugar-sweetened beverages and weight gain: a systematic review. Am J Clin Nutr. 84(2):274–88. PMID:16895873

18. Te Morenga L, Mallard S, Mann J (2012). Dietary sugars and body weight: systematic review and meta-analyses of randomised controlled trials and cohort studies. BMJ. 346:e7492. http://dx.doi.org/10.1136/bmj.e7492 PMID:23321486

19. Hu FB (2013). Resolved: there is sufficient scientific evidence that decreasing sugar-sweetened beverage consumption will reduce the prevalence of obesity and obesity-related diseases. Obes Rev. 14(8):606–19. http://dx.doi.org/10.1111/obr.12040 PMID:23763695

20. Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I, et al.; Dietary Intervention Randomized Controlled Trial (DIRECT) Group (2008). Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med. 359(3):229–41. PMID:18635428

21. Schwarzfuchs D, Golan R, Shai I (2012). Four-year follow-up after two-year dietary interventions. N Engl J Med. 367(14):1373–4. PMID:23034044

22. O'Keefe SJD, Li JV, Lahti L, Ou J, Carbonero F, Mohammed K, et al. (2015). Fat, fibre and cancer risk in African Americans and rural Africans. Nat Commun. 6:6342. http://dx.doi.org/10.1038/ncomms7342 PMID:25919227

23. Barlow GM, Yu A, Mathur R (2015). Role of the gut microbiome in obesity and diabetes mellitus. Nutr Clin Pract. 30(6):787–97. http://dx.doi.org/10.1177/0884533615609896 PMID:26452391

24. Ojeda P, Bobe A, Dolan K, Leone V, Martinez K (2016). Nutritional modulation of gut microbiota – the impact on metabolic disease pathophysiology. J Nutr Biochem. 28:191–200. http://dx.doi.org/10.1016/j.jnutbio.2015.08.013 PMID:26372091

25. Apostolopoulos V, de Courten MP, Stojanovska L, Blatch GL, Tangalakis K, de Courten B (2016). The complex immunological and inflammatory network of adipose tissue in obesity. Mol Nutr Food Res. 60(1):43–57. http://dx.doi.org/10.1002/mnfr.201500272 PMID:26331761

26. Gluckman PD, Hanson MA, Buklijas T (2010). A conceptual framework for the developmental origins of health and disease. J Dev Orig Health Dis. 1(1):6–18. http://dx.doi.org/10.1017/S2040174409990171 PMID:25142928

27. Cnattingius S, Villamor E, Lagerros YT, Wikström A-K, Granath F (2012). High birth weight and obesity – a vicious circle across generations. Int J Obes (Lond). 36(10):1320–4. http://dx.doi.org/10.1038/ijo.2011.248 PMID:22158263

28. Pirkola J, Pouta A, Bloigu A, Hartikainen AL, Laitinen J, Järvelin MR, et al. (2010). Risks of overweight and abdominal obesity at age 16 years associated with prenatal exposures to maternal prepregnancy overweight and gestational diabetes mellitus. Diabetes Care. 33(5):1115–21. http://dx.doi.org/10.2337/dc09-1871 PMID:20427685

29. Benyshek DC (2013). The "early life" origins of obesity-related health disorders: new discoveries regarding the intergenerational transmission of developmentally programmed traits in the global cardiometabolic health crisis. Am J Phys Anthropol. 152(Suppl 57):79–93. http://dx.doi.org/10.1002/ajpa.22393 PMID:24249592

30. United Kingdom Scientific Advisory Committee on Nutrition (2011). The influence of maternal, fetal and child nutrition on development of chronic disease in later life. London, UK: The Stationery Office. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/339325/SACN_Early_Life_Nutrition_Report.pdf.

31. Victora CG, Adair L, Fall C, Hallal PC, Martorell R, Richter L, et al.; Maternal and Child Undernutrition Study Group (2008). Maternal and child undernutrition: consequences for adult health and human capital. Lancet. 371(9609):340–57. http://dx.doi.org/10.1016/S0140-6736(07)61692-4 PMID:18206223

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