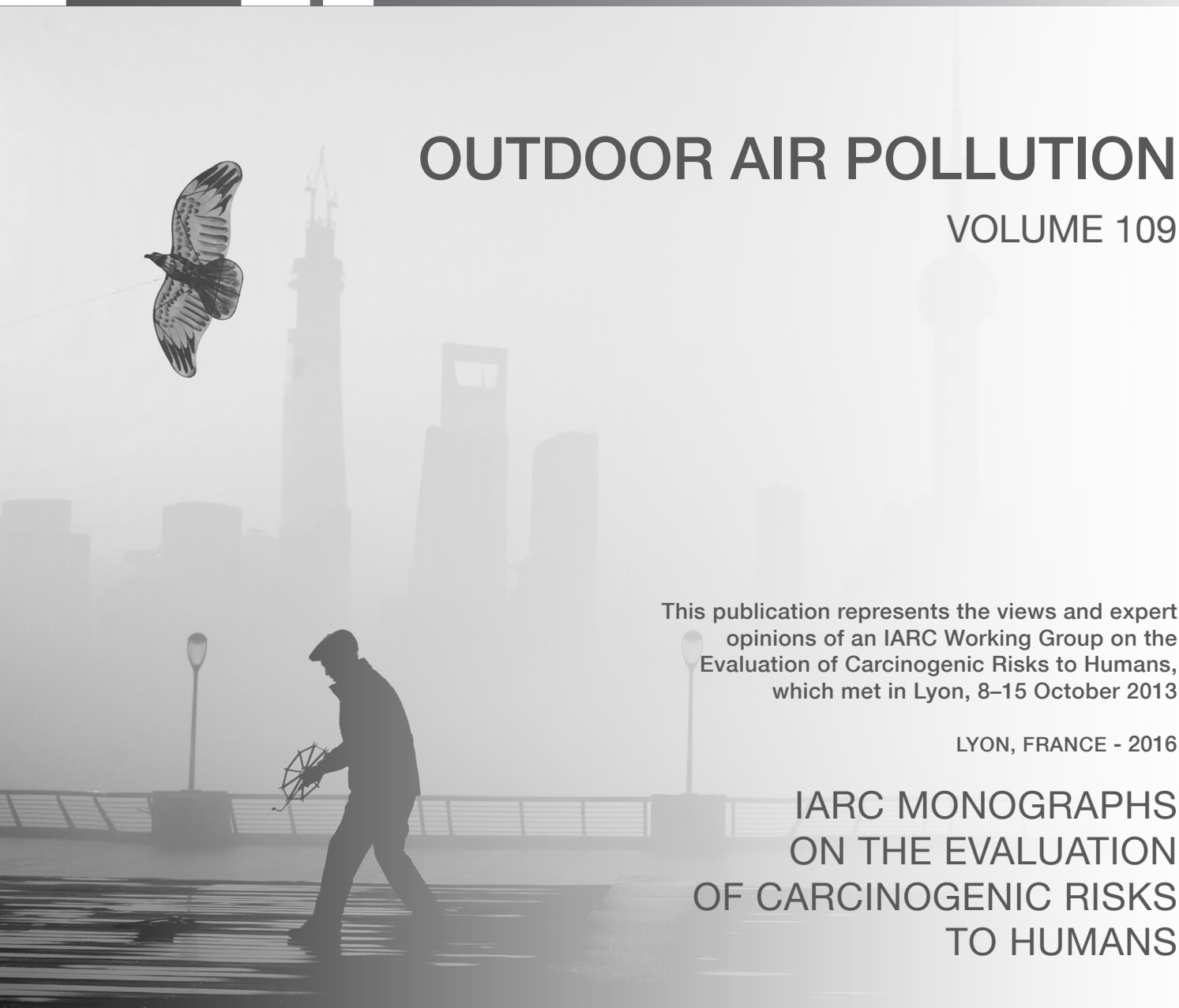
IARC MONOGRAPHS



OUTDOOR AIR POLLUTION

VOLUME 109

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 8–15 October 2013

LYON, FRANCE - 2016

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

2. CANCER IN HUMANS

2.1 Cancer of the lung

2.1.1 Cohort studies in North America

See Table 2.1.

To date, the association of exposure to outdoor air pollution with lung cancer risk has been assessed in six North American cohort studies: the Harvard Six Cities Study, the American Cancer Society study, the Adventist Health Study on Smog, the Trucking Industry Particle Study, the California Teachers Study, and the Ontario Tax Cohort Study. However, there have been multiple publications from the first three studies, representing different periods of follow-up and/or selected subsets of the population.

(a) Harvard Six Cities Study

The Harvard Six Cities Study was designed specifically to evaluate exposures to outdoor air pollution and their association with health among 8111 White adults aged 25–74 years recruited from six cities in the eastern USA representing a range of air pollution exposures: Steubenville, Ohio, and St. Louis, Missouri (high exposure); Watertown, Massachusetts, and Kingston-Harriman, Tennessee (medium exposure); and Portage (including Wyocena and Pardeeville), Wisconsin, and Topeka, Kansas (low exposure). Follow-up began between 1975 and 1977 in each city, and each participant completed a baseline questionnaire. Active follow-up, including information on vital status, continued by mail until 1991 (Dockery et al., 1993). In addition, the cohort was followed up through searches of the National Death Index, with the last update in 2009 (Lepeule et al., 2012).

Three follow-ups of the Harvard Six Cities Study have been published: through 1989 or 1991 (determined by the last date of search of the National Death Index or the ending date of the study, respectively) (Dockery et al., 1993), through 1998 (Laden et al., 2006), and through 2009 (Lepeule et al., 2012). Between 1979 and 1986–1988 (depending on the city) the researchers measured outdoor concentrations of total suspended particles (TSP), sulfur dioxide (SO_2), ozone, suspended sulfates, and particulate matter (PM) with particles of aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), less than 15 μm (PM_{15}) (before 1984), and less than 10 μm (PM_{10}) (after 1984) at central site air-monitoring stations in each community (Dockery et al., 1993; Laden et al., 2006). Measurements of PM_{10} from routine air-quality monitoring stations are available from monitors located near the original central sites in each community starting in 1985, and measurements of $PM_{2.5}$ are available starting in 1999. For follow-up after 1999, these measurements were used to obtain city-specific annual average $PM_{2.5}$ concentrations from representative monitors within 80 km of the original sampling locations (Lepeule et al., 2012). For the period between the end of the original monitoring activity and 1999, the authors predicted city-specific annual average $PM_{2.5}$ based on PM_{10} concentrations from the monitors, extinction

Table 2.1 Cohort studies of lung cancer and outdoor air pollution in North America

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Harvard Six Cities Study									
Lepeule et al. (2012) USA	8096 total	1974–2009	City-specific annual average $PM_{2.5}$ from study monitors and monitors in the US EPA AIRS (Air Quality System) database	Lung	1–3-year moving average $PM_{2.5}$ per 10 µg/m³; range, city-specific annual mean ~40–8 µg/m³ during follow-up	351 never-smokers NR former smokers NR current smokers NR	1.37 (1.07–1.75) 1.25 (0.54–2.89) 1.96 (1.29–2.99) 1.25 (0.95–1,64)	Pack-years of past smoking, less than high school education, and linear and quadratic terms for BMI	Mortality; update of Laden et al. (2006) and Dockery et al. (1993)
American Cancer Society study (ACS CPS-II)									
Krewski et al. (2009) USA	351 338	1982–2000	Metropolitan Statistical Area averages from US EPA air quality monitoring databases	Lung	$PM_{2.5}$ (1979–1983) per 10 µg/m³; range, 10.8–30.1; mean (var), 21.2 (21.4)		1.08 (1.03–1.14)	44 individual-level covariates, including age, sex, race, smoking, education level, marital status, alcohol consumption, occupational exposure, and diet	Update of Pope et al. (1995, 2002); adjustment for ecological covariates did not materially change results
	499 968				$PM_{2.5}$ (1999–2000) per 10 µg/m³; range, 5.8–22.2; mean (var), 14.0 (9.1)		1.11 (1.04–1.18)		
	572 312				Sulfate (1980) per 5 µg/m³; range, 1.4–15.6; mean (var), 6.5 (7.9)		1.05 (1.02–1.09)		
	268 336				Sulfate (1990) per 5 µg/m³; range, 2.0–10.7; mean (var), 6.2 (3.9)		1.04 (0.97–1.11)		
	513 450				SO_2 (1980) per 5 ppb; range, 0.02–29.3; mean (var), 9.7 (23.7)		1.00 (0.98–1.02)		
	531 826				O_3 (1980) per 10 ppb; range, 10.4–41.1; mean (var), 22.9 (21.5)		1.00 (0.96–1.04)		

Table 2.1 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Krewski et al. (2009) USA (cont.)	406 917				NO_2 (1980) per 10 ppb; range, 7.8–51.1; mean (var), 27.9 (85.3)		0.99 (0.97–1.01)		
	508 538				CO (1980) per 1 ppm; range, 0.2–4.0; mean (var), 1.7 (0.4)		0.99 (0.97–1.03)		
Subgroup in New York City, New York	44 056	1982–2000	Monthly average $PM_{2.5}$ LUR at the postal-code level		$PM_{2.5}$ per 1.5 μg/m³ (interdecile range); mean, 14.3; SD, 1.78; range, 10.8–18.6	853	0.96 (0.84–1.09)		
Jerrett et al. (2005) Los Angeles, California, USA	22 905	1982–2000	Monthly average $PM_{2.5}$ kriging at the postal-code level	Lung	$PM_{2.5}$ per 10 μg/m³; range, 9.0–27.1 μg/m³	434	1.44 (0.98–2.11)	Same as Krewski et al. (2009)	Results were attenuated but still elevated after addition of ecological covariates; kriging results also presented in Krewski et al. (2005), along with similar results from LUR models
Turner et al. (2011) USA, never-smokers	188 699	1982–2008	Metropolitan Statistical Area average $PM_{2.5}$ from US EPA air quality databases	Lung		1100		Sex, age, race, education level, marital status, BMI, passive smoking, diet, alcohol consumption, occupational exposure, and county-level radon	Never-smokers; extended follow-up of Krewski et al. (2009) and Pope et al. (2002)
					1979–1983 average $PM_{2.5}$ per 10 μg/m³; range, 10.3–37.8; mean (SD), 21.1 (4.7)	772	1.15 (0.99–1.35)		
					1999–2000 average $PM_{2.5}$ per 10 μg/m³; range, 5.8–22.2; mean (SD), 14 (3)	1042	1.27 (1.03–1.56)		
					Average of 2 time periods; range, 9.0–27.7; mean (SD), 17.6 (3.7)	714	1.19 (0.97–1.47)		
	50 805 men				1999–2000 average $PM_{2.5}$ per 10 μg/m³	334	1.19 (0.83–1.73)		

Table 2.1 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
	126 947 women					708	1.30 (1.01–1.68)		
Jerrett et al. (2013) California, USA	73 711	1982–2000	Residence-level average $PM_{2.5}$, NO_2, and O_3 from US EPA air quality database; satellite data also used for $PM_{2.5}$ (LUR for $PM_{2.5}$ and NO_2; inverse-distance weighting for O_3)	Lung	1998–2002 average $PM_{2.5}$ per 5.30 µg/m³; range, 4.3–25.1; mean (var), 14.1 (12.4) 1988–2002 average NO_2 per 4.12 ppb; range, 3.0–21.9; mean (var), 12.3 (8.5) 1988–2002 average O_3 per 24.18 ppb; range, 17.1–89.3; mean (var), 50.4 (212.2)	1481	1.06 (0.95–1.18) 1.11 (1.02–1.21) 0.86 (0.75–0.99)	42 individual-level covariates [including those listed for Pope et al. (2002)], 5 consolidated Metropolitan Statistical Area indicators, and 7 ecological covariates	Results are presented per IQR of each pollutant; in multipollutant models, associations with NO_2 persisted, while estimates for $PM_{2.5}$ were reduced to unity The authors considered NO_2 a possible marker of traffic, but it appears model included other sources
Adventist Health Study on Smog (AHSMOG)									
Beeson et al. (1998) California, USA	6340 2278 men	1977–1992	Residential and workplace postal code centroid cumulative averages for 1973–1992 from fixed monitors	Lung	PM_{10} per 24 µg/m³ (IQR) cumulative average with 3-year lag SO_2 per 3.7 ppb (IQR) cumulative average with 3-year lag NO_2 per 19.8 ppb (IQR) cumulative average with 3-year lag 8-h average O_3 per 12.0 ppb (IQR) cumulative average with 3-year lag	16 16 16 16	5.21 (1.94–13.99) 2.66 (1.62–4.39) 1.45 (0.67–3.14) 2.23 (0.79–6.34)	Attained age, pack-years of past smoking, years of education, and current alcohol consumption	Incident cases; update of Abbey et al. (1991a) and Mills et al. (1991); also present HRs for days above exceedance cut-off points, but these are not presented here
	4060 women				SO_2 per 3.7 ppb (IQR) cumulative average with 3-year lag	20	2.14 (1.36–3.37)	Attained age, pack-years of past smoking, and years of education	

Table 2.1 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Abbey et al. (1999) California, USA	6340	1977–1992	Residential and workplace postal code centroid cumulative averages for 1973–1992 from fixed monitors	Lung				Attained age, pack-years of past smoking, years of education, and current alcohol consumption	Mortality; update of Abbey et al. (1991a) and Mills et al. (1991); also presented HRs for days above exceedance cut-off points, but these are not presented here
	2278 men				PM_{10} per 24 μg/m³ (IQR) cumulative average with 3-year lag	17	3.36 (1.57–7.19)		
					SO_2 per 3.7 ppb (IQR) cumulative average with 3-year lag	17	1.99 (1.24–3.20)		
					NO_2 per 19.8 ppb (IQR) cumulative average with 3-year lag	17	1.82 (0.93–3.57)		
					8-h average O_3 per 12.0 ppb (IQR) cumulative average with 3-year lag	17	2.10 (0.99–4.44)		
	4060 women				PM_{10} per 24 μg/m³ (IQR) cumulative average with 3-year lag	12	1.08 (0.55–2.13)	Attained age, education level, and smoking	
					SO_2 per 3.7 ppb (IQR) cumulative average with 3-year lag	12	3.01 (1.88–4.84)		
					NO_2 per 19.8 ppb (IQR) cumulative average with 3-year lag	12	2.81 (1.15–6.89)		
					8-h average O_3 per 12.0 ppb (IQR) cumulative average with 3-year lag	12	0.77 (0.37–1.61)		

Table 2.1 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
McDonnell et al. (2000) California, USA	1228 men	1977–1992	Average $PM_{2.5}$ for the airshed of residence, predicted from visibility, relative humidity, and season	Lung	Average $PM_{2.5}$ per 24.3 μg/m³ (IQR)	13	2.23 (0.56–8.94)	Attained age, pack-years of past smoking, years of education, and current alcohol consumption	Mortality; results for 2422 women not presented
			Postal code centroid cumulative averages for 1973–1992 from fixed monitors		Average PM_{10} per 29.5 μg/m³ (IQR)		1.84 (0.59–5.67)		
			PM_{10} – $PM_{2.5}$		Average $PM_{2.5}$ – PM_{10} per 9.7 μg/m³ (IQR)		1.25 (0.63–2.49)		
Trucking Industry Particle Study (TrIPS)									
Hart et al. (2011) USA	53 814 men in the trucking industry in the USA	1985–2000	Residence-level geospatial model for PM_{10}, SO_2, and NO_2; nearest monitor for $PM_{2.5}$	Lung	2000 annual average $PM_{2.5}$ per 4 μg/m³ (IQR); mean (SD), 14.1 (4.0)	800	1.02 (0.95–1.10)	Age at entry, decade of hire, calendar year, race, region, healthy worker survivor effect, and occupational exposures	Results are presented per IQR of each pollutant
					1985–2000 average PM_{10} per 6 μg/m³ (IQR); mean (SD), 26.8 (6.0)	800	0.99 (0.92–1.08)		
					1985–2000 average SO_2 per 4 ppb (IQR); mean (SD), 4.8 (2.9)	800	1.09 (0.98–1.21)		
					1985–2000 average NO_2 per 8 ppb (IQR); mean (SD), 14.2 (7.1)	800	1.06 (0.97–1.15)		

Table 2.1 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Hart et al. (2011) USA (cont.)	39 948				2000 annual average $PM_{2.5}$ per 4 µg/m³ (IQR)	475	1.07 (0.97–1.17)		Excluding long-haul drivers who work away from home
					1985–2000 average PM_{10} per 6 µg/m³ (IQR)		1.05 (0.94–1.17)		
					1985–2000 average SO_2 per 4 ppb (IQR)		1.09 (0.95–1.25)		
					1985–2000 average NO_2 per 8 ppb (IQR)		1.07 (0.96–1.20)		
California Teachers Study									
Lipsett et al. (2011) California, USA	101 784 women	1997–2005	Monthly pollutant surfaces of PM_{10}, $PM_{2.5}$, SO_2, NO_2, CO, O_3, and NO_x calculated from fixed monitoring network; assigned to participant's residence using 250 m grids	Lung	Cumulative average $PM_{2.5}$ per 10 µg/m³; range, 3.1–28.4; mean (SD), 15.6 (4.5)	234	0.95 (0.70–1.28)	Age, race, smoking, BMI, marital status, alcohol consumption, second-hand smoke exposure, diet, physical activity, menopausal status, hormone therapy, family history of myocardial infarction/ stroke, use of blood pressure medication, aspirin use, and neighbourhood SES variables	Mortality; follow-up for $PM_{2.5}$ began in 2000 due to availability of data
					Cumulative average PM_{10} per 10 µg/m³; range, 9.2–82.6; mean (SD), 29.2 (9.7)	275	0.93 (0.81–1.07)		
					Cumulative average O_3 per 11.02 ppb (IQR); range, 25.4–82.6; mean (SD), 48.1 (8.7)	433	0.96 (0.84–1.09)		
					Cumulative average NO_x per 48.31 ppb (IQR); range, 7.3–221.4; mean (SD), 95.6 (34.5)	70	0.92 (0.60–1.40)		
					Cumulative average NO_2 per 10.29 ppb (IQR); range, 5.2–67.2; mean (SD), 33.6 (9.6)	67	1.00 (0.75–1.33)		
					Cumulative average CO per 0.49 ppm (IQR); range,0.3–3.3; mean (SD), 1.1 (0.4)	52	0.89 (0.57–1.39)		

Table 2.1 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Lipsett et al. (2011) California, USA (cont.)	83 491				Cumulative average $PM_{2.5}$ per 10 µg/m³	50	1.62 (0.83–3.16)		
					Cumulative average PM_{10} per 10 µg/m³	62	1.00 (0.75–1.31)		
					Cumulative average O_3 per 11.02 ppb (IQR)	103	0.98 (0.76–1.27)		
					Cumulative average NO_x per 49.31 ppb (IQR)	22	0.89 (0.41–1.92)		
					Cumulative average NO_2 per 10.29 ppb (IQR)	20	0.96 (0.54–1.71)		
					Cumulative average CO per 0.49 ppm (IQR)	15	0.37 (0.13–1.06)		
Ontario Tax Cohort Study									
Villeneuve et al. (2013) Toronto, Canada	58 760	1982–2004	LUR surfaces of VOCs (benzene, *n*-hexane, and total hydrocarbons) and NO_2 linked to baseline home address	Lung	Benzene per 0.13 µg/m³ (IQR)	1470	1.05 (0.96–1.14)	Age; sex; family income; marital status; census area measures of income, immigration, and unemployment; and NO_2; indirect adjustment for smoking and BMI	Mortality; splines indicated linearity for benzene–lung cancer exposure–response function; results for all cancers also presented; effect estimates stronger when follow-up restricted to first 5 years HR unadjusted for VOCs is presented in a figure; does not appear markedly different
					n-Hexane per 1.20 µg/m³ (IQR)		1.03 (0.97–1.10)		
					Total hydrocarbons per 9.02 µg/m³ (IQR)		1.04 (0.98–1.10)		
					NO_2 per 5.9 ppb (IQR)		0.96 (0.89–1.03)		

BMI, body mass index; CI, confidence interval; CO, carbon monoxide; h, hour or hours; HR, hazard ratio; IQR, interquartile range; LUR, land-use regression; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; O_3, ozone; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 µm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 µm; SD, standard deviation; SES, socioeconomic status; SO_2, sulfur dioxide; US EPA, United States Environmental Protection Agency; var, variance; VOCs, volatile organic compounds.

coefficients (humidity-corrected visibility data from the local airport), and indicators of season (Laden et al., 2006).

Publications on the first and second follow-ups of the cohort (Dockery et al., 1993; Laden et al., 2006) reported positive associations of lung cancer mortality with sulfate and $PM_{2.5}$, respectively. In the most recent follow-up of the full cohort, through 2009, 4495 deaths (7.8% from lung cancer) were identified. In adjusted models, the hazard ratio (HR) was 1.37 (95% confidence interval [CI], 1.07–1.75) for each 10 μg/m^3 increase in $PM_{2.5}$ averaged over the past 1–3 years (determined as the averaging period with the best fit). Analyses of penalized splines indicated a linear relationship. (The city-specific annual average $PM_{2.5}$ ranged from approximately 40 μg/m^3 to 8 μg/m^3 over the course of the entire follow-up period.) Other modelling options were also considered, with similar results (Lepeule et al., 2012). In stratified analyses, relative risks were elevated for never-smokers, current smokers, and former smokers, with former smokers appearing to have the highest risk compared with never-smokers or current smokers; however, the *P*-value for interaction was not statistically significant. In time-period-specific analyses, the hazard ratio for the past 8 years of follow-up (2001–2009) was the strongest (HR, 2.84; 95% CI, 1.06–7.59), but again the *P*-value for interaction was not significant. Because of the high correlation of exposures over time, the critical exposure window could not be determined (Lepeule et al., 2012).

[A limitation of the Harvard Six Cities Study is that it relied on central site monitoring for each city. Since all participants in the same city were assigned the same exposure value, there was no ability to assess intra-city spatial variation in exposures. In Dockery et al. (1993), a city-specific average value for each pollutant was created for 3–8 years during the late 1970s or the 1980s, depending on the pollutant; therefore, there was also no assessment of variation of air pollution over time. Furthermore, in some cases the measurements may actually have occurred after the relevant death. In the subsequent analyses, an annual average for $PM_{2.5}$ for each city was created and assigned to the follow-up time by calendar year; thus, temporal variation was accounted for. Other limitations are that there is no information on whether a person moved out of the city in which they were recruited during the follow-up period, and that only baseline information on covariates was included in the final analyses. However, in a reanalysis of the Dockery et al. (1993) study, Krewski and colleagues (HEI, 2000) found that the results were robust to updates of the covariates and changes in address. The strengths of the study are the detailed exposure monitoring, the assessment of different modelling options in the most recent follow-up, the prospective follow-up, and the control for potential confounders at the individual level: age, sex, body mass index (BMI), smoking status and pack-years of smoking, and education level.]

(b) American Cancer Society study

Six analyses of the association of measures of air pollution with lung cancer mortality have relied on data collected by the American Cancer Society (ACS) as part of the Cancer Prevention Study II (CPS-II) (Pope et al., 1995, 2002; Jerrett et al., 2005, 2013; Krewski et al., 2009; Turner et al., 2011). The ACS CPS-II is an ongoing prospective mortality study of approximately 1.2 million adults aged at least 30 years at enrolment in 1982 and residing throughout the USA. Before 1989, vital status was obtained from the study volunteers who enrolled the participants. After 1989, searches of the National Death Index were conducted. Individual-level risk factor information was available through a baseline questionnaire. The original analysis included 7 years of follow-up, through 1989 (Pope et al., 1995). Subsequent publications on the nationwide cohort included follow-up through 1998 (16 years) (Pope et al., 2002), through 2000 (18 years) (Krewski et al., 2009), and through

2008 (26 years), with the most recent follow-up restricted to never-smokers (Turner et al., 2011). Jerrett et al. (2005, 2013) and Krewski et al. (2009) conducted analyses focused on Los Angeles, New York City, and the state of California.

Analyses of air pollution effects in the ACS CPS-II took advantage of existing national monitoring networks to quantify air pollution exposures. Therefore, the study population was restricted to participants who resided in United States Metropolitan Statistical Areas (MSAs) with available pollution data (approximately 300 000–500 000 participants, depending on the follow-up and pollutants measured). Baseline average $PM_{2.5}$ levels were quantified by MSA of residence for 1979–1983 using data from the Inhalable Particle Monitoring Network. TSP and different size fractions of PM (PM_{15}, $PM_{15–2.5}$) were available for that time period as well. PM_{10} concentrations for 1982–1998 and $PM_{2.5}$ beginning in 1999 were available from the United States Environmental Protection Agency (US EPA) AIRS database. Average outdoor $PM_{2.5}$ concentrations from 1999–2000 were used to quantify exposures towards the end of the follow-up period, and an average of the two time periods was considered as an estimate of exposure over the course of the study. Sulfate concentrations were available for 1980–1981, and SO_2, nitrogen dioxide (NO_2), carbon monoxide (CO), and ozone levels were available for 1980 and 1982–1998. Ranges and/or means of exposure for all pollutants in each follow-up are presented in Table 2.1 when available (Pope et al., 2002; Krewski et al., 2009; Turner et al., 2011).

Reports of the first two follow-ups of the ACS CPS-II cohort (Pope et al., 1995, 2002) provided data on the association of lung cancer mortality with concentrations of $PM_{2.5}$ and sulfate. Positive associations were observed for both indicators. The second report also included data for SO_2, NO_2, CO, and ozone (Pope et al., 2002).

In the most recent analysis of the cohort, with 2 more years of follow-up and additional adjustment for individual-level covariates from the baseline questionnaire, hazard ratios were 1.08 (95% CI, 1.03–1.14) and 1.11 (95% CI, 1.04–1.18) for $PM_{2.5}$ in 1979–1983 and 1999–2000, respectively, and 1.05 (95% CI, 1.02–1.11) and 1.04 (95% CI, 0.97–1.11) for sulfate in 1980 and 1990, respectively (Krewski et al., 2009). No association with lung cancer was observed for ozone, SO_2, NO_2, or CO. Additional adjustment for ecological covariates derived at the postal code and MSA level did not materially change the results. Spatial autocorrelation was also included in sensitivity analyses, but results specific to lung cancer are not presented. No clear patterns emerged from analyses of time windows of exposure.

[The nationwide assessments of the ACS CPS-II rely on MSA-specific measurements from at most two time periods (near the beginning and near the end of the follow-up). There is no assessment of intra-city variability, which could enhance contrasts in exposure but should not hamper interpretation of the results that were obtained. Furthermore, there is no accounting for whether a participant moved out of their baseline location, which could contribute to measurement error. Covariates were not updated over time, potentially reducing the ability to control confounding. However, strengths of the studies are the assessment of a linear trend, the prospective follow-up, and that individual-level covariates are controlled for in both analyses. Krewski et al. (2009) also included a large battery of ecological covariates and assessment of autocorrelation.]

In the analysis with the longest follow-up period to date (26 years), Turner et al. (2011) assessed the association of $PM_{2.5}$ with lung cancer mortality among 188 699 lifetime non-smokers in the ACS CPS-II cohort. In Cox proportional hazard models adjusting for the same covariates as in the Pope et al. (2002) study with the addition of dietary variables, additional measures of occupational exposures, and mean county-level residential radon concentrations, each 10 μg/m^3

increase in $PM_{2.5}$ was associated with a 15–27% increase in lung cancer mortality, depending on the time window in which the $PM_{2.5}$ concentration was assessed. The fully adjusted hazard ratios were modestly attenuated compared with those not adjusted for residential radon. A plot of adjusted hazard ratios in relation to quartiles of $PM_{2.5}$ (1999–2000) suggests a linear trend, but a formal test was not presented. [The strengths and limitations of Turner et al. (2011) are the same as those described for Pope et al. (2002) and Krewski et al. (2009). The restriction of this study to never-smokers is a major additional strength, as is the control for other potential confounders – diet, occupation, and residential radon – as covariates in the models. Both features reduce the potential for confounding, although among the additional covariates considered, only radon had a notable effect on the association with $PM_{2.5}$.]

The ACS investigators also performed specific analyses in Los Angeles, the state of California, and New York City, where they had the ability to describe intra-city variability in exposure using land-use regression exposure models. In Los Angeles, the hazard ratio controlling for 44 individual-level covariates was 1.44 (95% CI, 0.98–2.11) per 10 μg/m³ increase in $PM_{2.5}$ estimated for each individual's postal code centroid. This was attenuated to 1.20 (95% CI, 0.79–1.82) when statistically significant contextual covariates were included (Jerrett et al., 2005). Results using a slightly different statistical technique to predict exposures were similar (Krewski et al., 2009). In equivalent analyses in New York City, the hazard ratio adjusted for individual-level covariates was 0.96 (95% CI, 0.84–1.09) per 1.5 μg/m³ increase in $PM_{2.5}$ (the interdecile range) (Krewski et al., 2009). Jerrett et al. (2013) modelled monthly averaged $PM_{2.5}$, NO_2, and ozone at the baseline residential address for all 73 711 ACS CPS-II participants residing in California. Monitoring data for $PM_{2.5}$ and NO_2 were supplemented with data from satellites. Exposure metrics were determined as averages for 1988–2002 for NO_2 and ozone and as averages for 1998–2002 for $PM_{2.5}$. In models adjusted for 42 individual-level covariates, as well as indicators of the MSAs and 7 ecological covariates, hazard ratios for lung cancer were elevated for an interquartile range (IQR) increase in $PM_{2.5}$ (HR, 1.06; 95% CI, 0.95–1.18) and NO_2 (HR, 1.11; 95% CI, 1.02–1.21) but not for ozone (HR, 0.86; 95% CI, 0.75–0.99). Analyses representing exposure with splines showed no evidence of nonlinearity. Associations with NO_2 remained statistically significant in two pollutant models that additionally included $PM_{2.5}$ and ozone, while estimates for $PM_{2.5}$ were reduced to unity. [The authors described NO_2 as a marker for traffic-related air pollution. However, since other exposure sources (i.e. heating and industrial) were included in the models, their contributions to the modelled concentrations cannot be ruled out. The results for NO_2 are more consistent with the European studies, which also assessed intra-city variability, than with the full-country ACS analysis, which assessed variation across larger areas.]

[The strengths of the three area-specific analyses of the ACS CPS-II (Los Angeles, New York City, and California) are the detailed adjustment for baseline and ecological confounders and the ability to consider intra-city variability and temporal variability.]

(c) Adventist Health Study on Smog

The Adventist Health Study on Smog (AHSMOG) cohort consists of 6340 Seventh-Day Adventists who were participants in the Adventist Health Study. They were non-Hispanic Whites residing in California, currently non-smokers, who had lived for at least 10 years within 5 miles (8 km) of their baseline residence and were aged 25 years to more than 80 years when they completed the baseline questionnaire in 1977 (Abbey et al., 1991a).

Monthly outdoor concentrations of TSP, PM_{10}, SO_2, NO_2, and ozone were estimated for each participant starting in 1966 from fixed-site

monitors maintained by the California Air Resources Board. Exposure predictions were restricted to postal code centroids within 50 km of a monitoring station and were not allowed to cross topographical obstructions or other barriers to air flow (Abbey et al., 1991b). Before 1987, PM_{10} was estimated from TSP, and before 1972, total oxidants were measured as opposed to ozone. For each pollutant, both means and exceedance frequencies (the sum of hours for gaseous pollutants or of days for particulate pollutants above a specified cut-off based on federal and California standards at the time) were used as exposure metrics in the majority of the epidemiological analyses. Cancer incidence was ascertained from linkage with cancer registries and medical record review of self-reported hospitalizations, and mortality was ascertained from linkage with the California death certificate file, the National Death Index, and the Seventh-Day Adventist church records (Mills et al., 1991).

In the initial follow-up through 1982, elevated hazard ratios were reported for the associations of lung cancer with TSP and total oxidants (Abbey et al., 1991a; Mills et al., 1991).

Results for associations of lung cancer with air pollution with follow-up extended through 1992 have been presented in three separate publications (Beeson et al., 1998; Abbey et al., 1999; McDonnell et al., 2000). In addition to exceedance frequencies, cumulative annual averages from January 1973 until 3 years before the date of the case defining the risk set (i.e. a 3-year lag) were estimated for PM_{10}, SO_2, and 8-hour average ozone. Among men, positive associations were observed for incident lung cancer (n = 16) after adjustment for age, years of education, pack-years of smoking, and alcohol consumption, for each 24 μg/m^3 (IQR) increase in PM_{10} (HR, 5.21; 95% CI, 1.94–13.99), each 3.7 ppb (IQR) increase in SO_2 (HR, 2.66; 95% CI, 1.62–4.39), each 19.8 ppb (IQR) increase in NO_2 (HR, 1.45; 95% CI, 0.67–3.14), and each 12.0 ppb (IQR) increase in 8-hour average ozone (2.23; 95% CI, 0.79–6.34). Among women (cases = 20), the equivalent hazard ratios were elevated only for SO_2 (HR, 2.14; 95% CI, 1.36–3.37) (Beeson et al., 1998). Among men, the equivalent hazard ratios for lung cancer mortality (n = 17) were 3.36 (95% CI, 1.57–7.19) for PM_{10}, 1.99 (95% CI, 1.24–3.20) for SO_2, 1.82 (95% CI, 0.93–3.57) for NO_2, and 2.10 (95% CI, 0.99–4.44) for 8-hour average ozone. Among women, the hazard ratios for lung cancer mortality (n = 12) were 1.08 (95% CI, 0.55–2.13) for PM_{10}, 3.01 (95% CI, 1.88–4.84) for SO_2, 2.81 (95% CI, 1.15–6.89) for NO_2, and 0.77 (95% CI, 0.37–1.61) for 8-hour average ozone (Abbey et al., 1999). [The Working Group noted a discrepancy in the IQRs for NO_2 and ozone as reported in the papers by Abbey et al. (1999), where the IQRs are given as 19.8 ppb and 12.03 ppb, respectively, and Beeson et al. (1998), where they are reported as 1.98 ppb and 2.12 ppb, respectively. The Working Group was unable to obtain clarification from the authors. Therefore, the former figures, which are of the same magnitude as those reported in other papers based on the same population, are assumed to be the correct ones.]

$PM_{2.5}$ data were available for a subcohort residing within an airshed adjacent to one of nine airports located throughout California (n = 1347 men, 2422 women) during the study baseline period (McDonnell et al., 2000). Visibility and $PM_{2.5}$ were measured concurrently at the nine airports from 1979 to 1993. These data were used to predict daily $PM_{2.5}$ concentrations for 1966–1993 using linear regression controlling for season and relative humidity, and monthly average $PM_{2.5}$ concentrations were calculated for each airshed. Monthly average $PM_{2.5-10}$ values were calculated as the monthly mean PM_{10} (modelled as in earlier publications) minus the monthly mean $PM_{2.5}$ value for each participant. In addition, monthly ozone, SO_2, and NO_2 for 1966–1992 and SO_4 for 1977–1992 were interpolated to the postal code centroid of the participants' residential and work addresses. Among the 1228 men with $PM_{2.5}$ data, 13 deaths

from lung cancer were identified. Hazard ratios adjusted for age, pack-years of smoking, years of education, and current alcohol consumption were elevated with wide confidence intervals for all size fractions of PM using the average for the baseline years 1973–1977. In models including $PM_{2.5}$ and $PM_{2.5–10}$ simultaneously, the magnitude of the hazard ratio for $PM_{2.5–10}$ was attenuated. Results for women were not presented but were described as weak or inverse. Numbers of deaths from lung cancer in the subcohort were too small to assess the other pollutants.

[The strengths of the AHSMOG studies are the long prospective follow-up, the detailed information on long-term work and home addresses, the control for individual covariates, and the ability to assess incidence as well as mortality. Major limitations are the very small sample size, the non-standard exposure assessment, and the lack of clarity and consistency in the published reports of the results.]

(d) Trucking Industry Particle Study

The Trucking Industry Particle Study (TrIPS) was a retrospective occupational cohort study of men in the trucking industry across the USA, which was originally designed to examine the association of occupational exposures to vehicle exhaust with lung cancer. The investigators subsequently examined the effect of annual outdoor exposures to PM_{10}, SO_2, and NO_2 on lung cancer mortality (Hart et al., 2009, 2011). Exposures to PM_{10} and NO_2 were estimated by modelling data obtained from the US EPA Air Quality System for 1985–2000 (Hart et al., 2009), and $PM_{2.5}$ was estimated based on the nearest Air Quality System monitor in 2000. (Mean concentrations for all pollutants are presented in Table 2.1.) In models stratified by age at entry, decade of hire, and calendar year, and adjusted for race, census region of residence, the healthy worker survivor effect, and occupational exposures, the hazard ratios for annual average (1985–2000) SO_2 and NO_2 were elevated in the full cohort. When long-haul drivers who spend days away from home were excluded, elevated hazard ratios were also observed for PM_{10}. The hazard ratio for a 4 μg/m³ (IQR) increase in $PM_{2.5}$ in 2000 was 1.02 (95% CI, 0.95–1.10) in the full cohort and 1.07 (95% CI, 0.97–1.17) in the cohort excluding long-haul drivers (Hart et al., 2011). In supplemental analyses using information from a survey administered to a sample of currently employed and recently retired workers in the industry, the authors evaluated the potential impact of not controlling for smoking and BMI. Current smoking, but not BMI, was associated with small increases in the hazard ratio for PM_{10} and NO_2 ($PM_{2.5}$ was not evaluated). Therefore, not adjusting for smoking may have led to inflation of the effect estimates.

[The limitations of this study are the lack of control for potential confounding by individual-level risk factors such as smoking history and the reliance on the most recent address to predict exposure. The strengths are the control for occupational exposures and the availability of time-varying residence-level predictions for most of the pollutants.]

(e) California Teachers Study

The California Teachers Study is a prospective cohort study of 133 479 female current and former public school professionals participating in the California State Teachers' Retirement System. All participants completed a baseline questionnaire in 1995. Subsequent questionnaires were mailed in 1997 and 2000, and name and residential address were updated annually. Cause-specific mortality data were obtained from record linkage with California state registries, the United States Social Security Administration, and the National Death Index. Monthly surfaces of $PM_{2.5}$, PM_{10}, ozone, nitrogen oxides (NO_x), NO_2, CO, and SO_2 in 250 m grids were estimated using inverse-distance weighting of data from monitors maintained by the state. (Ranges and means [standard deviations] for

each pollutant are presented in Table 2.1.) Individual monthly exposures were estimated by linking each residential address to the gridded pollutant surface, and cumulative averages were calculated for each risk set to represent long-term exposure. The final analytical data set included 101 784 women with available air pollution data (73 489 for $PM_{2.5}$, since monitoring began later). In adjusted multivariable models, there was no evidence of a positive association of any of the pollutants considered with lung cancer mortality risk (Lipsett et al., 2011). However, in analyses restricted to never-smokers, the hazard ratio for a 10 μg/m^3 increase in $PM_{2.5}$ was 1.62 (95% CI, 0.83–3.16).

[The strengths of this study are the spatially and temporally resolved air pollution measurements and the control for time-varying confounding by individual-level lung cancer risk factors. The limitations are that there were only 5.6 years of follow-up for the analyses of $PM_{2.5}$ and that $PM_{2.5}$ data were only available concurrently or for the 12 months before the start of follow-up. Therefore, there was no ability to look at truly long-term exposures, which might be necessary for assessment of an association with lung cancer risk.]

(f) Ontario Tax Cohort Study

Villeneuve et al. (2013) conducted a cohort study of intra-urban variations in volatile organic compounds (VOCs) and NO_2 and cause-specific mortality in Toronto, Canada. The population consisted of 58 760 residents of Toronto in 1982 who were part of the larger Ontario Tax Cohort Study, a cohort randomly selected from income tax filings of Canadians residing in one of 10 urban areas in the province of Ontario. Residential addresses at baseline were linked by postal code centroid to estimated exposure surfaces of benzene, *n*-hexane, total hydrocarbons, and NO_2 modelled from measurements (obtained in 2006 for the VOCs and in 2002 and 2004 for NO_2) and spatial covariates. Deaths were identified by linkage to the Canadian Mortality Database. Individual-level information on household income and marital status was obtained from the income tax return, and contextual measures of unemployment, average household income, and immigration were obtained from the 1981 Canadian census. Data from the 2001 Canadian Community Health Survey were used to indirectly adjust for smoking and obesity, using the spatial association between smoking, BMI, and pollution measurements.

The participants ranged in age from 35 to 85 years in 1982 (mean, 51.7 years). Through 2004, 1470 deaths from lung cancer were identified among 18 020 deaths. In Cox proportional hazards models adjusted for age, sex, the socioeconomic variables described above, and NO_2, the hazard ratios for all VOCs were elevated. After indirect adjustment for smoking and BMI, the effect estimates were attenuated. No independent association was observed of NO_2 with lung cancer mortality (Villeneuve et al., 2013).

[This study is the only cohort study to date to assess residential exposure to VOCs as well as other urban air pollutants. Individual-level information on smoking was not available, but the measurements of socioeconomic status that were obtained are a strength and could help to control indirectly for smoking.]

2.1.2 Cohort studies in Europe

The association between exposure to outdoor air pollution and the risk of lung cancer has been evaluated in several prospective cohort studies in Europe, which are summarized in Table 2.2. The table summarizes features of the study design, the exposure metrics used, and the main results after adjustment for relevant confounders. Several European countries have been included. The largest study is a pooled analysis of 17 European cohorts from the ESCAPE study, which included areas in Austria, Denmark, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the

Table 2.2 Cohort studies of lung cancer and outdoor air pollution in Europe

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Nafstad et al. (2003) Norway	16 209	1972–1998	Assessment at home addresses based on area emissions, dispersion modelling, and local traffic	Lung cancer incidence	NO_x (per 10 μg/m³; home address) 1974–1998 SO_2 (per 10 μg/m³)	418	1.08 (1.02–1.15) 1.01 (0.94–1.08)	Age, smoking habits, and length of education	Men only in Oslo, aged 40–49 yr
Filleul et al. (2005) PAARC Study	14 284	1974–2000	24 areas; exposure based on daily measurements for 1974–1976 at central site station in each area	Lung cancer mortality	Total suspended particulate (per 10 μg/m³); range, 45–243 μg/m³ Black smoke (per 10 μg/m³) NO (per 10 μg/m³) NO_2 (per 10 μg/m³); range, 12–61 μg/m³ SO_2 (per 10 μg/m³)	178	0.97 (0.94–1.01) 0.97 (0.93–1.01) 0.97 (0.94–1.01) 0.97 (0.85–1.10) 0.99 (0.92–1.07)	Age, sex, BMI, smoking, occupational exposure, and education level	Adults aged 25–59 yr, subjects enrolled in 1974; frailty models used to account for spatial correlation
Vineis et al. (2006) Gen-Air Study	197 cases, 556 controls (nested)	1993–1998	Exposure assessment for NO_2, SO_2, and PM_{10} for 1990–1994 or 1995–1999 from nearest stationary monitor; residence near heavy-traffic roads	Lung cancer incidence	PM_{10} (10 μg/m³ increase) NO_2 (10 μg/m³ increase) SO_2 (10 μg/m³ increase) Proximity of residence to major road (exposed vs non-exposed)	197	0.91 (0.70–1.18) 1.14 (0.78–1.67) 1.08 (0.89–1.30) 1.31 (0.82–2.09)	Age, BMI, education level, sex, smoking, alcohol consumption, intake of meat, intake of fruit and vegetables, time since recruitment, country, occupational index, and cotinine	Nested, never-smokers or ex-smokers; 10 European countries
Naess et al. (2007)	143 842 residents of Oslo	1992–1998	Air dispersion model for concentrations in 1992–1995	Lung cancer mortality	*Men, aged 51–70 yr* NO_2 (1 quartile) PM_{10} (1 quartile) $PM_{2.5}$ (1 quartile)	449	 1.07 (0.97–1.18) 1.07 (0.97–1.18) 1.07 (0.97–1.18)	Adjustment for age, occupation, and education level	Age range, 51–90 yr Quartile values for pollutants not reported

Table 2.2 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Naess et al. (2007) (cont.)					*Women, aged 51–70 yr*	295			
					NO_2 (1 quartile)		1.23 (1.10–1.38)		
					PM_{10} (1 quartile)		1.27 (1.13–1.43)		
					$PM_{2.5}$ (1 quartile)		1.27 (1.13–1.43)		
					Men, aged 71–90 yr	424			
					NO_2 (1 quartile)		1.09 (0.98–1.20)		
					PM_{10} (1 quartile)		1.08 (0.98–1.20)		
					$PM_{2.5}$ (1 quartile)		1.07 (0.97–1.18)		
					Women, aged 71–90 yr	285			
					NO_2 (1 quartile)		1.12 (0.98–1.27)		
					PM_{10} (1 quartile)		1.17 (1.03–1.33)		
					$PM_{2.5}$ (1 quartile)		1.16 (1.02–1.32)		
Beelen et al. (2008a)	111 816	1986–1997	LUR models	Lung cancer incidence	Black smoke (per 10 μg/m³); range, 8.7–35.8; mean (SD), 16.5 (3.5)	1940	0.96 (0.83–1.11)	Age, sex, smoking status, and area-level SES	Netherlands cohort study
					$PM_{2.5}$ (per 10 μg/m³); range, 22.9–36.8; mean (SD), 28.2 (2.1)		0.81 (0.63–1.04)		
					NO_2 (per 30 μg/m³); range, 14.6–66.7; mean, 36.9		0.86 (0.70–1.07)		
					SO_2 (per 20 μg/m³); range, 4.4–33.8; mean (SD), 13.7 (5.1)		0.9 (0.72–1.11)		
					Traffic intensity on nearest road		1.05 (0.94–1.16)		
					Living near a major road		1.11 (0.91–1.34)		
					Black smoke by tobacco smoking status				
					Never-smokers	252	1.47 (1.01–2.16)		
					Ex-smokers	500	0.91 (0.68–1.23)		
					Current smokers	1188	0.85 (0.70–1.03)		

Table 2.2 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Beelen et al. (2008b)	117 528	1987–1996	See Beelen et al. (2008a)	Lung cancer mortality	Black smoke (per 10 μg/m³)	1935	1.03 (0.88–1.20)	Age, sex, smoking status, and area-level SES	Adults aged 55–69 yr
					NO_2 (per 30 μg/m³)		0.91 (0.72–1.15)		
					$PM_{2.5}$ (per 10 μg/m³)		1.06 (0.82–1.38)		
					SO_2 (per 20 μg/m³)		1.00 (0.79–1.26)		
					Traffic intensity (increase of 10 000 motor vehicles/day)		1.07 (0.96–1.19)		
					Never-smokers				
					Black smoke (per 10 μg/m³)		1.47 (1.01–2.16)		
Raaschou-Nielsen et al. (2010)	Total 679 cases, 3481 controls (nested)	1993–2001	Dispersion modelling at all addresses since 1971	Lung cancer incidence	NO_x (30–72 μg/m³ vs < 30 μg/m³)	298 incident cases	1.30 (1.07–1.57)	Smoking, education level, BMI, alcohol consumption, sex, cohort, and birth cohort	
					NO_x (> 72 μg/m³ vs < 30 μg/m³)	87	1.45 (1.12–1.88)		
					NO_x at residence (per 100 μg/m³ increase); mean, 37.6 μg/m³	679 incident cases	1.37 (1.06–1.76)		
Raaschou-Nielsen et al. (2011a)	Total 52 970	1993–2006	Dispersion modelling at all addresses since 1971 and traffic indicators	Lung cancer incidence	NO_x at residence (per 100 μg/m³ increase)	592 incident cases	1.09 (0.79–1.51)	Age, smoking, second-hand smoke, length of school attendance, fruit intake, employment, and sex	Enrolment, 1993–1997; database on exposure in 1960–2005; residential addresses from 1971
					NO_x				
					17.2–21.8 μg/m³	NR	1.09 (0.84–1.40)		
					21.8–29.7 μg/m³	NR	0.93 (0.73–1.18)		
					> 29.7 μg/m³	NR	1.30 (1.05–1.61)		
					Per 1000 vehicle-km/day traffic load within 200 m of the residence	592	1.03 (0.90–1.19)		
					Major road within 50 m	NR	1.21 (0.95–1.55)		

Table 2.2 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Raaschou-Nielsen et al. (2013) ESCAPE Study	312 944		LUR models and traffic indicators	Lung cancer incidence	PM_{10} (per 10 μg/m³), all lung cancers	2095	1.22 (1.03–1.45)	Sex, calendar time, age (time axis), smoking status, smoking intensity, smoking duration, time since quitting smoking, second-hand smoke, occupation, fruit intake, marital status, education level, employment status, and SES	17 European cohorts in 9 countries
					Adenocarcinomas		1.51 (1.10–2.08)		
					Squamous cell		0.84 (0.50–1.40)		
					$PM_{2.5}$ (per 10 μg/m³), all lung cancers		1.18 (0.96–1.46)		
					Adenocarcinomas		1.55 (1.05–2.29)		
					Squamous cell		1.46 (0.43–4.90)		
					PM coarse (per 5 μg/m³), all cases		1.09 (0.88–1.33)		
					Absorbance $PM_{2.5}$ (per 10^{-5}/m)		1.12 (0.88–1.42)		
					NO_2 (per 10 μg/m³)		0.99 (0.93–1.06)		
					NO_x (per 20 μg/m³)		1.01 (0.95–1.07)		
					Traffic density on nearest road (5000 vehicles/day)		1.00 (0.97–1.04)		
					Traffic load on major roads within 100 m		1.09 (0.99–1.21)		
Heinrich et al. (2013)	4 752 women	1980–2008	Nearest monitoring station and proximity to a major road; PM_{10} estimated from TSP	Lung cancer mortality	PM_{10} (per 7 μg/m³)	41	1.84 (1.23–2.74)	Smoking status and age	Women only
					NO_2 (per 16 μg/m³)		1.46 (0.92–2.32)		
Cesaroni et al. (2013)	1 265 058	2001–2010	LUR model	Lung cancer mortality	NO_2 (per 10 μg/m³)	12 208	1.04 (1.02–1.07)	Sex, age, marital status, place of birth, education level, occupation, and SES	Age ≥ 30 yr
					NO_2 ≤ 36.5 μg/m³	2008	1.00 (ref)		
					36.5–42.7	2187	1.07 (1.01–1.14)		
					42.7–46.2	2568	1.09 (1.03–1.16)		
					46.2–50.4	2610	1.09 (1.03–1.16)		
					> 50.4	2835	1.11 (1.05–1.18)		P_{trend} = 0.002

Table 2.2 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Cesaroni et al. (2013) (cont.)					$PM_{2.5}$ (per 10 μg/m³)	12 208	1.05 (1.01–1.10)		
					$PM_{2.5}$ ≤ 19.4 μg/m³	2090	1.00 (ref)		
					19.4–22.5	2268	1.04 (0.98–1.10)		
					22.5–24.8	2397	1.09 (1.02–1.15)		
					24.8–26.8	2610	1.07 (1.01–1.13)		
					> 26.8	2842	1.08 (1.02–1.15)		P_{trend} = 0.006
					Distance to high-traffic road, *P* for trend		0.9		
					Quintiles of traffic intensity within 150 m, *P* for trend		0.3		
Carey et al. (2013)	835 607 patients from general practitioners in the United Kingdom	2003–2007	Emissions inventory combined with dispersion modelling	Lung cancer mortality	PM_{10} (per 3 μg/m³); mean (SD), 19.7 (2.3); range, 12.6–29.8	5244	1.03 (0.98–1.08)	Age, sex, smoking, BMI, and education level	Age range, 40–89 yr
					$PM_{2.5}$ (per 1.9 μg/m³); mean (SD), 12.9 (1.4); range, 8.5–20.2	5244	1.04 (0.99–1.09)		
					NO_2 (per 10.7 μg/m³); mean (SD), 22.5 (7.4); range, 4.5–60.8	5241	1.11 (1.05–1.17)		
					SO_2 (per 2.2 μg/m³); mean (SD), 3.9 (2.1); range, 0.1–24.2	5192	1.03 (0.99–1.06)		
					O_3 (per 3.0 μg/m³); mean (SD), 51.7 (2.4); range, 44.5–63.0	5210	0.94 (0.90–0.98)		

BMI, body mass index; CI, confidence interval; LUR, land-use regression; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; NR, not reported; O_3, ozone; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; ref, reference; SD, standard deviation; SES, socioeconomic status; SO_2, sulfur dioxide; TSP, total suspended particles; yr, year.

United Kingdom, with large differences in exposure levels. Both incidence and mortality have been considered in European studies. In the case of lung cancer the two are almost equivalent, since lung cancer is a highly lethal disease. However, incidence registration is usually more reliable than mortality registration, since the latter is affected by some degree of misclassification due to lung metastases.

Nafstad et al. (2003) conducted a study among 16 209 male residents of Oslo (1972–1998). Exposure to NO_x and SO_2 at home addresses was estimated for 1974–1995 based on area emissions, dispersion modelling, and an additional contribution from busy streets near the home. Traffic was the main source of NO_x and heating was the main source of SO_2 in Oslo. After controlling for age, smoking habits, and education level, the authors found a relative risk (RR) of 1.08 (95% CI, 1.02–1.15) for every 10 μg/m^3 increment in NO_x exposure and of 1.01 (95% CI, 0.94–1.08) for every 10 μg/m^3 increment in SO_2.

Filleul et al. (2005) studied 14 284 young adults (aged 25–59 years), enrolled in 1974, living in 24 areas of France (PAARC Study). Concentrations of TSP, black smoke, nitrogen oxide (NO), NO_2, and SO_2 were measured at one monitoring station in each area during 1974–1976. After a follow-up of 26 years, they identified 178 deaths from lung cancer, with no excess risk for any of the air pollutants. Using the ratio between NO and NO_2, the authors identified six monitoring stations located close to traffic and therefore considered less representative for the population in the area. A subanalysis based on the 18 other areas showed a mortality rate ratio of 1.48 (95% CI, 1.05–2.06) in association with a 10 μg/m^3 increase in NO_2 but no significant association with any of the other pollutants. [The population was particularly young, so the number of cases was small. Determinants of lung cancer in young subjects may differ from those in the elderly. Cumulative exposure may have been limited.]

Vineis et al. (2006) conducted a nested case–control study on lung cancer within the large European Prospective Investigation into Cancer and Nutrition (EPIC) cohort recruited in 1993–1998. Cases accrued after a median follow-up of 7 years among the ex-smokers (who had stopped smoking at least 10 years previously) and never-smokers. Three controls per case were matched by sex, age, smoking status, country, and time elapsed between recruitment and diagnosis. Residence in proximity to heavy-traffic roads was used as an indicator of exposure to air pollution. In addition, exposure to air pollutants (NO_2, PM_{10}, and SO_2) was assessed using concentration data from the routine monitoring station nearest to the address at the time of enrolment. Exposure data for single pollutants were limited by the relatively small number of monitoring stations. Exposure estimates were available for 197 cases and 556 controls. Cotinine was measured in plasma as an indicator of second-hand smoke exposure. There was a non-significant association between lung cancer and residence near heavy-traffic roads (odds ratio [OR], 1.31; 95% CI, 0.82–2.09). For NO_2, the odds ratio was 1.14 (95% CI, 0.78–1.67) for each increment of 10 μg/m^3, and 1.37 (95% CI, 1.06–1.75) for concentrations greater than 30 μg/m^3 after adjustment for cotinine and additional potential confounders, including occupational exposures. No clear association was found with other pollutants. [The restriction of the study to never-smokers and former smokers is a notable strength. The lack of information on traffic and single pollutants for some cases and controls may have introduced some misclassification of exposure. Follow-up was relatively short.]

Naess et al. (2007) investigated the concentration–response relationship between air pollution (NO_2, PM_{10}, and $PM_{2.5}$) and cause-specific mortality. The population included all inhabitants of Oslo, Norway, aged 51–90 years, with follow-up of deaths from 1992 to 1998. An air dispersion model was used to estimate exposure levels in

1992–1995. Several hazard ratios were reported for lung cancer mortality and different levels of NO_2, PM_{10}, and $PM_{2.5}$ exposure, and smoothed concentration–response curves were shown in figures. After adjustment for confounders (age, occupation, and education level), increased risks were found among women. The relative risks for an IQR increase in exposure to NO_2, PM_{10}, and $PM_{2.5}$ were 1.23 (95% CI, 1.10–1.38), 1.27 (95% CI, 1.13–1.43), and 1.27 (95% CI, 1.13–1.43), respectively, in women aged 51–70 years and 1.12 (95% CI, 0.98–1.27), 1.17 (95% CI, 1.03–1.33), and 1.16 (95% CI, 1.02–1.32), respectively, in women aged 71–90 years. Relative risks for men were lower (1.07–1.09) and not statistically significant. There was no direct adjustment for smoking at the individual level, but three indirect methods were used to assess the potential for confounding: (i) a health survey indicating that the correlation between residence in polluted areas and smoking was $r = 0.06$; (ii) adjustment for occupation and education level as proxies for smoking; and (iii) analyses of a separate cohort in the same area, which found no attenuation of estimates after adjustment for smoking. [The Working Group noted the lack of direct adjustment for smoking; however, indirect adjustment provides some reassurance that there was no significant confounding by smoking. Identical relative risks for $PM_{2.5}$, PM_{10}, and NO_2 were also noted in several analyses, implying very strong correlations between these pollutant indices.]

Beelen et al. (2008a, 2008b) investigated the association of lung cancer incidence and mortality with several indicators of exposure to air pollution in a prospective cohort study of more than 120 000 subjects in the Netherlands. Exposure assessment for the home address at the time of enrolment was based on regional background monitoring of black smoke, NO_2, and SO_2 during 1976–1996, land-use regression models for estimating intra-urban differences, and traffic intensity near the residence and field monitoring of black smoke, NO_2, and $PM_{2.5}$ for the very local contribution. Background $PM_{2.5}$ concentrations were estimated from PM_{10} using a conversion factor.

The incidence study (Beelen et al., 2008a) included 111 816 subjects with valid address data and no prevalent cancer at baseline. In the 11 years of follow-up, 1940 incident lung cancer cases were identified, giving relative risks adjusted for age, sex, smoking, and area indicators of socioeconomic status of 0.96 (95% CI, 0.83–1.11) per 10 μg/m³ of black smoke, 0.81 (95% CI, 0.63–1.04) per 10 μg/m³ of $PM_{2.5}$, 0.86 (95% CI, 0.70–1.07) per 30 μg/m³ of NO_2, and 0.90 (95% CI, 0.72–1.11) per 20 μg/m³ of SO_2. More detailed analyses were conducted for the association of lung cancer with a 10 μg/m³ increment in black smoke among never-smokers (RR, 1.47; 95% CI, 1.01–2.16; 252 cases), ex-smokers (RR, 0.91; 95% CI, 0.68–1.23; 500 cases), and current smokers (RR, 0.85; 95% CI, 0.70–1.03; 1188 cases). Relative risks for traffic intensity and proximity to a major road were elevated but not statistically significant. Case–cohort analyses with adjustment for additional covariates gave qualitatively similar results.

Analyses of the association of lung cancer mortality with air pollution including 117 528 individuals from the same cohort were reported by Beelen et al. (2008b). Further details of the study methods and analyses of mortality from non-cancer outcomes, as well as identical results for lung cancer, were also reported by Brunekreef et al. (2009). After adjustment for age, sex, smoking, and socioeconomic status, relative risks were 1.03 (95% CI, 0.88–1.20) per 10 μg/m³ of black smoke, 1.06 (95% CI, 0.82–1.38) per 10 μg/m³ of $PM_{2.5}$, 0.91 (95% CI, 0.72–1.15) per 30 μg/m³ of NO_2, and 1.00 (95% CI, 0.79–1.26) per 20 μg/m³ of SO_2. A slightly increased but not statistically significant relative risk was found with black smoke and traffic intensity. Relative risks for black smoke by tobacco smoking status were shown in a figure: in never-smokers the relative risk for an increment of 10 μg/m³ in black smoke was approximately 1.5 (95% CI,

approximately 1.0–2.2), whereas no association was indicated in current or former smokers.

Raaschou-Nielsen et al. (2010) conducted a case–cohort study nested within three Danish cohorts that were initiated at different times between 1970 and 1993 and followed up until 2001. Baseline data on tobacco smoking and other risk factors were obtained by self-administered questionnaire. Exposure to NO_x was estimated with the validated Danish AirGIS dispersion modelling system estimating traffic-related air pollution at all residential addresses of the study participants from 1971 to 2001. The study included 679 incident cases and 3481 people in a subcohort (comparison group). After controlling for sex, cohort, birth cohort, smoking, education level, BMI, and alcohol consumption, the relative risk was 1.30 (95% CI, 1.07–1.57) for exposure to NO_x between 30 μg/m³ and 72 μg/m³ and 1.45 (95% CI, 1.12–1.88) for NO_x > 72 μg/m³, corresponding to a relative risk of 1.37 (95% CI, 1.06–1.76) per 100 μg/m³ increase in NO_x. The rate ratio was higher among never-smokers, but there was no significant difference among never-smokers, former smokers, or current smokers. [The Working Group noted the short follow-up as a limitation of this study.]

The study of Raaschou-Nielsen et al. (2011a) is based on a cohort of 52 970 individuals followed up until 2006 and included 592 incident lung cancer cases (241 of these were also included in the 2010 study). NO_x concentrations at each home address from 1971 onwards were assessed for each cohort member with the AirGIS modelling system for traffic-related air pollution, and indicators of proximity to major roads and traffic load within 200 m were estimated. There were no estimates of exposure to PM or other air pollutants. After adjustment for age, smoking, second-hand smoke, education level, and dietary variables, the relative risk for an increment of 100 μg/m³ in NO_x was 1.09 (95% CI, 0.79–1.51). Analysis by quartile of NO_x showed an elevated relative risk in the highest exposure category, with NO_x > 29.7 μg/m³ (RR, 1.30; 95% CI, 1.05–1.61), but no increase at intermediate levels of exposure. Elevated risks were found in particular in association with proximity to a major road (RR, 1.21; 95% CI, 0.95–1.55).

The ESCAPE study (Raaschou-Nielsen et al., 2013) includes 17 European cohorts, for which exposure assessment was carefully standardized with a campaign of measurements, the creation of a common database of exposure data and covariates, and a common script for statistical analysis. Two cohorts had been published separately before: Raaschou-Nielsen et al. (2011a) and EPIC. For the former, only the Copenhagen part of the cohort was included and the follow-up was extended to 2010; 397 lung cancer cases were included in both studies. Part of the EPIC cohort was also included in Vineis et al. (2006) but included only never-smokers and ex-smokers, after a shorter follow-up and with different exposure assessment. In the ESCAPE study, exposures to air pollution were estimated using land-use regression models with the same methodology in all the areas. Estimates of exposure were generated for PM_{10}, $PM_{2.5}$, coarse particles, NO_2, NO_x, and two indicators of traffic. The overall population was 312 944, and 2095 incident cases of lung cancer were identified. After adjustment for potential individual-level confounders, including several indicators of smoking, and socioeconomic status at an area level (Table 2.2), the relative risks for lung cancer were 1.22 (95% CI, 1.03–1.45) for an increment of 10 μg/m³ of PM_{10} and 1.18 (0.96–1.46) per 10 μg/m³ of $PM_{2.5}$. Addition of the smoking variables to the models decreased the relative risks for PM_{10} and $PM_{2.5}$ from about 1.3 to about 1.2. The risk was particularly elevated for adenocarcinomas, rather than squamous cell carcinomas. No increase in lung cancer risk was observed for exposure to NO_2, NO_x, or indicators of traffic.

There was no evidence of heterogeneity between the hazard ratios for the 17 cohorts, since the *P*-values based on the Q statistics were

close to 1.0 for PM_{10} and $PM_{2.5}$ and the I^2 values (indicating the proportion of observed variation reflecting a real difference in effect size) were zero for both PM_{10} and $PM_{2.5}$. Furthermore, the 95% confidence interval of each cohort-specific hazard ratio in relation to PM_{10} and $PM_{2.5}$ enclosed the combined hazard ratio for all cohorts. [The Working Group regarded this as a highly informative study, for the wide range of exposures included, the quality of exposure assessment and degree of standardization in procedures, the large sample size, and the careful control for confounding by smoking and other factors.]

Heinrich et al. (2013) studied 4752 women and identified 41 deaths from lung cancer. Exposure was assessed at the baseline address using pollutant measurements from the nearest monitoring station and proximity to a major road. The PM_{10} concentration was estimated from measured TSP using a conversion factor. Elevated relative risks for lung cancer were found for an IQR increase in PM_{10} (RR, 1.84; 95% CI, 1.23–2.74) and NO_2 (RR, 1.46; 95% CI, 0.92–2.32). [The Working Group noted the very small sample size and expressed concern about potential publication bias affecting small studies.]

Cesaroni et al. (2013) investigated the association of lung cancer mortality with air pollution among 1 265 058 people in Rome, Italy, whose exposure was characterized with land-use regression models for NO_2 and dispersion models for $PM_{2.5}$. After adjustment for sex, age, marital status, place of birth, education level, occupation, and socioeconomic status, they found relative risks of 1.05 (95% CI, 1.01–1.10) for a 10 μg/m³ increment in $PM_{2.5}$ and 1.04 (95% CI, 1.02–1.07) for a 10 μg/m³ increment in NO_2. Tests for trend in analyses based on quintiles of exposure were statistically significant ($P < 0.01$) for both pollutants. An association was not observed for indicators of distance to heavy-traffic roads. The association of smoking with exposure to $PM_{2.5}$ was evaluated among a subgroup of 7845 SIDRIA cohort members. Smoking and exposure to air pollutants were not associated, and no change in results for total mortality was observed when adjusting for smoking status in the subcohort. However, this finding was for total mortality, not specifically lung cancer. [This was a very large study with good exposure assessment based on land-use regression models.]

Carey et al. (2013) conducted a study on a large (n = 835 607) cohort of primary care patients in the United Kingdom. Annual mean concentrations of PM_{10}, $PM_{2.5}$, NO_2, SO_2, and ozone were assessed at 1 km² resolution by an emissions inventory combined with dispersion modelling. Covariates were obtained from electronic patient records. The estimated hazard ratios were derived from emission-based models. They found elevated hazard ratios for lung cancer in particular in association with NO_2 after adjustment for age, sex, smoking, BMI, and education level (HR, 1.11; 95% CI, 1.05–1.17 for a 10.7 μg/m³ increment). The hazard ratios for the association of lung cancer with SO_2 and PM were modestly elevated with adjustment for the same covariates: 1.03 (95% CI, 0.99–1.06) per 2.2 μg/m³ increment in SO_2, 1.03 (95% CI, 0.98–1.09) per 3 μg/m³ of PM_{10}, and 1.04 (95% CI, 0.99–1.09) per 1.9 μg/m³ of $PM_{2.5}$. With adjustment for income instead of education level, the associations for PM and NO_2 were slightly weaker and not statistically significant, whereas the association for SO_2 was stronger (HR, 1.05; 95% CI, 1.01–1.08). [The particular nature of this cohort derived from a primary care database and the sensitivity of the associations to adjustment for different markers of social position makes the interpretation of the results difficult.]

2.1.3 Cohort studies in other regions

See Table 2.3.

Cao et al. (2011) examined the association of outdoor air pollution with mortality using the China National Hypertension Survey, a

Table 2.3 Cohort studies of lung cancer and outdoor air pollution in other regions

Reference and study location	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Cao et al. (2011) China National Hypertension Survey, China	70 947	1991–1999/ 2000	Annual average TSP, SO_2, and NO_x concentrations between 1991 and 2000 measured at 103 fixed-site monitoring stations in 31 cities Conversion factors (PM_{10}/TSP ≈ 0.5 and $PM_{2.5}/PM_{10}$ ≈ 0.65) were used to estimate RRs for $PM_{2.5}$	Lung	Per 10 μg/m³ increase in TSP; mean, 289; range, 113–499	624	1.01 (1.00–1.02)	Age, sex, BMI, physical activity, education level, occupation, smoking status, age at starting to smoke, years smoked, cigarettes per day, alcohol consumption, and hypertension	Multipollutant models were considered (the effects of SO_2 remained even after adjustment for TSP or NO_x, whereas the effects of TSP were attenuated after adjustment for SO_2 or NO_x); during 1991–2000
					Per 10 μg/m³ increase in SO_2; mean, 73; range, 11–174	624	1.04 (1.02–1.06)		
					Per 10 μg/m³ increase in NO_x; mean, 50; range, 19–122	624	1.03 (0.99–1.07)		
					Per 10 μg/m³ increase in $PM_{2.5}$	624	1.03 (1.00–1.07)		
Katanoda et al. (2011) Three-Prefecture Cohort Study, Japan	63 520	1983–1985	Annual mean concentrations of SPM, SO_2, and NO_2 during 1974–1983 measured at monitoring stations in or near each study area; $PM_{2.5}$ concentrations converted from SPM using a ratio of 0.7	Lung	Per 10 μg/m³ increase in SPM; range, 24.0–59.9	518	1.16 (1.08–1.25)	Sex, age, smoking status (current, former, never), pack-years of smoking, smoking status of family members living together, daily green and yellow vegetable consumption, daily fruit consumption, and use of indoor charcoal or briquette braziers for heating	
					Per 10 μg/m³ increase in $PM_{2.5}$; range, 16.8–41.9	518	1.24 (1.12–1.37)		
					Per 10 ppb increase in SO_2; range, 2.4–19.0	518	1.26 (1.07–1.48)		
					Per 10 ppb increase in NO_2; range, 1.2–33.7	518	1.17 (1.10–1.26)		
					Male current smokers	292	1.35 (1.20–1.52)	Age, pack-years of smoking, smoking status of family members living together, daily green and yellow vegetable consumption, daily fruit consumption, and use of indoor charcoal or briquette braziers for heating	The same tendency was observed for other pollutants (SPM, SO_2, and NO_2); other strata were not considered due to small number of the participants
					Male former smokers (per 10 μg/m³ increase in $PM_{2.5}$)	90	1.11 (0.77–1.60)		
					Female never-smokers (per 10 μg/m³ increase in $PM_{2.5}$)	73	1.16 (1.02–1.33)		

Table 2.3 (continued)

Reference and study location	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Hales et al. (2012) New Zealand Census–Mortality Study, New Zealand	1 065 645	1996–1999	Estimated exposure to PM_{10} for census area units modelled by a LUR model (developed for Christchurch)	Lung	Per 1 μg/m³ increase in PM_{10}; mean (SD), 8.3 (8.4) μg/m³	1686	1.02 (1.00–1.03)	Age, sex, ethnicity, social deprivation, income, education level, smoking history, and average minimum temperature	The validity of exposure modelling was examined by Kingham et al. (2008); the atmospheric dispersion model was developed for one city (Christchurch) and extrapolated to urban census units throughout the country
Yorifuji et al. (2013) Shizuoka Elderly Cohort, Japan	13 412	1999–2009	Traffic-related air pollution (indexed by NO_2) modelled by using a LUR model, assigned as concentration in the year of the outcome	Lung	All participants NO_2 (per 10 μg/m³ increase); mean (SD), 3.11 (12.10); range, 9.40–77.08 μg/m³	116	1.20 (1.03–1.40)	Age, sex, smoking, BMI, hypertension, diabetes, financial capability, and area mean taxable income	Update of Yorifuji et al. (2010); individual exposure assessment was conducted; the validity of exposure modelling was examined by Kashima et al. (2009) Loss to follow-up, 57%
					Never-smokers (per 10 μg/m³ increase)	NR	1.30 (0.98–1.71)		
					Ex/current smokers (per 10 μg/m³ increase)	NR	1.18 (0.98–1.43)		

BMI, body mass index; CI, confidence interval; LUR, land-use regression; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; NR, not reported; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; RR, relative risk; SD, standard deviation; SO_2, sulfur dioxide; SPM, suspended particulate matter; TSP, total suspended particles.

prospective cohort of approximately 160 000 adults enrolled in 1991 from 17 provinces in China. They limited the analysis to participants living in urban areas, due to a lack of air pollution exposure data in rural areas, leaving 70 947 participants in 31 cities. Baseline data on demographic characteristics, medical history, and lifestyle-related factors (including smoking variables) were obtained in 1991, and follow-up examinations were conducted in 1999 and 2000. During the follow-up period, there were 624 deaths from lung cancer. Annual average TSP, SO_2, and NO_x concentrations measured at a total of 103 fixed-site monitoring stations in the 31 cities were calculated for 1991–2000 and were assigned to the participants living in the cities. PM_{10}, $PM_{2.5}$, NO_2, and ozone were not measured. After adjustment for smoking, socioeconomic status (education level and occupation), and other potential confounders, the rate ratios per 10 μg/m³ increase in each pollutant were 1.01 (95% CI, 1.00–1.02) for TSP, 1.04 (95% CI, 1.02–1.06) for SO_2, and 1.03 (95% CI, 0.99–1.07) for NO_x. The effects of SO_2 remained even after adjustment for TSP or NO_x, whereas the effects of TSP were attenuated after adjustment for SO_2 or NO_x. Using conversion factors (PM_{10}/TSP ≈0.5 and $PM_{2.5}/PM_{10}$ ≈0.65), the estimated rate ratio per 10 μg/m³ increase in $PM_{2.5}$ was 1.03 (95% CI, 1.00–1.07). [Exposure assessment was conducted at the central monitoring sites in the cities and did not account for variations within each city. No information about loss to follow-up was provided. The lack of direct measurements of PM_{10} or $PM_{2.5}$ is a limitation. The authors used a single set of conversion factors recommended by the China Ministry of Environmental Protection for all areas.]

Katanoda et al. (2011) examined the associations between long-term exposure to air pollution and lung cancer in the Three-Prefecture Cohort Study in Japan. Each prefecture had one polluted (urban) area and one to three non-polluted (rural) areas. The participants were residents in these areas aged 40 years or older and were enrolled into the cohort between 1983 and 1985. Among 100 615 respondents, the authors restricted the analysis to 63 520 participants who had lived in the study areas for more than 10 years and had complete data for potential confounders. Annual mean concentrations of suspended PM (SPM), SO_2, and NO_2 during the period 1974–1983 measured at monitoring stations were assigned. $PM_{2.5}$ concentrations were estimated from SPM using a ratio of 0.7, which was assumed considering local data obtained in study areas during several periods between 1974 and 2005. During the 10-year follow-up, there were 518 deaths from lung cancer. The relative risks for lung cancer mortality associated with a 10-unit increase in SPM (μg/m³), $PM_{2.5}$ (μg/m³), SO_2 (ppb), and NO_2 (ppb) were 1.16 (95% CI, 1.08–1.25), 1.24 (95% CI, 1.12–1.37), 1.26 (95% CI, 1.07–1.48), and 1.17 (95% CI, 1.10–1.26), respectively, after adjustment for tobacco smoking and other confounding factors. Men had slightly higher effect estimates than women. The effect estimates were larger for male current smokers; for example, the relative risks for $PM_{2.5}$ were 1.35 (95% CI, 1.20–1.52) for male current smokers, 1.11 (95% CI, 0.77–1.60) for male former smokers, and 1.16 (95% CI, 1.02–1.33) for female never-smokers. [This study included adjustments for a wide range of risk factors, which could be expected to account for most confounding. The study is notable for having adjusted for indoor sources of air pollution. The Working Group questioned the validity of the factors used to estimate $PM_{2.5}$ from SPM.]

Hales et al. (2012) used the New Zealand Census–Mortality Study to examine the association between PM_{10} exposure and mortality. Records from the 1996 New Zealand census (n = 3 732 000) were anonymously and probabilistically linked to mortality data for the next 3 years, creating a cohort study with 3 years of follow-up. There were 1 065 645 adults aged 30–74 years living in urban areas for which data were available on all covariates. A land-use

regression model developed and evaluated for census area units in Christchurch was extrapolated to urban census area units throughout the country to estimate exposure to PM_{10} in 1996, which was validated by Kingham et al. (2008). Four PM_{10} exposure categories (0.1, 7, 14, and 19 μg/m³) were assigned to the participants and analysed as a linear term. The odds ratio for lung cancer mortality was 1.015 (95% CI, 1.004–1.026) per 1 μg/m³ increase in PM_{10} after adjustment for smoking history, socioeconomic status, and other potential confounders. [This study includes a very large and representative sample of the New Zealand population. This study also has the strength of modelling PM_{10} at the level of a small census unit, which includes approximately 2300 people. There is a concern that a land-use regression model developed for Christchurch was extrapolated to urban census area units throughout the country.]

Yorifuji et al. (2013) studied the association between long-term exposure to traffic-related air pollution and cause-specific mortality. This study is an update of an earlier study of the same cohort (Yorifuji et al., 2010). Individual data were extracted from an ongoing cohort study of elderly residents in Shizuoka Prefecture, Japan (the Shizuoka Elderly Cohort). In December 1999, 22 200 residents were randomly selected from all 74 municipalities in Shizuoka, by stratifying both sex and age group (65–74 years and 75–84 years). In the updated study, Yorifuji et al. (2013) extended the follow-up period by 3 years and evaluated the lung cancer risk associated with traffic-related air pollution. A total of 13 412 individuals completed questionnaires and were eligible to participate, of whom 7650 were lost to follow-up from December 1999 to January 2009. Annual individual exposure to NO_2, as an index of traffic-related exposure, was assessed for 1996 to 2009 using a land-use regression model and assigned to the participants. Participants were assigned an estimated NO_2 exposure in the fiscal year of the outcome. The relative risk for lung cancer mortality associated with a 10 μg/m³ increase in NO_2 was 1.20 (95% CI, 1.03–1.40) after adjustment for smoking, socioeconomic status, and other potential confounders. The relative risk among never-smokers was 1.30 (95% CI, 0.98–1.71), whereas among ex-smokers and current smokers it was 1.18 (95% CI, 0.98–1.43). [The never-smoker category was described as non-smokers in the paper.]

Analyses using other windows of exposure (the preceding 1, 2, or 3 years before the outcome) gave similar results, and assigning the average concentration from the first year of the study slightly attenuated the relative risk (RR, 1.16; 95% CI, 0.97–1.39). Restricting the analysis to participants living within 10 km of sampling sites increased the relative risk to 1.27 (95% CI, 1.07–1.50). [The strength of this study is the exposure assessment at the individual level and the use of individual NO_2 exposure as an index of traffic-related exposure. A somewhat stronger association was found after restricting the participants to those living within 10 km of sampling sites, presumably reducing measurement error. Although there is considerable loss to follow-up, the Working Group concluded that this was unlikely to have resulted in significant bias.]

2.1.4 Case–control studies

See Table 2.4.

The case–control studies investigating the role of air pollution in lung cancer are presented below according to the main type of exposure under study: all sources, including traffic-related air pollution, or specific industrial sources. The studies focused on all sources of air pollution have been divided according to the methodology – qualitative or quantitative – used for exposure assessment. In fact, the main development in the design of the studies is the evolution of exposure assessment methods from the rather crude classification of urban areas and air pollution zones (Vena, 1982; Samet et al., 1987), proximity to

Table 2.4 Case–control studies of lung cancer and outdoor air pollution

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Studies with qualitative or semiquantitative exposure assessment										
Vena (1982) New York, USA, 1957–1965	417 incident cases	752	Hospital	Interviewer-administered questionnaire; town of residence classified according to 2-year average TSP levels; duration of residence considered	Lung	Duration of residence in zones with high or medium air pollution 0–29 yr 30–49 yr ≥ 50 yr ≥ 50 yr	 54 114 249 249	 1 1.32 (NR), $P > 0.05$ 1.58 (1.09–2.29) 1.26 (NR), $P > 0.05$	Age and occupation Adding adjustment for smoking	Men only; response rate NR
Samet et al. (1987) New Mexico, USA, 1980–1982	422 incident cases	727	Population	Interviewer-administered standardized questionnaire to the cases or relatives; duration of residence in areas with different urbanization levels and industry	Lung	Duration of residence in counties with > 500 000 residents *Non-Hispanic Whites* 1–10 yr ≥ 11 yr *Hispanic Whites* ≥ 1 yr	 	 0.9 (0.6–1.4) 1.1 (0.8–1.7) 0.9 (0.4–2.1)	Age, smoking, and occupation	Response rate: 91% for cases and 81.3% for controls
Katsouyanni et al. (1991) Athens, Greece, 1987–1989	101 incident cases	89	Hospital	Interviewer-administered questionnaire; area of residence classified according to 1983–1985 average smoke and NO_2 levels; inverse of distance from fixed monitors was considered	Lung	Quartile of air pollution exposure		1.22 (0.91–1.63) 1.09 (NR)	Age, education level, and interviewer Smoking	Women only; response rate: 96% for cases and 90.6% for controls

Table 2.4 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Jöckel et al. (1992) Germany	194 incident cases	194 hospital and 194 population controls	Both	Interviewer-administered questionnaire; area of residence classified according to SO_2 emission for 1955–1980 and a semiquantitative index based on TSP, SO_2, and B[*a*]P	Lung	Air pollution exposure Emission index high Semiquantitative index high	 39 44	 1.01 (0.53–1.91) 1.16 (0.64–2.13)	Age, smoking, and occupation	Response rate NR for cases or hospital controls, 40.7% for population controls
Barbone et al. (1995) Trieste, Italy, 1979–1981, 1985–1986	755 deaths	755 (from the Autopsy Department)	Population	Interviewer-administered questionnaire to next of kin; distance from 4 pollution sources (city centre, shipyard, iron foundry, incinerator); data from 28 PM deposition meters linked to each residential address	Lung	Level of particulate deposition (g/m²/day) < 0.175 0.176–0.298 > 0.298 *P* for trend	 188 256 311	 1 1.1 (0.8–1.5) 1.4 (1.1–1.8) 0.022	Age, smoking, occupation, and social status	Men only; response rate: 80.6% for cases and 83% for controls. Deceased cases and controls. Relative risks were also increased for those living in the city centre and close to the iron foundry and the incinerator
Gupta et al. (2001) Chandigarh, India, 1995–1997	265 incident cases	525	Hospital	Interviewer-administered questionnaire; lifetime (> 75%) residence in urban, mixed, or rural area	Lung	Residence in urban, mixed, or rural area *Men* Rural Mixed Urban	 153 36 45	 1 0.89 (0.62–1.64) 0.82 (0.53–1.27)	Age, smoking, religion, and education level	Response rates NR

Table 2.4 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Gupta et al. (2001) Chandigarh, India, 1995–1997 (cont.)						*Women*				
						Rural	5	1		
						Mixed	1	0.08 (0.01–0.78)		
						Urban	24	0.29 (0.07–1.17)		
Edwards et al. (2006) Teesside, England, 2000–2004	204 incident cases	339	Population	Interviewer-administered questionnaire; residential addresses classified in three exposure zones on the basis of proximity to heavy industry	Lung	Duration of residence in areas close to heavy industry (adjusted for latency)			Age, smoking, asbestos exposure, marital status, and type of job	Response rate: 82.3% for cases and 47.8% for controls
						0 yr	45	1		
						1–25 yr	60	0.83 (0.43–1.60)		
						> 25 yr	99	1.85 (0.80–4.24)		
						Per 10 yr of exposure		1.21 (0.99–1.47)		
Chiu et al. (2006) Taiwan, China, 1994–2003	962 deaths	972 deaths	Population	Municipality-based composite index of air pollution exposure based on fixed monitors for PM_{10}, SO_2, NO_2, O_3, and CO	Lung	*Air pollution exposure index*			Age and urbanization index	Only housewives according to the death certificate were included. No interview was conducted
						0.62–0.74	312	1.11 (0.88–1.40)		
						≥ 0.75	345	1.28 (1.02–1.61)		
Liu et al. (2008a) Taiwan, China, 1995–2005	1676 deaths	1676 deaths	Population	Municipality-based composite index of air pollution exposure based on fixed monitors for NO_2 and CO	Lung	*Air pollution exposure index*			Age, urbanization index, and marital status	No interview was conducted. No smoking status available. Women only
						Medium	710	1.24 (1.03–1.50)		
						High	547	1.46 (1.18–1.81)		
						P for trend		< 0.001		

Table 2.4 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Chang et al. (2009) Taiwan, China, 1997–2006	4087 deaths	4087 deaths	Population	Municipality-based index of petrol-station density	Lung	Petrol-station density (per km^2)			Age and urbanization index	Only housewives according to the death certificate were included. No interview was conducted
						0.159–0.444	1417	1.14 (1.01–1.30)		
						0.452–2.692	1552	1.19 (1.02–1.38)		
López-Cima et al. (2011) Asturias, Spain, 2000–2008	626 incident cases	626	Hospital	Interviewer-administered questionnaire; last residential addresses geocoded using GIS; distance from city centre and industry estimated	Lung	*Residence area*			Age, sex, smoking, hospital area, occupation, and family history of cancer	Residents near industry: increased risk of small cell carcinoma (RR, 2.23; 95% CI, 1.01–4.92). Residents in urban areas: increased risk of adenocarcinoma (RR, 1.92; 95% CI, 1.09–3.38)
						Urban	63	1.33 (0.86–2.06)		
						Semi-urban	63	1.34 (0.86–2.07)		
						Industrial	63	1.49 (0.93–2.39)		
Studies of exposure to industrial pollution										
Brown et al. (1984) Pennsylvania, USA, 1974–1977	335 deaths	332	Population (death certificates)	Interviewer-administered questionnaire to next of kin; metals in soil and proximity to a zinc plant used for exposure assessment	Lung	Heavy arsenic	16	2.3 (1.0–5.4)	Age, smoking, and occupation	Men only; response rate: 96% for cases and 94% for controls
						Heavy cadmium	16	2.0 (0.9–4.6)		
						Far from the zinc smelter	292	1		
						Middle distance	26	1.2 (0.6–2.1)		
						Near distance	16	1.6 (0.6–4.3)		
Pershagen (1985) Sweden, 1961–1979	212 deaths	424 deaths	Population (death certificates)	Mailed questionnaire to next of kin; subjects living in parishes close to an arsenic-emitting smelter were "exposed"	Lung	Residence in exposed parishes			Age, smoking, and occupation	Men only; response rate: 96% for cases and 91% for controls. All subjects were deceased
						Yes	42	2.0 (1.2–3.4)		

Table 2.4 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Xu et al. (1989) Shenyang, China, 1985–1987	1249 incident cases	1345	Population	Interviewer-administered standardized questionnaire; perceived smokiness of outdoor environment; duration of residence close to industrial factories	Lung	*Smokiness of outdoor environment* Men Somewhat/slightly smoky Smoky Women Somewhat/slightly smoky Smoky	 190 262 118 161	 1.5 (1.2–2.0) 2.3 (1.7–2.9) 1.4 (1.1–2.0) 2.5 (1.8–3.5)	Age, education level, smoking, and indoor air pollution	Response rate: 95% for cases and 99.8% for controls. Subsequent analysis (Xu et al., 1991) indicated an OR of 3.0 (95% CI, 1.6–6.0) for men living within 1 km of the large smelter plant
Ko et al. (1997) Kaohsiung, Taiwan, China, 1992–1993	117 incident cases	117	Hospital	Interviewer-administered questionnaire; residence for at least 5 yr within 3 km of a major industrial site	Lung	Residence close to an industrial site 0–20 yr ≥ 20 yr	 7 20	 0.8 (0.2–3.9) 2.7 (0.9–7.8)	Age, date of interview (matched), SES, residential area, education level, cooking fuels, tuberculosis, use of fume extractor, and consumption of vegetables	Women only; analyses for residence close to an industrial site were restricted to non-smokers; response rate: 91% for cases and 94% for controls
Yang et al. (1999) Taiwan, China, 1990–1994	399 deaths	399	Population	Proportion of a municipality's total population employed in the petrochemical industry	Lung	Proportion employed in petrochemical industries 0.07–0.50 ≥ 0.51	 141 148	 1.50 (1.03–2.17) 1.66 (1.05–2.61)	Sex, year of birth, year of death (matched), non-petrochemical air pollution index, marital status, and urbanization of residence	Only housewives according to the death certificate were included. No interview was conducted

Table 2.4 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Petrauskaite et al. (2002) Lithuania, 1981–1991	277 deaths	1108	Population	Questionnaire mailed to next of kin; area of residence classified according to distance from a chemical plant	Lung	Distance from the plant < 5 km	96	1.02 (0.76–1.38)	Age, smoking, and occupation	Men only; response rate: 81.6% for cases and 80% for controls
Bessö et al. (2003) Sweden, 1961–1990	316 deaths	727	Population	Mailed questionnaire to next of kin; duration of residence in the area close to the smelter was the exposure under study	Lung	*Residence in the smelter area* Men Ever < 20 yr > 20 yr Women Ever < 20 yr > 20 yr	 19 37 10 15	 1.38 (0.89–2.14) 1.65 (0.80–3.38) 1.28 (0.77–2.12) 0.88 (0.48–1.62) 0.72 (0.29–1.80) 1.00 (0.48–2.12)	Age, smoking, and occupation	Response rate: 94% for cases and 91% for controls

Table 2.4 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Pisani et al. (2006) Lampang Province, Thailand, 1993–1995	211 incident cases	202 controls (set 1) and 211 controls (set 2)	Set 1: population; set 2: hospital	Interviewer-administered questionnaire; air pollution exposure index incorporating linear distance from power plants, SO_2, NO_2, or TSP emissions, and the percentage of wind from the plants	Lung	Cumulative index of exposure to air pollutants (tons per km^2 per yr) SO_2 or NO_2 1808–3507 > 3507 Suspended particulate 214–392 > 392	 86 71 84 71	 1.3 (0.8–2.1) 1.2 (0.7–2.0) 1.2 (0.7–2.0) 1.1 (0.7–1.8)	Age, sex (matched), and cumulative number of cigarettes smoked	Only the results with population control are shown; response rate: 81% for cases and 81% for controls (set 1), 77% for controls (set 2)
Studies with quantitative exposure assessment										
Jedrychowski et al. (1990) Cracow, Poland, 1980–1985	1099 deaths	1073	Population (death certificates)	Mailed questionnaire to next of kin; measured levels of TSP and SO_2 were used, and isopleths were estimated	Lung	*Air pollution index* Men Low (TSP < 150 µg/m^3 and SO_2 < 104 µg/m^3) Medium (TSP > 150 µg/m^3 or SO_2 > 104 µg/m^3 but not both) High (TSP > 150 µg/m^3 and SO_2 > 104 µg/m^3) Women Low Medium and high combined	 650 129 122 124 74	 1 1.0 (0.75–1.83) 1.46 (1.06–1.99) 1 1.17 (0.70–1.96)	Age, smoking, and occupation	Response rate: 70.7% for male cases, 65.1% for female cases, 73.5% for male controls, and 64.0% for female controls

Table 2.4 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Nyberg et al. (2000) Stockholm, Sweden, 1985–1990	1042 incident cases	2364 population controls, 1090 deaths controls	Population	Mailed questionnaire to the subjects and next of kin; dispersion models used for annual mean levels of SO_2 and NO_2; annual levels of SO_2 and NO_2 were estimated for each year from 1950 to 1990 (Bellander et al., 2001)	Lung	NO_2 for traffic air pollution and SO_2 for air pollution related to heating (10-yr average, lagged 20 yr)			Age, smoking, occupation, social status, and radon	Men only; response rate: 87% for cases, 88% for population controls, and 82% for deceased controls
						NO_2 from traffic air pollution (effect per 10 μg/m³)		1.10 (0.97–1.23)		
						≥ 12.78–17.35 μg/m³	264	1.15 (0.91–1.46)		
						≥ 17.35–23.17 μg/m³	250	1.01 (0.79–1.29)		
						≥ 23.17–29.26 μg/m³	165	1.07 (0.81–1.42)		
						≥ 29.26 μg/m³	120	1.44 (1.05–1.99)		
						SO_2 from heating (effect per 10 μg/m³)		1.01 (0.98–1.03)		
						≥ 66.20–87.60 μg/m³	270	1.16 (0.91–1.47)		
						≥ 87.60–110.30 μg/m³	259	1.00 (0.79–1.27)		
						≥ 110.30–129.10 μg/m³	151	0.92 (0.70–1.21)		
						≥ 129.10 μg/m³	123	1.21 (0.89–1.66)		

Table 2.4 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Hystad et al. (2013) Canada, 1994–1997	2390 incident cases	3507 population controls	Population	Mailed questionnaire to the subjects and next of kin; national spatial surface estimates using satellite ($PM_{2.5}$ and NO_2) or chemical transport model (O_3); annual pollutant concentrations and residential histories were used (Hystad et al., 2012)	Lung	Effects per 10-unit increase in $PM_{2.5}$, NO_2, and O_3			Individual (age, sex, smoking, occupation, SES, etc.) and a large set of geographical confounders	Response rate: 62% for cases and 67% for population controls
						Exposure from national spatial model				
						$PM_{2.5}$ (per 10 μg/m³)	2154	1.29 (0.95–1.76)		
						NO_2 (per 10 ppb)	2154	1.11 (1.00–1.24)		
						O_3 (per 10 ppb)	2154	1.09 (0.85–1.39)		
						Exposure from fixed monitors within 50 km of residential address				
						$PM_{2.5}$ (per 10 μg/m³)	1200	1.33 (0.82–2.15)		
						NO_2 (per 10 ppb)	983	1.34 (1.07–1.69)		
						O_3 (per 10 ppb)	1015	1.11 (0.79–1.54)		

B[*a*]P, benzo[*a*]pyrene; CI, confidence interval; CO, carbon monoxide; GIS, geographic information system; NO_2, nitrogen dioxide; NR, not reported; O_3, ozone; OR, odds ratio; PM, particulate matter; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; RR, relative risk; SES, socioeconomic status; SO_2, sulfur dioxide; TSP, total suspended particles; yr, year.

industry (Brown et al., 1984; Pershagen, 1985), and proximity to traffic (Vineis et al., 2006) to more advanced use of fixed-monitor data (Jedrychowski et al., 1990), exposure modelling (Nyberg et al., 2000), and national spatiotemporal air pollution maps (Hystad et al., 2012, 2013).

(a) Studies with qualitative or semiquantitative assessment of air pollutant exposure

Vena (1982) conducted a hospital-based case–control study in Erie County, New York, USA. Retrospective data on residential and employment history and on smoking were obtained from 417 White male lung cancer patients and 752 controls with non-respiratory, non-neoplastic diseases, admitted from 1957 to 1965. Two-year TSP data and a historical review of point sources of air pollution were used to define air pollution zones. Subjects were classified by duration of residence in zones with medium or high air pollution levels. The results did not show a clear association of lung cancer with air pollution alone; the relative risk for exposure of 50 years or longer in medium- or high-pollution zones went from 1.58 (95% CI, 1.09–2.29) after adjustment for age and occupation to 1.26 (CI not reported; $P > 0.05$) after adjustment also for smoking. There was a suggestion of effect modification for air pollution as there was increased risk from smoking and occupational exposures if there was also long-term exposure to air pollution. The risk for heavy smokers with heavy exposure to air pollution was more than 4 times that of men with none of the high-exposure conditions. [Exposure assessment was rather crude. No response rates by case–control status were provided.]

Samet et al. (1987) conducted a population-based case–control study of lung cancer in New Mexico, USA, between 1980 and 1982, including 422 cases and 727 controls. Subjects were asked to identify all locations where they had resided for 6 months or longer and were interviewed about other personal characteristics, including smoking and occupation. The residential data were coded at the county and state levels and combined with county-level socioeconomic data from population censuses to generate indices of time lived in counties or metropolitan areas of different sizes, degrees of urbanization, and extents of employment in manufacturing industries. Residential history patterns were the same in cases and controls. There was no association of the residential history variables with lung cancer risk; relative risks were constantly close to unity. [Exposure assessment was rather crude in this study.]

Katsouyanni et al. (1991) conducted a case–control study exploring the role of smoking and outdoor air pollution in the causation of lung cancer. The study was undertaken in Athens, Greece, between 1987 and 1989 and included women only; 101 women with lung cancer and 89 comparison women with fractures or other orthopaedic conditions were included. Smoking habits were ascertained through interviews, whereas lifetime exposure to air pollution was assessed by linking lifelong residential and employment addresses with objectively estimated or presumed air pollution levels. Pollution isopleths were based on smoke and NO_2 levels measured at fixed-monitor stations in the period 1983–1985. Air pollution levels were associated with increased risk of lung cancer with an odds ratio of 1.22 (95% CI, 0.91–1.63) per quartile of exposure, which was reduced to 1.09 (CI not reported) after adjustment for tobacco smoking. The *P*-value for the interaction of air pollution and tobacco smoking was 0.10. There was no effect of air pollution among non-smokers [crude OR, 0.7], but the relative risk contrasting extreme quartiles of air pollution among smokers of 30 years' duration was 2.23 (CI not reported). [Detailed information on occupational exposure and smoking was available, but the size of the study is limited.]

Jöckel et al. (1992) conducted a hospital-based case–control study in five cities in Germany, including 194 lung cancer cases, 194 hospital

controls, and 194 population controls (only a sample of all hospitals was included). Subjects were interviewed for their smoking, occupational, and residential history by trained interviewers, using a standardized questionnaire. For the quantification of occupational exposure to known carcinogens of the lung, an approach was developed with exposure information obtained by supplemental questionnaires. Quantification of air pollution was based on emission data for SO_2 and a semiquantitative index. After adjustment for smoking and occupational exposures, relative risks of 1.01 (95% CI, 0.53–1.91) for the emission index and 1.16 (95% CI, 0.64–2.13) for the semiquantitative index were obtained. [Exposure assessment was rather crude, on a county basis, and the statistical power was rather low.]

Barbone et al. (1995) investigated the relationship between air pollution and lung cancer with a case–control study among men who had died in Trieste, Italy, from 1979 to 1981 and from 1985 to 1986. From an autopsy registry, 755 cases and 755 controls were identified, and information on smoking, occupation, and residence was obtained from the next of kin. Air pollution at the residence of each subject was estimated from the average value of total PM deposition at the nearest monitoring station. After adjustment for age, smoking habits, likelihood of exposure to occupational carcinogens, and social group, the risk of lung cancer increased with increasing level of air pollution for all types of lung cancer combined ($P = 0.022$; RR, 1.4; 95% CI, 1.1–1.8 for the highest exposure category vs the lowest), for small cell carcinoma ($P = 0.016$), and for large cell carcinoma ($P = 0.049$). Compared with inhabitants of the residential area, the relative risk was 1.5 (95% CI, 1.0–2.2) for residents of the centre of the city and 1.4 (95% CI, 1.0–2.1) for residents of the industrial area. The increased relative risk of the industrial area was mainly due to exposure to an iron foundry (RR, 1.7; 95% CI, 0.7–4.1) and an incinerator (RR, 2.6; 95% CI, 1.3–5.1).

Gupta et al. (2001) conducted a case–control study on lung cancer in Chandigarh, northern India, involving 265 lung cancer cases and 525 hospital controls matched by age and sex. Data were collected in face-to-face interviews. The exposure assessment of air pollution was based on lifetime residence in areas classified by the investigators as predominantly urban, rural, or mixed. Residence in urban areas was not associated with increased risk of lung cancer: the odds ratio for men living in urban areas was 0.82 (95% CI, 0.53–1.27) and for women living in urban areas it was 0.29 (95% CI, 0.07–1.17). [Response rates were not reported. Exposure assessment was crude, and the precision was rather low.]

Edwards et al. (2006) conducted a case–control study of lung cancer among women in the highly industrialized area of Teesside, in north-eastern England. A total of 204 women aged 80 years or younger with incident primary lung cancer and 339 age-matched community controls were recruited for a population-based case–control study. Life-course residential, occupational, and active and passive smoking histories were obtained using an interviewer-administered questionnaire. The adjusted odds ratio for lung cancer among women living near (within 0–5 km of) heavy industry in Teesside or elsewhere was 1.85 (95% CI, 0.80–4.24) for more than 25 years' residence versus 0 years, or 1.21 (95% CI, 0.99–1.47) for each period of 10 years living near industry (latency was allowed for by disregarding residential exposures within the past 20 years). [A low response rate among controls (47.8%) is noted.]

Chiu et al. (2006) investigated the relationship between air pollution and lung cancer among women in a matched case–control study on deaths (972 cases) that occurred in Taiwan, China, from 1994 to 2003. The control group consisted of women who had died from causes other than cancer or respiratory diseases (972 controls), pair-matched to the cases by sex, year of birth, and year of death. A municipality-based

aggregate index of long-term exposure to air pollution was created by dividing the annual average of the measured values for each pollutant by the National Ambient Air Quality Standard for that pollutant. The ratios for each pollutant were scaled to a 100-point scale and then averaged together to generate an index value representing the net burden of these pollutants. Women who lived in municipalities with the highest levels of the air pollution exposure index had a statistically significant increased risk of lung cancer compared with those living in municipalities with the lowest air pollution exposure index after controlling for the urbanization index (RR, 1.28; 95% CI, 1.02–1.61). [Only housewives according to the death certificate were included. Since only deceased subjects were in the controls and exposure to air pollution is linked with increased cardiorespiratory mortality, exposure to air pollution may have been overrepresented in the control group, with underestimation of the effect. In addition, controlling for urbanization, which is likely to be a predictor of pollution levels, could result in overadjustment. No smoking data were available, although smoking was rare among women in Taiwan, China.]

Using the same design as Chiu et al. (2006), Liu et al. (2008a) investigated the relationship between air pollution and lung cancer in a matched case–control study on deaths among women (1676 cases and 1676 controls) that occurred in Taiwan, China, from 1995 to 2005. The classification of exposure was based on the measured levels of PM_{10}, SO_2, NO_2, and CO. NO_2 and CO levels were used to classify subjects' areas of residence into tertiles of pollutant concentrations. An urbanization index and marital status were considered in the analyses in addition to the matching factors. Among individual pollutants, positive associations were observed only for NO_2 and CO. A composite index based on these two pollutants yielded adjusted odds ratios of 1.24 (95% CI, 1.03–1.50) and 1.46 (95% CI, 1.18–1.81) for groups with medium and high exposure, respectively, compared with the group with low exposure, with a statistically significant trend. [The study shares the methodology and the limitations of the initial study by Chiu et al. (2006), and there may be a partial overlap in the study populations.]

Chang et al. (2009) investigated the relationship between exposure to traffic-related air pollution and development of lung cancer in women in Taiwan, China, using the density of petrol stations as a surrogate measure of exposure. A matched case–control study was based on lung cancer deaths among women (4087 cases and 4087 controls) from 1997 to 2006, using the same design as Chiu et al. (2006). Data on the number of petrol stations in study municipalities were collected from the two major petroleum supply companies. The petrol-station density per square kilometre for each municipality was used as an indicator of exposure. There was a statistically significant exposure–response relationship between the tertile of petrol-station density and the risk of lung cancer in women after controlling for possible confounders. [The study shares the methodology and the limitations of the studies by Chiu et al. (2006) and Liu et al. (2008a), and there may be an overlap in the study populations.]

López-Cima et al. (2011) conducted a hospital-based case–control study in Asturias, Spain. The study area included a large industrial setting. A total of 626 lung cancer patients and 626 controls were recruited and matched by ethnicity, hospital, age, and sex. Distances from the respective participants' residential locations to industrial facilities and city centres were used as a metric of exposure to urban and industrial air pollution. Odds ratios for distance to pollution sources were estimated with adjustment for sex, age, hospital area, tobacco smoking, family history of cancer, and occupation. Individuals living near industries had an excess risk of lung cancer (RR, 1.49; 95% CI, 0.93–2.39). The relative risk was higher for small cell carcinoma (RR, 2.23; 95% CI, 1.01–4.92). Residents in urban areas

showed a statistically significant increased risk of adenocarcinoma (RR, 1.92; 95% CI, 1.09–3.38) compared with those in rural areas.

(b) Studies of exposure to industrial pollution

Brown et al. (1984) reported the results of a case–control study on lung cancer deaths among residents near a zinc smelter and a steel manufacturing plant in Pennsylvania, USA. Lifetime residential, occupational, and smoking histories were obtained from the next of kin of 335 White male lung cancer cases and 332 White male controls. Relative risks were estimated according to the distance of the residence from the zinc smelter and the steel plant, and according to levels of several metals (arsenic, copper, lead, manganese, zinc, and cadmium) measured in soil samples. Twofold risks of lung cancer were associated with residence in areas with heavy levels of arsenic (RR, 2.3; 95% CI, 1.0–5.4) and cadmium (RR, 2.0; 95% CI, 0.9–4.6). Usual residence near the zinc plant was associated with an increased risk (RR, 1.6; 95% CI, 0.6–4.3), although the number of individuals living in the higher exposure area was small. These increases remained after accounting for cigarette smoking and employment in the zinc or steel industry. No excess risk was associated with living near the steel plant.

Pershagen (1985) studied 212 male lung cancer cases and 424 control men who had died between 1961 and 1979 in an industrialized county in northern Sweden. Data on smoking, occupation, and residence were obtained from the next of kin. A relative risk of 2.0 (95% CI, 1.2–3.4) for lung cancer was seen among men who had lived within 20 km of a large copper smelter that emitted arsenic.

Xu et al. (1989) conducted a case–control study in Shenyang, China, with data collected in interviews with 1249 patients with lung cancer and 1345 population-based controls. After adjustment for smoking, the relative risks were twice as high among those who reported living in smoky outdoor environments (RR, 2.3; 95% CI, 1.7–2.9 in men, and RR, 2.5; 95% CI, 1.8–3.5 in women) compared with subjects living in an environment that was not smoky. There were also associations with duration of residence within 200 m of industrial factories such as chemical and rubber plants, cement, glass, and asbestos factories, and ferrous and non-ferrous smelters in men, and wood and paper plants and ferrous and non-ferrous smelters in women.

In a subsequent publication on the case–control study of Xu et al. (1989), Xu et al. (1991) performed an additional analysis on residential distance from the industrial area. Soil levels of arsenic and other metals rose with increasing proximity to the Shenyang copper smelter, and elevated risks of lung cancer were found among men, but not women, living within 1 km of the smelter (OR, 3.0; 95% CI, 1.6–6.0).

Biggeri et al. (1996) used the data collected by Barbone et al. (1995) to better investigate the relationship of lung cancer with the four sources of air pollution (shipyard, iron foundry, incinerator, and city centre). Spatial models were used to evaluate the effect of sources of pollution on lung cancer adjusted for age, smoking habits, exposure to occupational carcinogens, and levels of PM. The excess relative risk at the city centre was 2.2 (P = 0.0098; CI not reported). At the incinerator source, the excess relative risk was 6.7 (P = 0.0098; CI not reported). [This is a rather large study with improved exposure assessment relative to earlier studies and detailed information on occupational exposure and smoking.]

A case–control study involving interviews with 117 women with lung cancer and 117 matched hospital controls was conducted in Taiwan, China, from 1992 to 1993 (Ko et al., 1997). Information on cigarette smoking and suspected risk factors for lung cancer, including residential distance from industrial plants, was collected by interview. Only a small proportion (9.4%) of female cases had smoked. Among non-smoking women, the odds ratio for the association of lung

cancer with living near an industrial district for 20 years or longer was 2.7 (95% CI, 0.9–7.8) after adjustment for several covariates, including indoor air pollution from cooking. [This is a relatively small study with a rather crude exposure assessment.]

To investigate the relationship between petrochemical air pollution and lung cancer, Yang et al. (1999) conducted a matched case–control study among women who had died in Taiwan, China, from 1990 to 1994, using a similar design to Chiu et al. (2006); 399 lung cancer cases and 399 controls were matched by sex, year of birth, and year of death. The proportion of a municipality's total population employed in the petrochemical manufacturing industry was used as an indicator of exposure to air emissions from this industry. For women who lived in municipalities with the highest level of petrochemical industry employment, the odds ratio was 1.66 (95% CI, 1.05–2.61) compared with women who lived in municipalities with the lowest petrochemical industry employment level after controlling for possible confounders. [The study shares the methodology and the limitations of the studies by Chiu et al. (2006) and Liu et al. (2008a).]

Petrauskaite et al. (2002) conducted a case–control study on lung cancer near an industry producing sulfuric acid and fertilizers in central Lithuania. Between 1967 and 1973, the levels of sulfuric acid exceeded 500 μg/m^3 within 2 km of the industry and 100 μg/m^3 more than 5 km away. A total of 277 men diagnosed with lung cancer during 1981–1991 and 1108 deceased controls, excluding deaths from respiratory cancer, were included. Information on residential history since 1960, smoking habits, and lifetime occupations and workplaces was obtained from questionnaires mailed to the next of kin. The relative risk of lung cancer associated with living within approximately 5 km of the plant was 1.02 (95% CI, 0.76–1.38) compared with never having lived in the area. No relationship with distance or with duration of residence was observed. [Since only deceased subjects were in the control group and exposure to air pollution is linked with increased cardiorespiratory mortality, exposure to air pollution may have been overrepresented in the control group, with underestimation of the effect. The Working Group noted a minor discrepancy in the odds ratios reported in the abstract and tables of this paper; the odds ratio from the abstract is shown here.]

Bessö et al. (2003) evaluated the association of exposure to industrial air pollution and lung cancer risk in a case–control study in the vicinity of a non-ferrous metal smelter in Sweden. The work was an extension of the study previously conducted by Pershagen (1985). The smelter started operations in 1930 and had very high emissions of arsenic and SO_2 in the early years. Among people who had died in 1961–1990 in the municipality where the smelter was located and who had not worked at the smelter, 316 lung cancer cases were identified and matched by sex and year of birth to 727 controls. Information on smoking habits, occupations, and residences was collected from questionnaires mailed to the next of kin and from registry data. Living close to the smelter was associated with a relative risk for lung cancer of 1.38 (95% CI, 0.89–2.14) among men after adjustment for smoking and occupational exposures. For women, however, no overall increased risk of lung cancer was observed (OR, 0.88; 95% CI, 0.48–1.62).

Pisani et al. (2006) conducted a case–control study in Lampang Province, Thailand, to assess the risk of lung cancer associated with exposures in the area, including power plants and coal mines, and to investigate possible interactions with genetic susceptibility. A total of 211 cases of lung cancer diagnosed in 1993–1995 among residents of the province were recruited at the provincial hospital. Community (n = 202) and hospital (n = 211) controls were frequency-matched to the cases by sex and age. Sociodemographic information, complete residential history, and characteristics of the household related to cooking

and heating, occupational history, and history of tobacco smoking were obtained by interview. An air pollution exposure index was calculated for each village or township reported in residential histories, based on the linear distance from the power plants, the annual SO_2, NO_2, and TSP emissions from the power plant, and the percentage of time that wind blew from the power plant centre. For the highest category of estimated cumulative exposure to SO_2 and NO_2 emissions versus the lowest category, the overall odds ratio was 1.2 (95% CI, 0.7–2.0). The cumulative index of exposure to PM was not associated with lung cancer. [The controls included individuals hospitalized for causes related to air pollution exposure, such as cardiovascular disease, with a possibility of a bias to the null.]

(c) Studies with quantitative assessment of air pollutant exposure

Jedrychowski et al. (1990) reported the results of a case–control study of 1099 lung cancer deaths and 1073 age- and sex-matched control deaths from other, non-respiratory causes that occurred in 1980–1985 in Cracow, Poland. Information on occupation, smoking habits, and residency was collected from the next of kin. Exposure to outdoor air pollution was estimated from levels of TSP and SO_2 measured by an urban monitoring network from 1973 to 1980. In men exposed to the highest air pollution level (TSP > 150 μg/m³ and SO_2 > 104 μg/m³), the relative risk was 1.46 (95% CI, 1.06–1.99). In women exposed in the combined medium and high air pollution categories, the relative risk was 1.17 (95% CI, 0.70–1.96). The joint action of the risk factors of smoking, occupational exposure, and air pollution was found to fit a multiplicative model. [This is a large study with detailed information on occupational exposure and smoking, and improved exposure assessment relative to earlier case–control studies, which did not quantify exposure.]

Nyberg et al. (2000) conducted a population-based case–control study among men aged 40–75 years with incident lung cancer in 1985–1990 in Stockholm County, Sweden. A total of 1042 cases and 2364 controls were studied, with a response rate of more than 85%. Local annual source-specific air pollution levels were estimated by dispersion modelling of emission data for NO_x/NO_2 and SO_2 and linked to residential addresses. More details on the exposure assessment are available from Bellander et al. (2001). Average traffic-related NO_2 exposure over 10 years (lagged 20 years) was associated with a relative risk of 1.10 (95% CI, 0.97–1.23) for each 10 μg/m³ increase in NO_2. The relative risk for the top decile of NO_2 exposure was 1.44 (95% CI, 1.05–1.99). In contrast, no association was found for SO_2 from heating: the relative risk was 1.01 (0.98–1.03) for each 10 μg/m³ increase in SO_2. All the risk estimates were adjusted for age, year, tobacco smoking, socioeconomic status, residential radon, and occupational exposures. The relative risk for never-smokers exposed to NO_2 above the 90th percentile (> 29.3 μg/m³) versus below the first quartile (< 12.7 μg/m³) was 1.68 (95% CI, 0.67–4.19). [This is a large study with high-quality historical exposure assessment and detailed information on smoking.]

Hystad et al. (2013) investigated lung cancer incidence in relation to long-term exposure to outdoor air pollutants and proximity to major roads in a population-based case–control study. Annual residential exposure to fine PM ($PM_{2.5}$), NO_2, and ozone over a 20-year period was compared among 2390 incident lung cancer cases and 3507 population controls in eight Canadian provinces from 1994 to 1997. Residential exposure to air pollutants was estimated using self-reported residential histories from 1975 to 1994 and national spatial surfaces of outdoor air pollution compiled from satellite-based estimates (for $PM_{2.5}$ and NO_2) and a chemical transport model (for ozone) and then adjusted with historical annual air pollution monitoring data. Details

of the exposure assessment are presented by Hystad et al. (2012). Hierarchical logistic regression models incorporated a comprehensive set of individual and geographical covariates. There was an increase in lung cancer incidence, with relative risks of 1.29 (95% CI, 0.95–1.76) with a 10-unit increase in $PM_{2.5}$ (μg/m³), 1.11 (95% CI, 1.00–1.24) with a 10-unit increase in NO_2 (ppb), and 1.09 (95% CI, 0.85–1.39) with a 10-unit increase in ozone (ppb). A subanalysis conducted in urban centres using exposures derived from fixed-site air pollution monitors supported the national results, with larger associations for NO_2 (RR, 1.34; 95% CI, 1.07–1.69) and $PM_{2.5}$ (RR, 1.33; 95% CI, 0.82–2.15) per 10-unit increase. An elevated relative risk was found among those living within 50 m of highways (RR, 1.23; 95% CI, 0.76–1.98) but not among those living near major roads. There was an increased risk of adenocarcinoma with an increase of 10 ppb in NO_2 exposure (OR, 1.17; 95% CI, 1.01–1.35) and an increased but non-significant risk with an increase of 10 μg/m³ in $PM_{2.5}$ exposure (OR, 1.27; 95% CI, 0.84–1.90). The odds ratio for $PM_{2.5}$ among never-smokers was 0.95 (95% CI, 0.38–2.34) based on 120 cases. [This is a large study, and notable strengths are the historical exposure estimation at an individual level, data for lung cancer subtypes, and adjustment for an extensive list of potential confounders, including known lung cancer risk factors. Despite the large size, the study had limited power to examine associations among never-smokers.]

2.1.5 Studies of outdoor workers and cancer of the lung

See Table 2.5.

Outdoor air pollution can be an occupational exposure for workers in polluted outdoor environments. Studies have been conducted on workers exposed to urban air pollution or specific sources of pollution, such as diesel and gasoline engine emissions. This group of studies was previously analysed in the *IARC Monograph* on diesel and gasoline engine exhausts (IARC, 2013). Therefore, there is an overlap between the present volume and the previous *IARC Monograph* on diesel and gasoline engine exhausts, since these two sources are important contributors to urban air pollution. On this basis, occupational cohorts and case–control studies considering professional drivers, traffic police, mail carriers, and filling station attendants are reviewed here, as the occupation can be considered an estimator of air pollution exposure shared with the general population. The studies on occupations with specific exposure to diesel exhaust, such as underground miners and railway workers, have already been reviewed in the *IARC Monograph* on the carcinogenicity of diesel and gasoline engine exhausts, and they are not considered in detail here.

(a) Cohort studies

(i) Professional drivers (bus drivers, taxi drivers, and lorry drivers)

Balarajan & McDowall (1988) studied a total of 3392 male professional drivers in London, United Kingdom, with a retrospective mortality study. The cohort was enrolled from the National Health Service Central Register with occupational information since 1939. Subjects whose occupational description was bus, coach, lorry, or taxi driver were enrolled and followed up for mortality during the period 1950–1984. During the follow-up period, there were significantly fewer deaths (n = 2182) than expected (in England and Wales) from all causes (standardized mortality ratio [SMR], 0.91; [95% CI, 0.87–0.95]). Overall, the standardized mortality ratio for lung cancer was 1.47 [95% CI, 1.32–1.64]. Lorry drivers showed excess deaths from lung cancer (SMR, 1.59; [95% CI, 1.41–1.79]), a pattern not evident among taxi drivers. [No estimate of air pollution exposure was available in the study. No measure of duration of exposure was available. No individual information on smoking habits was available.]

Table 2.5 Lung cancer in cohort studies of professional drivers, urban police officers, mail carriers, and filling station attendants

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Professional drivers									
Balarajan & McDowall (1988) London, United Kingdom. Professional drivers	3392	1950–1984	Occupational history from the National Health Service Central Register: bus, coach, lorry, and taxi drivers	Lung	All drivers Taxi drivers Bus and coach drivers Lorry drivers	328 30 18 280	1.47 [0.32–1.64] 0.86 [0.58–1.23] 1.42 [0.84–2.24] 1.59 [1.41–1.79]	Age	SMRs. Men only. Air pollution levels not known. No information on duration of exposure or on smoking habits
Carstensen et al. (1988) Sweden. Professional drivers	1.6 million (total cohort)	1961–1979	Swedish Cancer–Environment Register: all subjects employed and aged 30–64 yr in 1960; professional drivers	Lung	All drivers	1021 cases	1.14 (1.03–1.25)	Age and smoking	SIRs. Men only. Air pollution levels not known. No information on duration of exposure
Paradis et al. (1989) Montreal, Canada. Bus drivers	2134	1962–1985	Subjects employed by the Montreal Urban Community Transit Commission	Lung	Bus drivers *Employment duration* < 30 yr ≥ 30 yr	78 34 44	0.92 (0.73–1.14) 1.01 (0.70–1.38) 0.85 (0.62–1.13)	Age	SMRs. Men only. Air pollution levels not known. No information on smoking habits
Rafnsson & Gunnarsdóttir (1991) Reykjavik, Iceland. Truck and taxi drivers	868 truck drivers; 726 taxi drivers	1951–1988	Membership rolls of the Truck Drivers' Union and the Cooperative Taxi Agency	Lung	Truck drivers Taxi drivers	24 12	2.14 (1.37–3.18) 1.39 (0.72–2.43)	Age	Men only. Air pollution levels not known. Smoking status known for a sample of the cohort
Gubéran et al. (1992) Geneva, Switzerland. Professional drivers	1726	1949–1986 (1970–1986 for cancer incidence)	Licensing Authority, Canton of Geneva	Lung	Professional drivers (lorry, taxi, bus, and coach)	77 64	1.50 (1.23–1.81) 1.61 (1.29–1.98)	Age	SMR. 15 yr latency. Men only. Air pollution levels not known. No information on smoking habits SIR. 15 yr latency

Table 2.5 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Borgia et al. (1994) Rome, Italy. Taxi drivers	2311	1965–1988	Rome taxi cooperatives; taxi drivers	Lung	All	76	1.23 (0.97–1.54)	Age	SMR. Men only. Air pollution levels not known. Smoking status known for a sample of the cohort
Jakobsson et al. (1997) Sweden. Professional drivers	96 438	1971–1984	Swedish national census; bus drivers, taxi drivers, long-distance and short-distance lorry drivers	Lung	*All Sweden*				RRs. Men only. Air pollution levels not known. No information on duration of exposure. Indirect adjustment for smoking
					Bus drivers	52 cases	0.9 (0.7–1.2)	Age and region	
					Taxi drivers	104 cases	1.2 (1.0–1.4)	Age, region, and smoking	
					Long-distance lorry drivers	304 cases	1.1 (0.9–1.2)	Age, region, and smoking	
					Short-distance lorry drivers	144 cases	1.2 (1.0–1.4)	Age, region, and smoking	
					Stockholm County only				
					Taxi drivers	42 cases	1.3 (1.0–1.8)	Age and smoking	
					Long-distance lorry drivers	76 cases	1.4 (1.1–1.8)	Age and smoking	
					Short-distance lorry drivers	50 cases	1.7 (1.3–2.3)	Age and smoking	

Table 2.5 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Soll-Johanning et al. (1998) Copenhagen, Denmark. Bus drivers and tramway employees	18 174	1943–1992	Copenhagen Traffic Company; bus and tramway employees	Lung	Bus drivers and tramway workers	473	1.6 (1.5–1.8) men	Age and sex (men only)	SIRs. Air pollution levels not known. No information on duration of exposure. Confounding by smoking unlikely. In a subsequent case–control study on lung cancer within the cohort (Soll-Johanning & Bach, 2004), OR for high vs low air pollution index was 0.99 (95% CI, 0.36–2.75)
						15	2.6 (1.5–4.3) women	Age and sex (women only)	
					Time since first employment				
					0–14 yr	35 male cases; 3 female cases	1.2 [0.84–1.67] men; 1.3 [0.27–3.80] women		
					15–29 yr	77 male cases; 10 female cases	1.5 [1.18–1.87] men; 3.5 [1.68–6.44] women		
					≥ 30 yr	361 male cases; 2 female cases	1.7 [1.53–1.88] men; 3.8 [0.46–13.73] women		
Soll-Johanning et al. (2003) Copenhagen, Denmark. Bus drivers and tramway employees	18 174	1900–1994	Employment records for all bus drivers and tramway employees employed in 1900–1994	Lung	Air pollution index: Low	14	1.00 (ref)	Smoking	RRs for lag time of > 10 yr. Nested case–control study that overlaps with Soll-Johanning et al. (1998)
					High	39	0.99 (0.36–2.75)		
					Cumulative employment				
					< 3 months	4	0.50 (0.14–1.81)		
					3 months to < 2 yr	27	1.00		
					2 yr to < 10 yr	45	1.03 (0.54–1.95)		
					10 yr to < 20 yr	22	1.34 (0.65–2.77)		
					≥ 20 yr	43	0.54 (0.28–1.03)		

Table 2.5 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Pukkala et al. (2009) Nordic countries. Several occupations	15 million	1960–1990	Job history reported through self-administered census questionnaires	Lung	Drivers (men)	12 882	1.28 (1.26–1.31)	Country, sex, age, and time period	SIR
					Drivers (women)	210	1.46 (1.27–1.67)		
					Postal workers (men)	1783	0.95 (0.90–0.99)		
					Postal workers (women)	962	1.01 (0.95–1.08)		
Petersen et al. (2010) Copenhagen, Aarhus, and Odense, Denmark. Bus drivers	2037	1979–2003	Baseline responses to mailed questionnaires (1978) to bus drivers	Lung	Bus drivers (men)	100	1.2 (1.0–1.4)	Age	SIRs. Men only
					Employment (yr)			Age, calendar time, city, bus route, and smoking	Internal survival analysis
					< 15	49	1		
					> 15–24	24	0.89 (0.59–1.48)		
					> 24	25	0.95 (0.55–1.63)		
					P for trend		0.79		
Merlo et al. (2010) Genoa, Italy. Bus drivers	9267 men (6510 bus drivers; 2073 maintenance workers; 601 white-collar workers)	1970–2005	Bus company records	Lung	Bus drivers	235	1.11 (0.98–1.26)	Age	RR. Men only. No information on smoking habits
Urban police officers, mail carriers, and filling station attendants									
Forastiere et al. (1994) Rome, Italy. Urban police officers	3868	1972–1991	Local Council of Rome; urban police officers including traffic wardens, car drivers, motorcyclists, and office workers	Lung	All urban police officers	82	1.05 (0.84–1.30)	Age	SMR. Men only. No association of lung cancer with job category
					Employment duration				
					≥ 30 yr	18	0.86 (0.51–1.36)		
					Latency since first employment				
					≥ 30 yr	56	1.11 (0.84–1.45)		

Table 2.5 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Soll-Johanning & Bach (2004) Copenhagen, Denmark. Mail carriers	17 233	1898–1996	Post Denmark files; mail carriers	Lung	All mail carriers (men) All mail carriers (women)	298 6	0.96 (0.86–1.08) 1.28 (0.47–2.79)	Age	SIRs. No smoking data. No association with time since first employment. Overlaps with Soll-Johanning et al. (1998)
Lagorio et al. (1994) Lazio, Italy. Filling station attendants	2665	1981–1992	National Survey of Service Stations; shelf managers	Lung	All filling station attendants (men)	29	0.87 (0.64–1.23)	Age	SMR. No smoking data. No information on duration of employment

CI, confidence interval; OR, odds ratio; ref, reference; RR, relative risk; SIR, standardized incidence ratio; SMR, standardized mortality ratio; yr, year.

Carstensen et al. (1988) reported the results of an occupational morbidity analysis based on the Swedish Cancer–Environment Register to evaluate the relationship between occupation and lung cancer incidence during the period 1961–1979 in 1.6 million men aged 30–64 years in 1960. By adding information about smoking habits from a sample of 1% of the Swedish population, smoking-adjusted [indirect adjustment] standardized incidence ratios (SIRs) were estimated for different occupational categories according to the population census of 1960. Smoking-adjusted excess risks ($P < 0.01$) were found in assemblers and machine erectors, professional drivers, miners, packers, and longshoremen as well as in sheet metal workers. The smoking-adjusted standardized incidence ratio for professional drivers, based on 1021 lung cancer cases, was 1.14 (95% CI, 1.03–1.25). [The number of subjects in the category "Drivers, road transport" was not given.]

Paradis et al. (1989) studied 2134 male bus drivers in Montreal, Canada, employed for at least 5 years as of January 1962 and followed up until 31 December 1985. They were compared with the male population of the Greater Montreal area. The number of deaths observed was 804. The overall mortality was somewhat lower than expected (SMR, 0.97). No excesses were observed for lung cancer (SMR, 0.92; 95% CI, 0.73–1.14), and no excess was found among those with a longer duration of employment (≥ 30 years; SMR, 0.85; 95% CI, 0.62–1.13). [No measure of air contamination was available. No information on smoking habits was available.]

Rafnsson & Gunnarsdóttir (1991) studied the mortality of truck drivers and taxi drivers in Reykjavik, Iceland. The subjects were enrolled from the membership rolls of the Truck Drivers' Union and the Cooperative Taxi Agency. The cohort was assembled in 1951, and the follow-up lasted until 1 December 1988. The national mortality rate was used for comparison. The 868 truck drivers had an excess of lung cancer deaths (SMR, 2.14; 95% CI, 1.37–3.18) but fewer deaths than expected from respiratory diseases (15 observed vs 30.1 expected). The standardized mortality ratio from lung cancer did not steadily increase as the duration of employment increased, nor did it change with the length of follow-up. The standardized mortality ratio for lung cancer among the 726 taxi drivers was 1.39 (95% CI, 0.72–2.43). Information on smoking was available from a subset of the cohorts participating in a cross-sectional survey. A slightly higher prevalence of ever-smokers among truck drivers than among taxi drivers or the entire surveyed population was found. [No measure of air contamination was available.]

Gubéran et al. (1992) conducted a historical prospective cohort study of 6630 drivers from the Canton of Geneva, Switzerland, to evaluate cancer mortality and incidence in this occupation. The study population was all men (of all occupations) who held in 1949 a special licence for driving lorries, taxis, buses, or coaches; all new licence holders in the period 1949–1961 were also included. According to the occupation registered on their licence, the 6630 drivers were divided into three groups: (i) professional drivers ($n = 1726$), (ii) non-professional drivers "more exposed" to exhaust gas and fumes (this group included occupations such as vehicle mechanic, police officer, and road sweeper; $n = 712$), and (iii) non-professional drivers "less exposed," composed of all other occupations ($n = 4192$). The cohort was followed up from 1949 to December 1986. Compared with the general population living in the Canton of Geneva, professional drivers experienced significant excess risks, taking into account 15 years of latency, for all causes of death (SMR, 1.15; 90% CI, 1.07–1.23) and for all malignant neoplasms (SMR, 1.25; 90% CI, 1.12–1.40; SIR, 1.28; 90% CI, 1.15–1.42). Cause-specific analysis showed significant excesses for lung cancer (SMR, 1.50; 90% CI, 1.23–1.81; SIR, 1.61; 90% CI, 1.29–1.98). Risk of lung cancer increased significantly with

time from first exposure. Among non-professional drivers, no significant excess risk was found except for lung cancer mortality among the "less exposed" group (SMR, 1.21; 90% CI, 1.03–1.40) and for lung cancer incidence among the "more exposed" group (SIR, 1.61; 90% CI, 1.11–2.27). [No measure of air contamination was available. No information on smoking habits was available.]

Borgia et al. (1994) conducted a historical cohort study to evaluate the mortality patterns of taxi drivers in Rome, Italy. A total of 2311 male subjects registered as taxi drivers between 1950 and 1975 with the local taxi cooperatives were followed up from 1965 to 1988. The overall mortality was lower than expected on the basis of the regional reference rates (692 deaths; SMR, 0.89; 95% CI, 0.82–0.96), whereas the number of recorded deaths for malignant neoplasms was about the expected number (205 deaths; SMR, 0.99; 95% CI, 0.86–1.13). Mortality from circulatory and respiratory diseases was lower than expected [suggesting that smoking was of less importance in the cohort]. An increased standardized mortality ratio was seen for respiratory cancer (SMR, 1.23; 95% CI, 0.98–1.50), mainly due to lung cancer (observed = 76; SMR, 1.23; 95% CI, 0.97–1.54); two pleural cancers were also recorded. The excess of lung cancer deaths was present only among those enrolled in the most recent period (1965–1975) (45 deaths; SMR, 1.40; 95% CI, 1.02–1.87), especially among those of younger age (< 65 years; SMR, 1.86); there was no relationship between lung cancer mortality and latency since first enrolment in the cooperatives or duration of membership. A survey among 400 currently employed taxi drivers at the time of the study indicated that the age-adjusted prevalence of current (55.8%) and former (18.8%) smokers among taxi drivers was slightly higher than that of the general population (50.8% and 9.3%, respectively). [No measure of air contamination was available. Exposure to second-hand smoke and the higher prevalence of smoking among taxi drivers are possible sources of confounding.]

Jakobsson et al. (1997) studied the risk of lung cancer in different subgroups of professional drivers in urban and rural areas of Sweden. Information on occupation and geographical region was obtained from the Swedish census of 1970, and data on the incidence of lung cancer between 1971 and 1984 from the Swedish Cancer Registry. Professional drivers were separated into bus drivers, taxi drivers, and long- and short-distance lorry drivers. Comparisons of cumulative incidence of lung cancer were made between each particular group of drivers and all employed men in the same region. After indirect adjustment for differences in smoking habits (based on the 1963 Swedish survey on smoking habits), the relative risks were significantly increased for taxi drivers (RR, 1.3; 95% CI, 1.0–1.8), long-distance lorry drivers (RR, 1.4; 95% CI, 1.1–1.8), and short-distance lorry drivers (RR, 1.7; 95% CI, 1.3–2.3) in Stockholm but not for other groups of drivers in mainly rural areas of Sweden (counties other than Stockholm, Gothenburg/Bohus, and Malmöhus): taxi drivers (RR, 0.9; 95% CI, 0.6–1.2), short-distance lorry drivers (RR, 1.0; 95% CI, 0.7–1.2), and long-distance lorry drivers (RR, 0.9; 95% CI, 0.8–1.1).

Soll-Johanning et al. (1998) conducted a retrospective cohort study of 18 174 bus drivers and tramway employees (of both sexes) in Copenhagen, Denmark, who were employed during the period 1900–1994. The follow-up was conducted for the period 1943–1992. Cancer rates were compared with the general population of Denmark by linkage to the Danish Cancer Registry and the National Death Index to identify cancers that occurred since 1943. The standardized incidence ratio of lung cancer among those employed for 3 months or longer was 1.6 (95% CI, 1.5–1.8; 473 cases) for men and 2.6 (95% CI, 1.5–4.3; 15 cases) for women. In both men and women, there was a greater risk of lung cancer with greater time since first employment.

There was no trend in lung cancer risk based on the period of predominantly gasoline or diesel vehicle use, and the risks were similarly elevated for workers starting before, at the onset of, or during the use of diesel buses. [There was no specific exposure information. Compared with other men in Copenhagen, the smoking rates among the bus drivers were slightly greater during some time periods, suggesting the possibility of some confounding by smoking, but this is unlikely to explain the elevated risks found.]

The same investigators (Soll-Johanning et al., 2003) conducted a nested case–control study of 153 lung cancer cases included in the previous cohort of bus drivers and tramway employees (Soll-Johanning et al., 1998). The cases and controls or their next of kin were interviewed about smoking history. Deaths were excluded from the control group if the person had died of cancer or non-neoplastic respiratory disease. Cases and controls were matched by date of birth as well as vital status. One of the main exposure variables was an air pollution index, estimated on the basis of a predicted estimate of air pollution along each segment along the bus lines when considering the local traffic, the street configuration, and the urban background. Both 10-year-lag and no-lag models based on employment duration were assessed, adjusting for smoking history in seven categories based on pack-years. There was no consistent elevation in lung cancer risk based on categories of employment duration in either lag model. The risk increased, although the increase was not statistically significant, with more years of employment, but then decreased for a duration of 20 years or longer. The odds ratio for lung cancer associated with the high versus the low air pollution index was 0.99 (95% CI, 0.36–2.75), with a lag time of more than 10 years. [This study also reported results for several other cancers, including bladder cancer and leukaemia.]

Pukkala et al. (2009) conducted a cohort study with linkage of individual records in all the Nordic countries. The study covers the 15 million people aged 30–64 years in the 1960–1990 censuses in five countries and the 2.8 million incident cancer cases diagnosed in these people in a follow-up until about 2005. In the censuses, information on occupation for each person was provided through free text in self-administered questionnaires. The original occupational codes were reclassified into 53 occupational categories, including professional drivers and postal workers. The observed number of cancer cases in each group of people defined by country, sex, age, period, and occupation was compared with the expected number calculated from the stratum-specific person-years and the incidence rates for the national population. The standardized incidence ratios for lung cancer in men were 1.28 (95% CI, 1.26–1.31; 12 882 cases) for drivers and 0.95 (95% CI, 0.90–0.99; 1783 cases) for postal workers. The corresponding standardized incidence ratios for women were 1.46 (95% CI, 1.27–1.67; 210 cases) for drivers and 1.01 (95% CI, 0.95–1.08; 962 cases) for postal workers. [This study may partially overlap with other studies previously described in the Nordic countries.]

Petersen et al. (2010) reported on cancer incidence in a cohort of 2037 male urban bus drivers in Denmark that was established in 1978, with a 25-year follow-up period from 1979 to 2003. In 1978, public bus drivers in the three largest cities in Denmark were sent a mailed questionnaire, which requested an occupational history and information regarding bus route and smoking habits. Information on incident cases of cancer through 2003 was obtained by linkage to the Danish Cancer Registry. Using external rates from the men in the three cities, the standardized incidence ratio for lung cancer among bus drivers was 1.2 (95% CI, 1.0–1.4; 100 cases), and 1.3 (95% CI, 1.0–1.8) with employment of 15 years or longer. A Cox regression model was used to assess the relationship between risk and employment duration. After adjustment for smoking, city of employment, and usual type of

bus route operated (urban or rural), in addition to age and calendar time, no overall increased risk was observed for lung cancer per year of extra employment as a bus driver (RR, 1.00; 95% CI, 0.98–1.03). Compared with drivers employed for less than 15 years, the incidence rate ratios (IRRs) were 0.89 (95% CI, 0.59–1.48) for those employed for 15–24 years and 0.95 (95% CI, 0.55–1.63) for those employed for 25 years or longer. There was no change in the estimates in a 10-year-lag model. [These data indicate that when adjusted for smoking and other risk factors and using an internal comparison group, there was little to no increased risk of lung cancer in bus drivers with increasing duration of work. This finding is in contrast to the elevated risks for bus drivers suggested by the standardized incidence ratio results also reported. This study partially overlaps with Pukkala et al. (2009). Data were reported for several other cancer sites, including the bladder.]

Merlo et al. (2010) conducted a historical mortality cohort study among public transportation workers ever employed between 1949 and 1980 in Genoa, Italy. They estimated overall and cause-specific mortality from January 1970 to December 2005. A total of 9267 men were studied, including 6510 bus drivers. Standardized mortality ratios were computed by applying Italian and regional male death rates to person-years of observation for the entire cohort. An analysis by longest held job title, length of employment, and time since first employment was done using the Poisson regression model. The standardized mortality ratio for lung cancer was 1.16 (95% CI, 1.05–1.28; 386 deaths), and 1.11 (95% CI, 0.98–1.26; 235 deaths) among bus drivers. [No smoking information was available. Data were reported for several other cancers.]

(ii) Urban police officers

Forastiere et al. (1994) evaluated a total of 3868 urban police officers (including traffic wardens, car drivers, motorcyclists, and office workers) in Rome, Italy, through a historical cohort study with emphasis on mortality from cardiovascular disease and cancer. Male subjects employed as of 31 December 1972 (or subsequently hired through 1975) as urban police officers were followed up until 1991. Mortality from all causes, cardiovascular disease, respiratory conditions, digestive and genitourinary diseases, and accidents was lower than expected. The standardized mortality ratio for lung cancer mortality was 1.05 (95% CI, 0.84–1.30; 82 deaths). Analysis for lung cancer by duration of employment and time since employment did not reveal increased lung cancer mortality among those in the longest duration category (≥ 30 years; 18 deaths; SMR, 0.86; 95% CI, 0.51–1.36) and in the last latency category (≥ 30 years since hiring; 56 deaths; SMR, 1.11; 95% CI, 0.84–1.45). In nested case–control analyses conducted to evaluate lung cancer mortality risk by police officers' job category while considering smoking habits, no significant associations were observed (81 lung cancer cases; 405 controls). [The length of follow-up might be considered insufficient to detect an increase of lung cancer. No smoking data were available for the cohort analysis. Data for several other cancers were also reported.]

(iii) Mail carriers

Soll-Johanning & Bach (2004) evaluated cancer incidence among mail carriers in Copenhagen, Denmark. The retrospective cohort study included 17 233 people who had been mail carriers for Post Denmark during the period 1898–1996. Data on employment were obtained from company files, and cancer incidence was obtained from the Danish Cancer Registry. Male mail carriers employed for longer than 3 months had a standardized incidence ratio for cancer of 0.92 (95% CI, 0.88–0.97) and for lung cancer of 0.96 (95% CI, 0.86–1.08; 298 cases). [Data were also reported for other cancers.]

(iv) Filling station attendants

Lagorio et al. (1994) evaluated the mortality of a cohort of 2665 filling station managers from the Latium region, Italy. Only self-employed individuals were available for study (about 50% of the whole workforce). The follow-up period extended from 1981 to 1992. The mortality of the cohort was compared with that of the regional population. The overall analysis showed a significantly decreased mortality from all causes, mainly due to a deficit of cardiovascular diseases and malignant neoplasms. Mortality due to lung cancer (SMR, 0.87; 95% CI, 0.64–1.23; 29 deaths) was lower than expected. [No analysis was reported by duration or time since first employment. No smoking data were available. Data were reported for several other cancers.]

(b) Case–control studies

Several case–control studies of lung cancer have evaluated risks among professional drivers and other outdoor occupations potentially exposed to air pollution. The case–control studies of truck drivers exposed to diesel exhaust have been reviewed in the *IARC Monograph* on diesel and gasoline engine exhausts (IARC, 2013), whereas the studies on other drivers (including broad groupings of drivers that sometimes included truck drivers) and other outdoor workers are briefly reviewed here.

Hansen et al. (1998) conducted a nationwide case–control study (1970–1989) based on employees, including 28 744 men with primary lung cancer and incidence density sampled matched controls (1:1 match). Employment histories were reconstructed back to 1964 for each study subject from the records of a nationwide pension scheme with compulsory membership, and socioeconomic status was derived from the individual job title taken from the national population registry. The adjusted odds ratio for lung cancer was 1.6 (95% CI, 1.2–2.2; 277 cases) for taxi drivers (considered to be the most highly exposed to outdoor air pollution), 1.3 (95% CI, 1.2–1.5; 972 cases) for bus and lorry drivers, and 1.4 (95% CI, 1.3–1.5; 1002 cases) for unspecified drivers. The risk of lung cancer increased significantly with increasing duration of employment as a driver.

Brüske-Hohlfeld et al. (1999) conducted a pooled analysis of two case–control studies of lung cancer in Germany on 3498 male cases with histologically or cytologically ascertained lung cancer and 3541 male population controls. Information about lifelong occupational and smoking history was obtained by interview. The group of professional drivers (e.g. trucks, buses, and taxis) showed an increased risk in western Germany (OR, 1.44; 95% CI, 1.18–1.76) but not in eastern Germany (OR, 0.83; 95% CI, 0.60–1.14) after adjustment for smoking and asbestos exposure.

Menvielle et al. (2003) investigated all lung cancer cases diagnosed between January 1993 and December 1995 (228 lung cancers) in New Caledonia and 305 population controls. Information on lifetime job history, smoking, and other potential risk factors was collected by interview. Among men, an excess risk of lung cancer was found for bus, lorry, and van drivers (OR, 2.7; 95% CI, 1.1–7.0; 13 exposed cases) after adjustment for age, ethnicity, and smoking.

Consonni et al. (2010) examined the relationship between occupation and lung cancer in a case–control study (2002–2005) in the Lombardy region of northern Italy, including 2100 incident lung cancer cases and 2120 randomly selected population controls. The odds ratio for bus and truck drivers was 1.23 (95% CI, 0.90–1.68) after adjustment for area of residence, age, smoking, and number of jobs held.

(c) Meta-analyses

Tsoi & Tse (2012) conducted a systematic review on the association between professional drivers and lung cancer, taking into consideration the potential confounding effect of

cigarette smoking. They systematically searched all published cohort and case–control studies in English from January 1996 to January 2011. A total of 19 studies were included in the meta-analysis (8 cohort studies and 11 case–control studies), and a significantly increased risk of lung cancer (pooled smoking-adjusted RR, 1.18; 95% CI, 1.05–1.33) among professional drivers was observed after combining 4 cohort studies and 9 case–control studies. A higher pooled relative risk was observed among smoking-adjusted studies reporting 10 years or longer of employment (RR, 1.19; 95% CI, 1.06–1.34) compared with the study reporting shorter duration of employment (6 years; RR, 1.00; 95% CI, 0.92–1.09). [There was no information on never-smokers or non-smokers.]

2.2 Cancer of the urinary bladder

Compared with studies focusing on lung cancer, there are a limited number of studies considering cancers of the urinary bladder as an outcome of exposure to outdoor air pollution. Some studies addressed occupations preferentially exposed to specific components of urban outdoor air pollution, such as diesel and gasoline engine emissions. Fewer studies focused on the general population, using population density or measures of specific pollutants as estimates of exposure. This section presents a summary of the studies that assessed the association between exposure to outdoor air pollution and bladder cancer, stratified by exposure scenario or occupation and also by adjustment for smoking, a potential confounder and an important risk factor for bladder cancer. Stratification by study design was not informative, due to few studies of case–control or cohort design within the analyses stratified by smoking and occupation. Another important consideration is that among several studies from Taiwan, China, not all assessed arsenic exposure, an important risk factor for bladder cancer.

Details of occupational studies that assessed bladder cancer as well as lung cancer have been described above in the section on studies of lung cancer in outdoor workers (Section 2.1.4).

2.2.1 Ecological studies

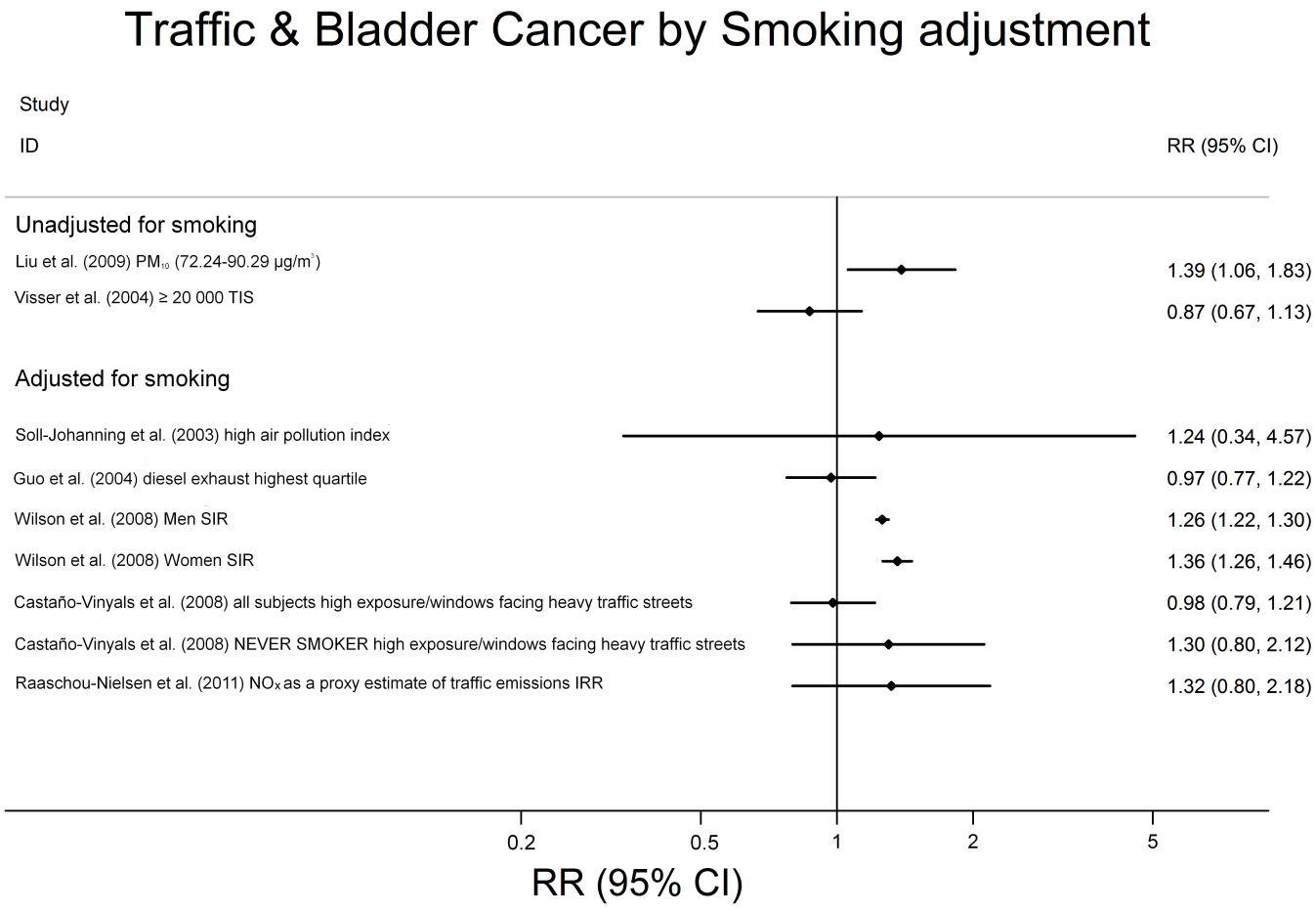
Ecological studies in the USA reported increased mortality from bladder cancer among people living in urban areas compared with rural areas. Blot & Fraumeni (1978) reported increased age-adjusted mortality during 1950–1969 in people living in urban areas compared with rural areas within 3056 counties of the contiguous USA after controlling for several variables in the multivariate regression models, such as ethnicity, occupation, income, and education level. Considering population density as a proxy estimate of urban air pollution (traffic and industrial pollution), Colli et al. (2012) reported significant increases in bladder cancer mortality rates with increases in population density (in quartiles) in 2248 counties of the USA during the period 1950–1994. [The Working Group noted that the interpretation of these findings is limited by the ecological design, the aggregate level of information on exposure to air pollution, and a limited ability to assess the importance of potential confounders, such as smoking. However, there was evidence of increasing risk with increasing population density in the study of Colli et al. (2012).]

2.2.2 Exposure to traffic

See Fig. 2.1

Several studies have examined the association between exposure to outdoor air pollution from traffic, using various metrics, and the risk of bladder cancer. Most studies adjusted for smoking (Soll-Johanning et al., 2003; Guo et al., 2004; Castaño-Vinyals et al., 2008; Wilson et al., 2008; Raaschou-Nielsen et al., 2011b), although two studies did not adjust for smoking (Visser et al., 2004; Liu et al., 2009). All but three studies

Fig. 2.1 Exposure to outdoor air pollution from traffic indicators and the risk of bladder cancer, stratified by adjustment for smoking



Compiled by the Working Group.

observed an increased risk of bladder cancer (25–40% increase) associated with various metrics of traffic exposure.

2.2.3 Taxi drivers

See Fig. 2.2

The studies that evaluated the association between occupation as a taxi driver and the risk of bladder cancer are presented in Fig. 2.2. Both the studies that adjusted for smoking (Schoenberg et al., 1984; Jensen et al., 1987; Silverman et al., 1989a, b; Colt et al., 2004, 2011; Gaertner et al., 2004; Guo et al., 2004; Band et al., 2005; Dryson et al., 2008; Samanic et al., 2008) and those that did not adjust for smoking (Decouflé et al., 1977; Rafnsson & Gunnarsdóttir, 1991; Dolin & Cook-Mozaffari, 1992; Borgia et al., 1994) generally showed an increased risk of bladder cancer.

2.2.4 Bus drivers

See Fig. 2.3

The studies that evaluated the association between occupation as a bus driver and the risk of bladder cancer are presented in Fig. 2.3. The results of studies that did not adjust for smoking (Decouflé et al., 1977; Wynder et al., 1985; Paradis et al., 1989; Dolin & Cook-Mozaffari, 1992; Soll-Johanning et al., 1998) as well as those that adjusted for smoking (Schoenberg et al., 1984; Jensen et al., 1987; Silverman et al., 1989a; Hrubec et al., 1992; Colt et al., 2004; Gaertner et al., 2004; Guo et al., 2004; Dryson et al., 2008; Samanic et al., 2008; Petersen et al., 2010) were inconsistent.

2.2.5 Truck drivers

See Fig. 2.4

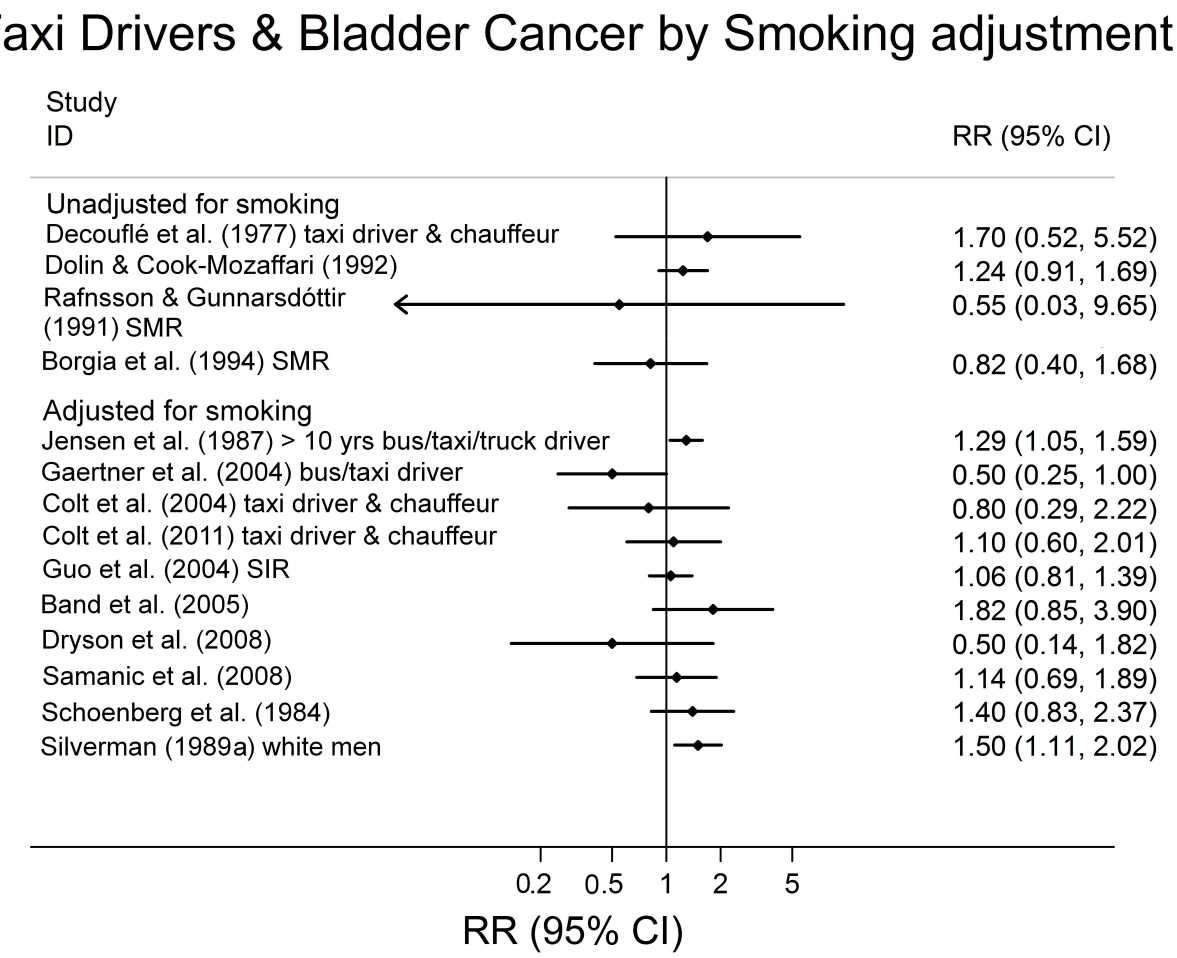
The studies that evaluated the association between occupation as a truck driver and the risk of bladder cancer are presented in Fig. 2.4. Both the studies that did not adjust for smoking (Decouflé et al., 1977; Vineis & Magnani, 1985; Wynder et al., 1985; Steenland et al., 1987; Rafnsson & Gunnarsdóttir, 1991; Dolin & Cook-Mozaffari, 1992) and those that adjusted for smoking (Schoenberg et al., 1984; Hoar & Hoover, 1985; Coggon et al., 1986; Brownson et al., 1987; Jensen et al., 1987; Schifflers et al., 1987; Claude et al., 1988; Bonassi et al., 1989; Silverman et al., 1989a; Iyer et al., 1990; Hrubec et al., 1992; Kunze et al., 1992; Siemiatycki et al., 1994; Porru et al., 1996; Colt et al., 2004, 2011; Gaertner et al., 2004; Guo et al., 2004; Band et al., 2005; Dryson et al., 2008; Samanic et al., 2008; Cassidy et al., 2009) generally demonstrated an increased risk of bladder cancer.

2.2.6 Other jobs with high exposure to outdoor air pollution

See Fig. 2.5

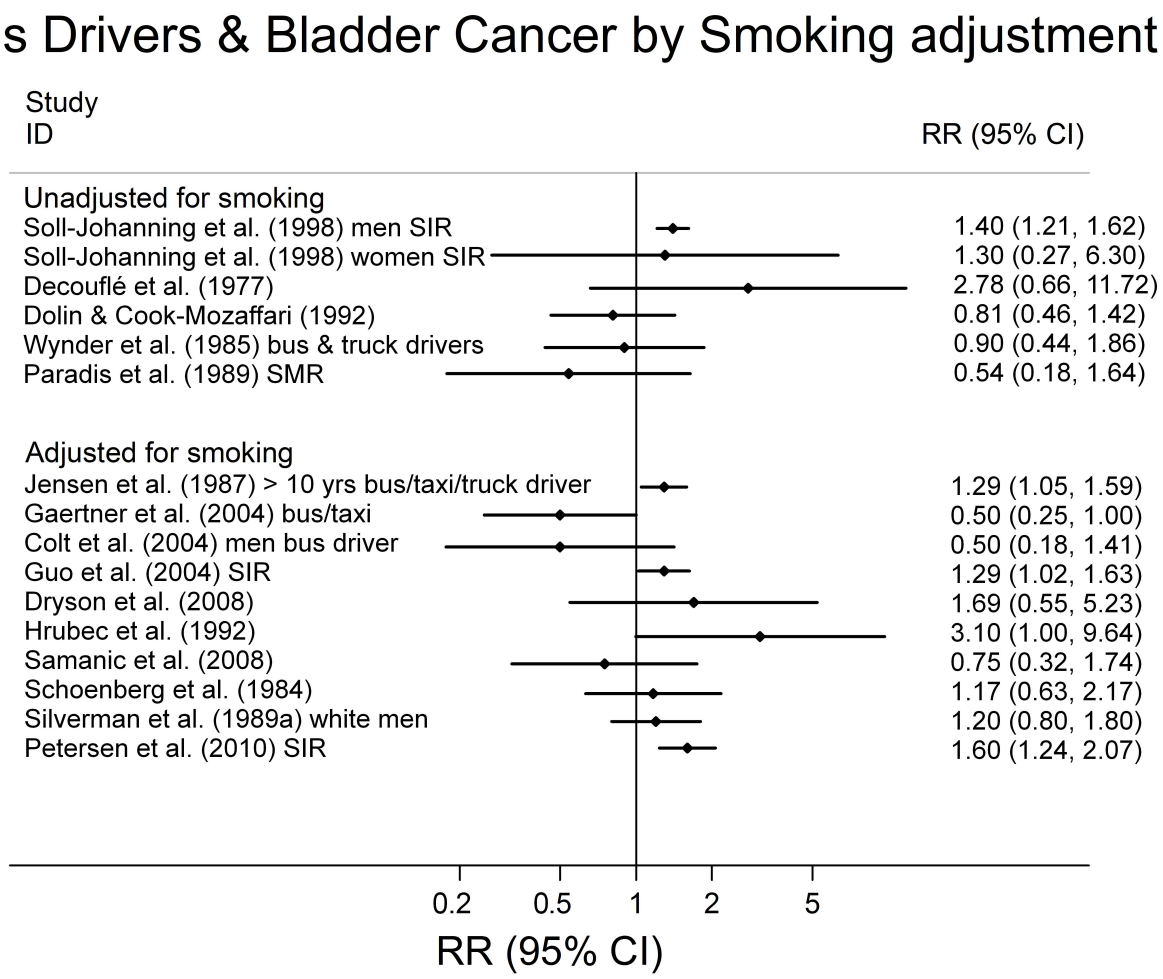
There were several studies that evaluated the association between other jobs with a priori higher exposure to outdoor air pollution than the general population and the risk of bladder cancer (see Fig. 2.5). Many other jobs were included in this category, including mail carrier, driver, urban police officer, and service station attendant. Both the studies that did not adjust for smoking (Balarajan & McDowall, 1988; Gubéran et al., 1992; Forastiere et al., 1994; Lagorio et al., 1994; Soll-Johanning & Bach, 2004; Pukkala et al., 2009) and those that adjusted for smoking (Jensen et al., 1987; Risch et al., 1988; Burns & Swanson, 1991; Cordier et al., 1993; Porru et al., 1996; Pesch et al., 2000; Kogevinas et al., 2003; Colt et al., 2004; Gaertner et al., 2004; Kellen et al., 2007; Reulen et al., 2007; Wilson et al., 2008) generally demonstrated an increased risk of bladder cancer.

Fig. 2.2 Risk of bladder cancer in taxi drivers, stratified by adjustment for smoking



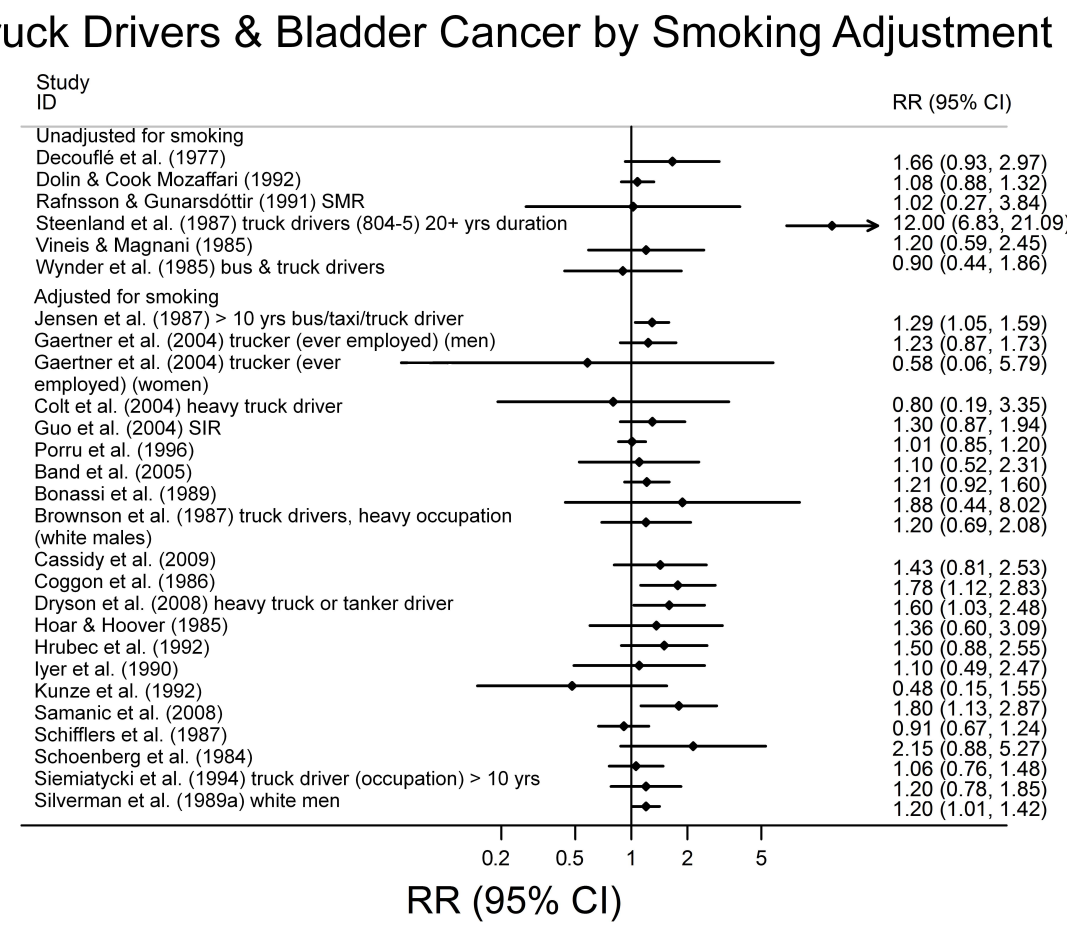
Compiled by the Working Group.

Fig. 2.3 Risk of bladder cancer in bus drivers, stratified by adjustment for smoking



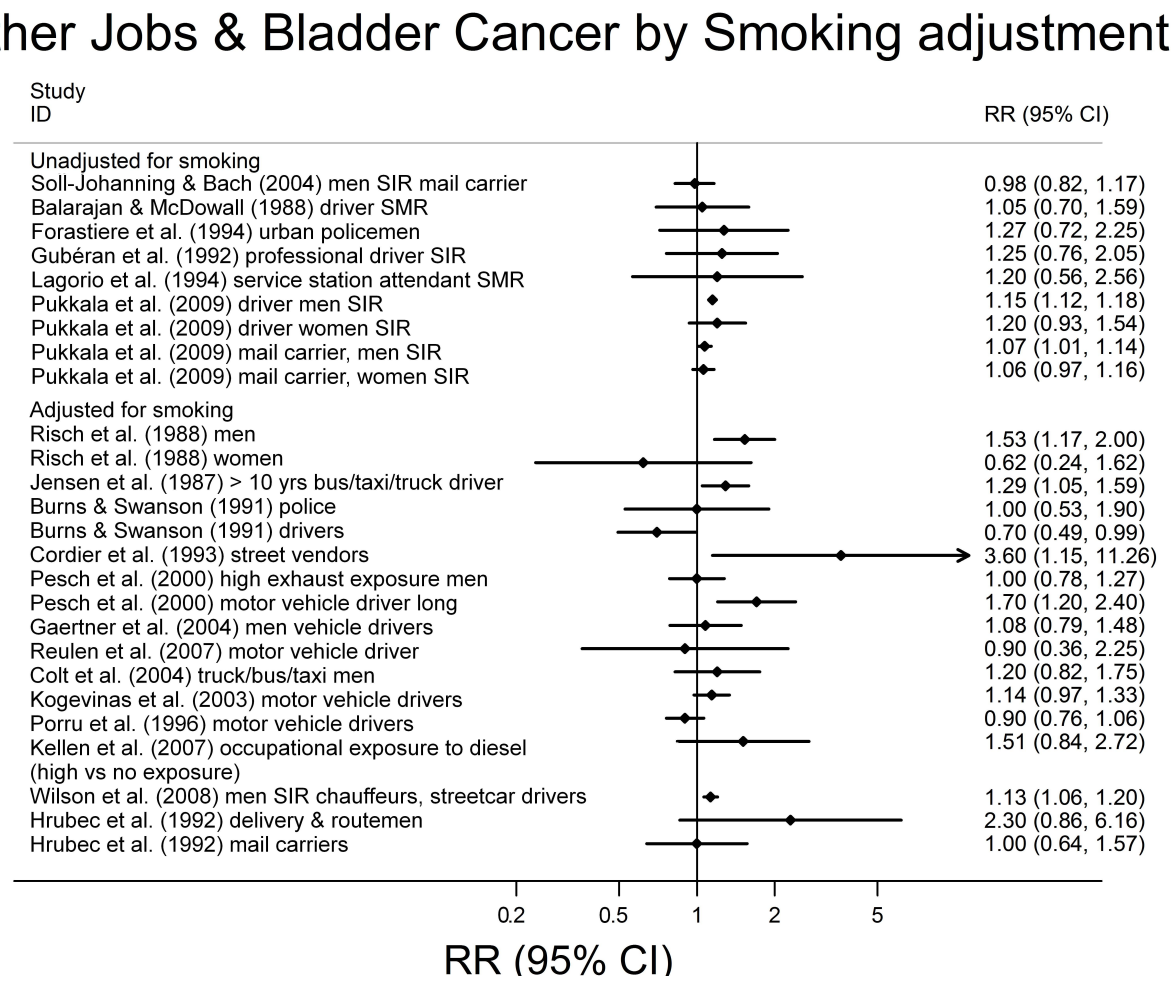
Compiled by the Working Group.

Fig. 2.4 Risk of bladder cancer in truck drivers, stratified by adjustment for smoking



Compiled by the Working Group.

Fig. 2.5 Risk of bladder cancer in other jobs with higher exposure to outdoor air pollution, stratified by adjustment for smoking



Compiled by the Working Group.

2.3 Cancer of the breast

2.3.1 Outdoor air pollution, including traffic emissions

(a) Cohort studies

See Table 2.6.

One of the outcomes evaluated in the AHSMOG study (a prospective cohort study of 6340 adults) by Mills et al. (1991) was incidence of breast cancer among women. The cohort was followed up between April 1977 and December 1982, with a follow-up rate of 99%. (For more study details, see Section 2.1.1c.) During the follow-up, there were 65 new cases of breast cancer. Education level and total years of past smoking were adjusted for in the model. For 1000 hours per year in excess of 200 μg/m^3 of TSP, the risk of breast cancer was elevated, and the relative risk was 1.51 (95% CI, 0.92–2.47). The relative risk with mean concentration of TSP was elevated but was not significant (data not shown in the paper). [A strength of the study is the high follow-up rate, but the study is limited by a lack of control for known breast cancer risk factors.]

Visser et al. (2004) used a population-based regional cancer registry in Amsterdam (n = 718 000 in January 1998) and examined the association between cancer incidence in 1989–1997 and residential traffic intensity. Data on daily traffic intensity in Amsterdam in 1986, 1991, and 1993 were obtained, and a daily traffic intensity score (TIS) was calculated for each of the three available years (passenger cars counted as 1, and trucks, with their larger emissions, were assigned 10). Roads with a TIS of 10 000 or higher for at least one of the three available years were considered as main roads, and those with a TIS of less than 10 000 in all three available years or with residential traffic only were considered as other roads. About 15% of the total number of addresses in Amsterdam (373 157 addresses) were classified as main road addresses (55 719 addresses). Subsequently, cancer registry data were linked to the data on traffic intensity for individual addresses. Annual population data according to sex and 5-year age group were obtained for each year of the study period. Data on smoking and socioeconomic status were obtained in a separate survey of a sample of 2693 people consisting of residents living along main roads and those living along other roads. The survey showed that smoking history did not differ across resident groups but that socioeconomic status was higher among the residents living along the main roads than among the residents living along other roads. Using the age- and sex-specific cancer incidence rate in the population living along other roads as the reference, standardized incidence ratios for the population living along the main roads were calculated. During 1989–1997, 459 new cases of breast cancer were identified. The standardized incidence ratio for breast cancer was not elevated (SIR, 1.00; 95% CI, 0.91–1.09). [The lack of information on potential confounders poses a limitation to the validity of the findings.]

Raaschou-Nielsen et al. (2011b) examined the associations between air pollution from traffic and cancers other than lung cancer. During 1993–1997, 57 053 participants aged 50–64 years living in the Copenhagen and Aarhus areas in Denmark were recruited to the Danish Diet, Cancer, and Health cohort. After a baseline examination was conducted, each cohort member was followed up until June 2006 to investigate occurrence of 20 selected cancers. The participants' residential addresses were traced from 1971 onwards, and outdoor concentrations of NO_x were calculated for each year at the residential address of each participant with the Danish AirGIS modelling system. The mean and median of NO_x concentrations were 28.4 μg/m^3 and 21.9 μg/m^3 (5th–95th percentile, 14.8–69.4), respectively. Then, the time-weighted average NO_x concentrations at all addresses were calculated and used as a time-dependent variable. In addition, two indicators of the amount of traffic near the residence (at the

Table 2.6 Cohort studies of breast cancer and outdoor air pollution

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Outdoor air pollution, including traffic emissions								
Mills et al. (1991) California, USA	6340	1977–1982	Interpolations using inverse-distance weighting from fixed-site monitoring stations to postal code centroids	Annual average exceedance frequency above 200 µg/m³ of TSP during 1973–1977 (1000 h/y)	65	1.51 (0.92–2.47)	Education level and smoking	Response rate to baseline questionnaire: 87%; follow-up rate of participants: 99%; lack of control for known breast cancer risk factors. Incident cases
Visser et al. (2004) Amsterdam, Netherlands	718 000	1989–1997	Residence along main roads (TIS ≥ 10 000)	*Adult women* TIS ≥ 10 000 10 000 ≤ TIS < 20 000 TIS ≥ 20 000	459 228 231	1.00 (0.91–1.09) 0.98 (0.86–1.12) 1.01 (0.89–1.15)	Age and sex	Reference: residence along other roads; lack of control for potential confounders
Raaschou-Nielsen et al. (2011b) Copenhagen and Aarhus, Denmark	57 053	1993–2006	Outdoor concentrations of NO_x at the residential addresses derived from the Danish AirGIS modelling system	Per 100 µg/m³ increase in NO_x Major street within 50 m (yes vs no) Per 10^4 vehicle-km/day traffic load within 200 m of the residence	987 incidences 987 incidences 987 incidences	1.16 (0.89–1.51) 0.98 (0.78–1.22) 0.98 (0.88–1.10)	BMI, education level, alcohol consumption, number of births, age at first birth, lactation, HRT use, benign breast disease, physical activity, and occupation	Two traffic indicators were not associated with the outcome: street with a traffic density > 10 000 vehicles/day within 50 m of the residence, and total number of kilometres driven by vehicles within 200 m of the residence/day

Table 2.6 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Emissions from waste incinerators, industrial facilities, or other sources								
Ranzi et al. (2011) Forlì, Italy	31 347	1990–2003	Atmospheric Dispersion Model System software used to model concentrations of heavy metals (annual average) as indicators of pollution from incinerators	Lowest quartile exposure category (< 0.5 ng/m³)	21 deaths	1.00 (ref)	Age and area-based SES	Rate ratios for breast cancer incidence were not elevated; concerns are residual confounding and multiple comparisons; in Table 5, the ICD-9 code of breast cancer is shown as "175" but it would be incorrect
				Second quartile (0.5–1 ng/m³)	22 deaths	1.33 (0.73–2.43)		
				Third quartile (1–2 ng/m³)	18 deaths	1.02 (0.55–1.92)		
				Highest quartile (> 2 ng/m³)	13 deaths	2.00 (1.00–3.99)		
				Lowest quartile exposure category (< 0.5 ng/m³)	125 incident cases	1.00 (ref)		
				Second quartile (0.5–1 ng/m³)	90 incident cases	0.89 (0.68–1.17)		
				Third quartile (1–2 ng/m³)	81 incident cases	0.78 (0.59–1.03)		
				Highest quartile (> 2 ng/m³)	30 incident cases	0.76 (0.51–1.13)		

BMI, body mass index; CI, confidence interval; ICD, International Classification of Diseases; HRT, hormone replacement therapy; NO_x, nitrogen oxides; NR, not reported; ref, reference; SES, socioeconomic status; TIS, traffic intensity score; TSP, total suspended particles.

time of enrolment) were obtained: the presence of a street with a traffic density of more than 10 000 vehicles per day within 50 m of the residence, and the total number of kilometres driven by vehicles within 200 m of the residence per day. Cox proportional hazards models were used to estimate incidence rate ratios per 100 μg/m^3 increase in NO_x. A total of 54 304 cohort members were included in the analysis. During the follow-up, there were 987 new breast cancer cases. The crude incidence rate ratio per 100 μg/m^3 increase in NO_x was 1.39 (95% CI, 1.09–1.77) but was attenuated (IRR, 1.16; 95% CI, 0.89–1.51) after adjustment for BMI, education level, alcohol consumption, number of births, age at first birth, lactation, hormone replacement therapy use, benign breast disease, physical activity, and occupation. The two traffic indicators were not associated with the outcome. [Strengths of this study include a 10-year prospective follow-up of a relatively large cohort with complete follow-up for vital status. This study also has the strength of modelling exposure since 1971. This study shows the necessity of adjustment for known breast cancer risk factors in evaluating the association between air pollution and breast cancer risk.]

(b) Case–control studies

See Table 2.7.

Lewis-Michl et al. (1996) conducted a population-based case–control study in Nassau and Suffolk counties in New York State, USA. A total of 1420 cases of breast cancer in women aged 20–79 years diagnosed in 1984–1986 at any hospital and 1420 age- and county-matched controls identified through driver's license records were included. The response rates were 88% for cases (1436 of 1616 contacted) and 67% for controls (1420 of 2097 contacted). After restricting to participants with continuous residence for 20 years, address information, and driver's license, there were 793 cases and 966 controls. Geographically based exposure indices of industrial concentration (chemical and other facilities) in 1965 and 1975 and traffic density in 1990–1992 were obtained and assigned to the participants based on 1 km^2 grid cells of residence. Although the industrial data were obtained on 1 km^2 grid cells, the traffic data (i.e. vehicle count data) were originally aggregated for 25 km^2 grid cells and resampled to produce 1 km^2 grid cells. Multiple logistic regression was used to control for family history of breast cancer, history of benign breast disease, age at first live birth, years of education, and attained age. Residence in a grid cell with a chemical facility (i.e. one or more facilities, for 1 year or longer) increased the risk of breast cancer among postmenopausal women in both counties: the odds ratios were 1.61 (95% CI, 1.06–2.43) in Nassau County and 1.58 (95% CI, 0.71–3.51) in Suffolk County. However, proximity to other facilities or to traffic (100 000 vehicles per mile of highway) did not increase the risk. No meaningful associations were found among premenopausal women either. [A strength of the study is the adjustment for several known breast cancer risk factors. However, the traffic data were originally aggregated for 25 km^2 grid cells and resampled to produce 1 km^2 grid cells; thus, the geographical units of that size are probably too large to reflect meaningful differences of traffic exposure, which may induce exposure misclassification. Selection bias is another concern, due to a relatively low response rate of controls.]

Bonner et al. (2005) conducted a population-based case–control study among women living in Erie and Niagara counties in western New York State, USA, during 1996–2001 (Western New York Exposures and Breast Cancer [WEB] study). Cases included 1166 women aged 35–79 years with histologically confirmed primary incident breast cancer. Controls (n = 2105) were frequency-matched to cases by age, race, and county of residence. The response rates were 71% for cases (1166 of 1638) and 62% for controls (2105 of 3396). TSP, a measure of outdoor air pollution, was used as a proxy for exposure to polycyclic aromatic hydrocarbons

Table 2.7 Case–control studies of breast cancer and outdoor air pollution

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Outdoor air pollution, including traffic emissions									
Lewis-Michl et al. (1996) Nassau and Suffolk counties, New York, USA, 1984–1986	793	966	Population	Geographically based exposure indices of industrial concentration (chemical and other facilities) in 1965 and 1975, and traffic density (> 100 000 vehicle miles of travel) in 1990–1992	*Postmenopausal women in Nassau County* Proximity (i.e. residence in a grid cell) to chemical or other facilities	127	1.11 (0.83–1.48)	Family history of breast cancer, history of benign breast disease, age at first live birth, years of education, and attained age	Response rate: 88% of contacted cases and 67% of contacted controls; the adjusted ORs for premenopausal women in both counties are not provided because no meaningful associations were found in the crude models
					Proximity to chemical facilities	58	1.61 (1.06–2.43)		
					Proximity to other facilities	NR	1.08 (0.80–1.46)		
					Proximity to traffic	33	1.29 (0.77–2.15)		
					Postmenopausal women in Suffolk County Proximity to chemical or other facilities	44	1.12 (0.72–1.74)		
					Proximity to chemical facilities	14	1.58 (0.71–3.51)		
					Proximity to other facilities	NR	0.99 (0.62–1.56)		
					Proximity to traffic	11	0.89 (0.40–1.99)		

Table 2.7 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Bonner et al. (2005) New York, USA, 1996–2001	1166	2105	Population	Prediction maps of historical TSP (at birth, at menarche, at first birth, and cumulative) generated using inverse-distance-squared-weighted interpolation	*Premenopausal women: TSP (μg/m³) at birth* < 84	5	1.00 (ref)	Age, education level, and parity	Response rate: 71% for cases and 62% for controls; lifetime cumulative exposure was associated with an increased risk of postmenopausal breast cancer but not with that of premenopausal breast cancer.
					84–114	26	1.96 (0.64–3.01)		
					115–140	64	2.23 (0.77–6.44)		
					> 140	69	1.78 (0.62–5.10)		
					P for trend		0.38		
					Postmenopausal women: TSP (μg/m³) at birth < 84	7	1.00 (ref)		
					84–114	52	2.32 (0.89–6.10)		
					115–140	142	1.94 (0.77–4.86)		
					> 140	156	2.42 (0.97–6.09)		
					P for trend		0.01		
					Premenopausal women: TSP (μg/m³) at menarche < 84	32	1.00 (ref)		
					84–114	53	0.98 (0.56–1.70)		
					115–140	62	1.25 (0.71–2.23)		
					> 140	57	0.66 (0.38–1.16)		
					P for trend		0.21		

Table 2.7 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Bonner et al. (2005) New York, USA, 1996–2001 (cont.)					*Postmenopausal women: TSP (μg/m³) at menarche* < 84	14	1.00 (ref)		
					84–114	81	1.36 (0.67–2.77)		
					115–140	171	1.20 (0.61–2.36)		
					> 140	203	1.45 (0.74–2.87)		
					P for trend		0.18		
					Premenopausal women: TSP (μg/m³) at first birth < 84	147	1.00 (ref)		
					84–114	19	1.06 (0.55–2.02)		
					115–140	5	0.41 (0.14–1.67)		
					> 140	10	0.52 (0.22–1.20)		
					P for trend		0.04		
					Postmenopausal women: TSP (μg/m³) at first birth < 84	54	1.00 (ref)		
					84–114	89	1.30 (0.83–2.03)		
					115–140	142	1.28 (0.83–1.97)		
					> 140	150	1.33 (0.87–2.06)		
					P for trend		0.61		

Table 2.7 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Crouse et al. (2010) Montreal, Canada, 1996–1997	383	416	Hospital	LUR model to predict outdoor concentrations of NO_2 across Montreal for 2006; in addition, the estimates for 1985 and 1996 were back-extrapolated by combining the observed concentrations and the predicted estimates of NO_2 for 2006	Outdoor concentrations of NO_2 (per 5 ppb increase)			Hospital of diagnosis; mother or sister with breast cancer; oophorectomy; years of education; ethnicity; age at menarche; age at first full-term pregnancy; breastfeeding history; oral contraceptive use; hormone replacement therapy use; with reactive metabolites, extremely low magnetic fields, CO, and PAHs; and two neighbourhood ecological covariates (median household income and percentage of adults without a high school diploma)	Postmenopausal breast cancer; response rate: 81.1% for cases and 75.7% for controls; NO_2 was used as a continuous variable *Extrapolated using observed concentrations of NO_2 at each fixed-site monitoring station **Extrapolated using predicted concentrations of NO_2 derived from the LUR model for 2006 at each fixed-site monitoring station
					Exposure surface in 2006	383	1.35 (0.94–1.94)		
					Exposure surface in 1996*	383	1.36 (0.99–1.88)		
					Exposure surface in 1985*	383	1.17 (0.91–1.50)		
					Exposure surface in mean of 1996 and 1985*	383	1.25 (0.94–1.65)		
					Exposure surface in 1996**	383	1.31 (1.00–1.71)		
					Exposure surface in 1985**	383	1.16 (0.94–1.42)		
					Exposure surface in mean of 1996 and 1985**	383	1.22 (0.97–1.54)		

B[*a*]P, benzo[*a*]pyrene; BMI, body mass index; CI, confidence interval; CO, carbon monoxide; LUR, land-use regression; NO_2, nitrogen dioxide; NR, not reported; OR, odds ratio; PAHs, polycyclic aromatic hydrocarbons, ref, reference; TSP, total suspended particles; yr, year.

(PAHs). Prediction maps of TSP (in the 1960s and 1970–1997) were generated using inverse-distance-squared-weighted interpolation, and historical exposure (at birth, at menarche, at first birth, and lifetime cumulative exposure) was assigned to the participants. The interpolated concentrations in the 1960s were also used for TSP concentrations before 1960. Age, race, education level, age at first birth, age at menarche, parity, previous benign breast disease, family history of breast cancer, BMI, and age at menopause were first considered as potential confounders, but the final models presented include only age, education level, and parity because other variables did not alter the effect estimates by more than 10%. In postmenopausal women, exposure to high concentrations of TSP (> 140 μg/m^3) at birth was associated with an increased risk (OR, 2.42; 95% CI, 0.97–6.09) compared with exposure to low concentrations (< 84 μg/m^3). On a continuous scale, the odds ratio with each increase of 30 μg/m^3 in TSP concentration at birth was 1.20 (95% CI, 1.04–1.38) for postmenopausal women. The odds ratios for other exposure periods were elevated but lower than those at birth. The results for premenopausal women were equivocal. [A strength of the study is that the study predicted historical exposure (at birth, at menarche, at first birth, and lifetime cumulative exposure) at each participant's address using geographic information system (GIS) data. The low response rate of controls and the assumption that TSP concentrations before 1960 were equal to those in the 1960s hamper interpretation. Another concern is potential residual confounding, although it is stated that adjustment for other variables did not alter effect estimates by more than 10%.]

Crouse et al. (2010) used data from a hospital-based case–control study conducted in Montreal, Canada, in 1996–1997. The cases were 383 women aged 50–75 years with incident invasive breast cancer, and the controls were 416 women with other incident, malignant cancers, excluding those potentially associated with selected occupational exposures. The response rates were 81.1% for cases and 75.7% for controls. The controls were matched by hospital and approximately frequency-matched by age. Concentrations of NO_2 were used as a marker for traffic-related pollution. A land-use regression model was developed to predict concentrations of NO_2 across Montreal for 2006 (Crouse et al., 2009). The estimates in 1985 and 1996 were back-extrapolated in two methods by combining the observed concentrations and the predicted estimates of NO_2 for 2006: the first method was extrapolation using observed concentrations at each fixed-site monitoring station, and the second method was extrapolation using predicted concentrations from the land-use regression model at each fixed-site monitoring station. These estimates were linked to addresses of residences of subjects at the time of the interview. Several known and suspected breast cancer risk factors (e.g. age at menarche, age at first full-term pregnancy, breastfeeding history, oral contraceptive use, hormone replacement therapy use, and BMI), occupational exposures, and neighbourhood ecological covariates were adjusted for in the model. The odds ratios with each increase of 5 ppb in NO_2 in 2006 were 1.15 (95% CI, 0.89–1.48) in the age-adjusted model and 1.35 (95% CI, 0.94–1.94) in the fully adjusted model. For two NO_2 estimates (obtained from extrapolation using observed concentrations or predicted concentrations) in 1996, the corresponding fully adjusted odds ratios were 1.36 (95% CI, 0.99–1.88) and 1.31 (95% CI, 1.00–1.71), respectively. [The historical exposure prediction at an individual level is an advantage of this study but also introduces uncertainty. An adjustment for an extensive list of potential confounders, including known breast cancer risk factors, is a strength.]

2.3.2 Emissions from waste incinerators, industrial facilities, or other sources

(a) Ecological studies

Cambra et al. (2011) examined the association between proximity to air polluting industries and mortality in small geographical areas in the Basque Country, Spain, from 1996 to 2003. Breast cancer mortality was higher within 2 km of mineral industries. Amaral et al. (2006) compared age-standardized rates of cancer incidence between an area affected by volcanic activity and an area without volcanic activity, both in the Azores, Portugal. They showed higher breast cancer incidence in the area with volcanic activity. [Because these studies cannot account for individual potential confounding and are limited by multiple testing, the findings should be considered preliminary.]

(b) Cohort studies

Ranzi et al. (2011) evaluated the health effects of emissions from two incineration plants located near Forlì, Italy, in a pilot cohort study. The study area was defined as the area of radius 3.5 km around the two incinerators. Subjects who lived in the study area in January 1990 or who subsequently became residents until December 2003 were enrolled in the study (n = 31 347), and their cancer mortality and morbidity were followed up from 1990 to 2003. Atmospheric Dispersion Model System software was used to simulate the impact of the different emission sources; modelled concentrations of heavy metals (annual average) were considered as the indicators of pollution from incinerators. In addition, NO_2 concentration was modelled as an indicator of air pollution from other sources. [Waste incinerators also generate NO_2.] Each subject in the cohort was assigned a value of estimated concentrations of heavy metals and NO_2 based on the residential address. Rate ratios were estimated with Poisson regression, using the lowest quartile exposure category to heavy metals as a reference, and adjusted for age and area-based socioeconomic status. During the follow-up, there were 326 incident cases and 74 deaths from breast cancer. The rate ratios for breast cancer mortality were elevated in the highest exposure category (RR, 2.00; 95% CI, 1.00–3.99). The result did not change substantially even after adjustment for NO_2. The rate ratios for breast cancer incidence were not elevated. [Strengths of the study are exposure modelling of emissions from the incinerators and the relatively large sample size. However, multiple comparisons and residual confounding are potential weaknesses of this study. A positive association with breast cancer mortality but not with incidence in the highest exposure category (RR, 0.76; 95% CI, 0.51–1.13) hampers interpretation of the study findings.]

2.4 Haematological malignancies: leukaemia and lymphoma

2.4.1 Outdoor air pollution, including traffic emissions

(a) Cohort studies

See Table 2.8

Mixed results were reported in several studies that assessed associations of exposure to air pollution or occupations involving exposure to outdoor air pollution with all haematopoietic cancers combined (Forastiere et al., 1994; Pukkala & Pönkä, 2001; Visser et al., 2004; Ranzi et al., 2011). One study in Italy reported an increased risk of Hodgkin lymphoma in bus drivers, white-collar workers, and maintenance workers (Merlo et al., 2010). Mixed results were reported in several studies for non-Hodgkin lymphoma (Forastiere et al., 1994; Lagorio et al., 1994; Soll-Johanning & Bach, 2004; Merlo et al., 2010; Raaschou-Nielsen et al., 2011b; Ranzi et al., 2011).

The incidence of leukaemia and lymphoma was one of the outcomes evaluated in the AHSMOG study (Mills et al., 1991) (see

Section 2.1.1c for a more detailed study description). During the follow-up, there were 12 incident cases of leukaemia (6 women, 6 men) and 15 incident cases of lymphoma (6 women, 9 men). Education level, total years of past smoking, and past or present employment in occupations that involved exposure to airborne contaminants (only for men) were adjusted for in the model. For 1000 hours per year in excess of 200 μg/m^3 of TSP, the risk of leukaemia and lymphoma combined was not elevated among women (HR, 1.05; 95% CI, 0.33–3.37). The hazard ratio for men was not elevated either (data not shown). [The strength of the study is the high follow-up rate. Assessing the risk of leukaemia and lymphoma as a combined measure may not be appropriate because they have different and poorly understood etiologies.]

One of the outcomes evaluated by Visser et al. (2004) was haematological malignancies (see Section 2.3.1a for a more detailed study description). During 1989–1997, 122 and 148 new haematological malignancies were identified for adult men and women, respectively. Using the age group- and sex-specific cancer incidence rates in the population living along other roads as the reference, standardized incidence ratios for the population living along the main roads were calculated. The standardized incidence ratio for haematological malignancies was 0.98 (95% CI, 0.81–1.17) for adult men and 1.23 (95% CI, 1.04–1.44) for adult women. The standardized incidence ratios for specific types of haematological malignancies among adult women were 1.23 (95% CI, 0.97–1.54) for non-Hodgkin lymphoma, 1.33 (95% CI, 0.90–1.90) for multiple myeloma, and 1.60 (95% CI, 1.01–2.40) for myeloid leukaemia. However, the standardized incidence ratio for haematological malignancies among adult women was higher in residents living along less-busy main roads (10 000 ≤ TIS < 20 000) (SIR, 1.41; 95% CI, 1.13–1.73) than for residents living along the busiest main roads (TIS ≥ 20 000) (SIR, 1.03; 95% CI, 0.78–1.32). [An increased risk was noted only in the intermediate category of exposure, and this could suggest a chance finding.]

Two of the outcomes evaluated by Raaschou-Nielsen et al. (2011b) were non-Hodgkin lymphoma and leukaemia (see Section 2.3.1a for a more detailed study description). During the follow-up, there were 197 incident cases of non-Hodgkin lymphoma and 117 incident cases of leukaemia. The incidence rate ratios per 100 μg/m^3 increase in NO_x were 1.11 (95% CI, 0.61–2.03) for non-Hodgkin lymphoma after adjustment for education level and occupation, and 0.47 (95% CI, 0.16–1.39) for leukaemia after adjustment for smoking status and occupation. The two traffic indicators were not associated with either outcome. [Strengths of this study include a 10-year prospective follow-up of a relatively large cohort with complete follow-up for vital status, modelling exposure since 1971, and adjustment for potential confounders.]

2.4.2 Emissions from waste incinerators

Cohort studies

See Table 2.8

Ranzi et al. (2011) evaluated the effects of emissions from two incineration plants located near Forlì, Italy, on multiple outcomes, including non-Hodgkin lymphoma and leukaemia, in a pilot cohort study (see Section 2.3.2b for a more detailed study description). Rate ratios were estimated with Poisson regression, using the lowest quartile exposure category to heavy metals as a reference, and adjusted for age and area-based socioeconomic status. During the follow-up, there were 43 deaths and 93 incident cases of non-Hodgkin lymphoma and 46 deaths and 48 incident cases of leukaemia. The rate ratios for non-Hodgkin lymphoma mortality were elevated among women with the highest exposure category (RR, 2.03; 95% CI, 0.48–8.67) but were not elevated among men for incident non-Hodgkin lymphoma or leukaemia. The results did not change substantially even after adjustment for NO_2 (data not shown), and rate ratios for NO_2 were not shown either. [Strengths of the study

Table 2.8 Cohort studies of leukaemia and lymphoma and outdoor air pollution

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Outdoor air pollution, including traffic emissions									
Mills et al. (1991) California, USA	6340	1977–1982	Interpolations using inverse-distance weighting from fixed-site monitoring stations to postal code centroids	Leukaemia and lymphoma combined (ICD code: NR)	Annual average hours in excess of 200 μg/m^3 of TSP during 1973–1977 (1000 h/y)	20 incident cases for leukaemia; 26 incident cases for lymphoma	1.05 (0.33–3.37) for women	Education level, total years of past smoking, and past or present employment in occupations that involved exposure to airborne contaminants (only for men)	There was no association for men
Visser et al. (2004) Amsterdam, Netherlands	718 000	1989–1997	Residence along main roads (TIS ≥ 10 000)	Haematological malignancies (ICD-10 code: C81–95)	*Adult men* Other roads	NR	1.00 (ref)	Age and sex	
					Main roads (TIS ≥ 10 000)	122	0.98 (0.81–1.17)		
					Main roads (10 000 ≤ TIS < 20 000)	57	0.92 (0.70–1.20)		
					Main roads (TIS ≥ 20 000)	65	1.03 (0.80–1.32)		
					Adult women Other roads	NR	1.00 (ref)		
					Main roads (TIS ≥ 10 000)	148	1.23 (1.04–1.44)		
					Main roads (10 000 ≤ TIS < 20 000)	89	1.41 (1.13–1.73)		
					Main roads (TIS ≥ 20 000)	59	1.03 (0.78–1.32)		

Table 2.8 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Raaschou-Nielsen et al. (2011b) Copenhagen and Aarhus, Denmark	57 053	1993–2006	Outdoor concentration of NO_x at the residential addresses derived from the Danish AirGIS modelling system	Non-Hodgkin lymphoma (ICD-7 code: 200, 202)	Per 100 µg/m³ increase in NO_x	197 incident cases	1.11 (0.61–2.03)	Education level and occupation (rubber industry)	Two traffic indicators (major street within 50 m, and total number of kilometres driven by vehicles within 200 m of the residence/ day) were not associated with non-Hodgkin lymphoma and leukaemia
					Major street within 50 m: No	NR	1.00 (ref)		
					Yes	NR	0.90 (0.54–1.51)		
					Per 10^4 vehicle-km/day traffic load within 200 m of the residence	197 incident cases	1.06 (0.83–1.35)		
				Leukaemia	Per 100 µg/m³ increase in NO_x	117 incident cases	0.47 (0.16–1.39)	Smoking status and occupation (chemical industry [oil refinery] and rubber industry)	
					Major street within 50 m: No	NR	1.00 (ref)		
					Yes	NR	0.81 (0.39–1.66)		
					Per 10^4 vehicle-km/day traffic load within 200 m of the residence	117 incident cases	0.75 (0.51–1.11)		

Table 2.8 (continued)

Reference, study location and period	Total no. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Emissions from waste incinerators									
Ranzi et al. (2011) Forlì, Italy	31 347	1990–2003	Atmospheric Dispersion Model System software used to model heavy metals concentrations (annual average) as indicators of pollution from incinerators	Non-Hodgkin lymphoma (200, 202)	Women: Lowest quartile of heavy metals air concentration (< 0.5 ng/m^3)	7 deaths	1.00 (ref)	Age and area-based SES	Rate ratios for mortality in men and for incidences in both sexes were not elevated
					Second quartile (0.5–1 ng/m^3)	7 deaths	0.83 (0.27–2.56)		
					Third quartile (1–2 ng/m^3)	2 deaths	0.47 (0.09–2.44)		
					Highest quartile (> 2 ng/m^3)	3 deaths	2.03 (0.48–8.67)		
				Leukaemia (204–208)	Women: Lowest quartile of heavy metals air concentration (< 0.5 ng/m^3)	5 deaths	1.00 (ref)	Age and area-based SES	
					Second quartile (0.5–1 ng/m^3)	6 deaths	1.82 (0.54–6.19)		
					Third quartile (1–2 ng/m^3)	7 deaths	1.69 (0.52–5.55)		
					Highest quartile (> 2 ng/m^3)	2 deaths	1.31 (0.25–6.95)		

CI, confidence interval; ICD, International Classification of Diseases; NO_x, nitrogen oxides; NR, not reported; ref, reference; SES, socioeconomic status; TIS, traffic intensity score; TSP, total suspended particles.

are exposure modelling of emissions from the incinerators and the relatively large sample size.]

2.4.3 Emissions from petrochemical plants or other industries

(a) Ecological studies

Sans et al. (1995) included a general population sample of 115 721 people living within 7.5 km of the petrochemical plant in southern Wales. Leukaemia or lymphoma incidence and mortality were examined within distances of 7.5 km and 3 km from the plant, standardized for age, sex, and index of deprivation, and adjusted for region. There was no increased risk of leukaemia or lymphoma. Wilkinson et al. (1999) examined the incidence of lymphohaematopoietic malignancy from 1974 to 1991 within 7.5 km of all 11 oil refineries in Great Britain. After standardization for age, sex, and index of deprivation, there was no increased risk of the diseases. [These studies suffer from multiple testing and imprecise exposure assessment.]

(b) Case–control studies

See Table 2.9.

Linos et al. (1991) conducted a population-based case–control study to evaluate the association of residential proximity to industrial plants and incident cases of leukaemia and non-Hodgkin lymphoma among men living in Iowa and Minnesota in the USA. Cases included 622 people with non-Hodgkin lymphoma and 578 people with leukaemia diagnosed from 1980 to 1983. Controls were 1245 people frequency-matched to cases by year of birth, vital status, and state of residence (and year of death if the case was deceased). The response rates were 87% for non-Hodgkin lymphoma, 86% for leukaemia, and 81% for controls. Interviews were conducted of the subjects or their next of kin, and residential history with proximity to the factory and type of the factory was queried. Polychotomous logistic regression was conducted to estimate odds ratios adjusting for age, state of residence, vital status, and several risk factors for the cancers. Living within 0.8 km of any type of factory, compared with living in an unexposed area (> 3.2 km from the factory, or with no factory), was associated with odds ratios of 1.5 (95% CI, 1.1–1.9) for non-Hodgkin lymphoma and 1.1 (95% CI, 0.9–1.5) for leukaemia. In an analysis stratified by type of factory, the elevated risks of non-Hodgkin lymphoma were associated with living near stone, clay, or glass industry facilities; the odds ratio for living within 3.2 km of a factory was 1.6 (95% CI, 1.0–2.7; 31 exposed cases). In addition, the risk of leukaemia was greater among people who lived within 3.2 km of either a chemical plant (OR, 1.7; 95% CI, 1.0–3.0) or a petroleum plant (OR, 2.0; 95% CI, 1.0–4.2). [The interpretation of this study is difficult because of imprecise exposure assessment, which asked the subjects to recall their residential proximity to the factory and its type (i.e. potential for recall bias). Matching on year of death, as well as year of birth, may have overmatched in this study.]

Shore et al. (1993) used an existing population-based case–control study to evaluate the association between residential proximity to industrial plants and the risk of acute leukaemia. Cases were 712 patients aged 18–79 years who were residents of either the USA or Canada and were diagnosed during a 3.5-year period starting in 1986. Controls were 637 people who were selected by random telephone sampling and frequency-matched by age categories (10 years), race, sex, and region of residence. Cases (or their next of kin) were interviewed within 2 days of diagnosis, and controls were interviewed between June 1989 and January 1990. The response rates were 86% for cases and 80% for controls. In the interview, the subjects were asked whether they had lived near a factory before 2 years before the interview and the name and location of the factory. Logistic regression was used to estimate odds ratios adjusting for age, race, sex, region, level of schooling, smoking, and use of hair dye.

Table 2.9 Case–control studies of leukaemia and lymphoma and outdoor air pollution

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Emissions from petrochemical plant, oil refineries, and oil spill										
Belli et al. (2004) Brindisi, Italy	31	170	Population (deceased residents due to other causes)	Distance between the central point of the petrochemical plant and the residence of each subject	Lymphohaematopoietic malignancies (leukaemia, non-Hodgkin lymphoma, multiple myeloma, and Hodgkin lymphoma)	Distance: > 5 km 4–5 km 3–4 km 2–3 km ≤ 2 km	 10 5 5 7 4	 1.00 (ref) 0.57 (0.14–2.4) 0.26 (0.06–1.1) 0.39 (0.10–1.6) 2.7 (0.45–17)	Age, sex, smoking, and education level	Response rate: 98%
Yu et al. (2006) Kaohsiung, Taiwan, China	40	96	Population	Cumulative exposure score to petrochemicals considering proximity to the petrochemicals, monthly prevailing wind, subjects' mobility, and length of stay at each residence	Leukaemia (204–208)	Never lived in an exposed area Ever lived in an exposed area Per 1-unit increase in log-transformed exposure score	26 14 40	1.00 (ref) 4.56 (1.66–12.54) 1.54 (1.14–2.09)	Educational status of the subject; smoking status was further adjusted. Age (± 1 yr) and sex matched	Response rate: 91% for cases and 53% for controls; only results for those aged 20–29 yr are shown in this table
Emissions from other industrial facilities										
Linos et al. (1991) Iowa and Minnesota, USA	622 non-Hodgkin lymphoma cases and 578 leukaemia cases	1245	Population	Residential history (proximity to the factory and type of the factory)	Non-Hodgkin lymphoma (ICD code: NR) *Leukaemia*	Distance: > 3.2 km 0.8–3.2 km < 0.8 km Distance: > 3.2 km 0.8–3.2 km < 0.8 km	 272 304 182 272 248 142	 1.0 (ref) 1.4 (1.0–1.8) 1.5 (1.1–1.9) 1.0 (ref) 1.2 (0.9–1.9) 1.1 (0.9–1.5)	Age, state of residence, vital status, high-risk occupations, social class, smoking, use of hair dye, exposure to pesticides, and family history of cancer	Response rate: 87% for non-Hodgkin lymphoma, 86% for leukaemia, and 81% for controls; the results given refer to "any type of factory"

Table 2.9 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Shore et al. (1993) USA and Canada	712	637	Population	Residential history (proximity to the factory and types of the factory)	Leukaemia (ICD code: NR)	Distance: > 8 km < 8 km Distance: > 5 miles 2–5 miles ≤ 1 mile	 NR 117 NR 41 76	 1.0 (ref) 1.4 (1.0–1.9) 1.0 (ref) 1.0 (0.7–1.6) 1.7 (1.2–2.6)	Age, race, sex, region, level of schooling, smoking, and use of hair dye	Response rate: 86% for cases and 80% for controls; the results given refer to "any type of factory" (5 miles = 8 km)
Johnson et al. (2003) Canada	1499	5039	Population	Residential history (proximity to the factory and type of the factory)	Non-Hodgkin lymphoma (ICD code: NR)	Distance: > 3.2 km ≤ 3.2 km 0.8–3.2 km < 0.8 km	 1026 473 435 71	 1.00 (ref) 1.11 (0.97–1.26) 1.08 (0.95–1.24) 1.16 (0.87–1.54)	Age, sex, province, income adequacy level, education level, pack-years of smoking, alcohol consumption, urban/rural residential history, chemical exposure, and occupational exposure	Response rate: 62% for cases and 63% for controls; the results given refer to "any type of factory"
De Roos et al. (2010) 4 SEER regions, USA	864	684	Population	Residential history (proximity to the factory and type of the factory)	Non-Hodgkin lymphoma (ICD code: NR)	Distance: > 2 miles ≤ 2 miles > 1–2 miles > 0.5–1 miles ≤ 0.5 miles *P* for trend	 295 569 233 218 118	 1.0 (ref) 1.0 (0.8–1.2) 0.9 (0.7–1.2) 1.1 (0.8–1.4) 1.1 (0.8–1.5) 0.54	Age, sex, race, education level, and study site	Response rate: 59% for cases and 44% for controls (in the original study), and 76% for cases and 52% for controls (among eligible participants); the results given refer to "any type of factory" (5 miles = 8 km)

BMI, body mass index; CI, confidence interval; ICD, International Classification of Diseases; ICD-O, International Classification of Diseases for Oncology; NR, not reported; ref, reference; SEER, Surveillance, Epidemiology, and End Results; TEQ, toxic equivalence quotient; US EPA, United States Environmental Protection Agency; WHO, World Health Organization; yr, year.

Living within 8 km of any type of factory was associated with increased risk (OR, 1.4; 95% CI, 1.0–1.9) compared with living more than 8 km from the factory. In addition, the odds ratio for living within 1.6 km of the factory was 1.7 (95% CI, 1.2–2.6) and for living within 3.2–8 km of the factory was 1.0 (95% CI, 0.7–1.6). Confounder adjustment was not conducted due to the small number of cases. [This study is limited due to exposure assessment that depends on subjects' recall of their residential proximity to the factory and its type (i.e. potential for recall bias).]

Johnson et al. (2003) conducted a population-based case–control study to investigate the association between residential proximity to seven major types of industry (copper smelter, lead smelter, nickel smelter, steel production plant, petroleum refinery, kraft pulp plant, and sulfite pulp plant) and the risk of non-Hodgkin lymphoma. Cases were 1499 people diagnosed between April 1994 and December 1996 in 8 of the 10 Canadian provinces, and 5039 controls were randomly selected. The response rates were 62% for cases and 63% for controls. Questionnaires were used to collect detailed information as well as a lifetime Canadian residential history (exact address). Then, residential proximity to the seven major types of industry was calculated from 1960 to 5 years before the questionnaire was completed. Unconditional logistic regression was conducted to estimate odds ratios adjusting for age, sex, province, income adequacy level, education level, pack-years of smoking, alcohol consumption, urban/rural residential history, chemical exposure, and occupational exposure. Compared with living more than 3.2 km from the plants, the odds ratios were 1.11 (95% CI, 0.97–1.26) for having lived within 3.2 km of the plants, 1.08 (95% CI, 0.95–1.24) for having lived 0.8–3.2 km from the plants, and 1.16 (95% CI, 0.87–1.54) for having lived within 0.8 km of the plants. Increased risk of follicular non-Hodgkin lymphoma was observed among women who had lived within 3.2 km of a plant (OR, 1.48; 95% CI, 1.10–1.99). Proximity to copper smelters (within 3.2 km) (OR, 5.13; 95% CI, 1.49–17.71) and sulfite pulp mills (within 0.8 km) (OR, 3.71; 95% CI, 1.46–9.42) was associated with increased risk. [Strengths of this study are the large sample size and the control for several potential confounders. Multiple testing and small numbers of cases in analyses for types of industries hamper interpretation of the results.]

Belli et al. (2004) investigated cancer mortality and residential proximity to the petrochemical plant located in Brindisi, Italy. Cases included all residents in Brindisi and in three neighbouring municipalities who had died in the study area from 1996 to 1997 from lung cancer, pleural neoplasm, bladder cancer, and lymphohaematopoietic malignancies (i.e. leukaemia, non-Hodgkin lymphoma, multiple myeloma, and Hodgkin lymphoma) (n = 144, including 31 lymphohaematopoietic malignant cases). Controls were randomly selected from the residents in the study area who had died during the same period from any cause except those listed for the cases (n = 170). Distance between the central point of the plant and the residence of each subject was calculated. Logistic regression was used to estimate odds ratios adjusting for age, sex, smoking, and education level. The risk of lymphohaematopoietic malignancies was elevated for residents living within 2 km of the plant (OR, 2.7; 95% CI, 0.45–17). [The small number of cases poses threats to the validity of findings. Combining leukaemia and lymphoma cases may not be appropriate because they have different and poorly understood etiologies.]

Yu et al. (2006) conducted a population-based case–control study to examine the associations between residential exposure to petrochemical complexes and the risk of leukaemia among subjects aged 29 years and younger in Kaohsiung, Taiwan, China. There were four petrochemical complexes in the study area. Cases included 171 incident primary leukaemia cases during the period from November 1997 to January 2003

who were residents of the study area at diagnosis (response rate, 91%). Controls were 410 subjects randomly selected from the study area, matched by age (± 1 year) and sex (response rate, 53%). Based on information on residential history obtained by interview, a cumulative exposure score to petrochemicals was calculated for each individual, considering proximity to the petrochemical plants, monthly prevailing wind, subjects' mobility, and length of stay at each residence. Conditional logistic regression models were used to estimate odds ratios further adjusting for educational status and smoking status. For subjects aged 20–29 years, there were 40 cases and 96 controls, and the risk of leukaemia was elevated among the subjects who had ever lived in an exposed area (i.e. within an area of radius 3 km around the complexes) (OR, 4.56; 95% CI, 1.66–12.54) compared with those who had never lived in an exposed area. For the subjects aged 20–29 years, the odds ratio per 1-unit increase in log-transformed exposure score was 1.54 (95% CI, 1.14–2.09). [The study has the strength of exposure modelling but is limited due to the low response rate among controls. There is potential for selection bias in this study as controls appeared to vary in several characteristics of socioeconomic status: more controls completed college or above (56%) compared with cases (30%) among the subjects aged 20–29 years.]

De Roos et al. (2010) used an existing population-based case–control study to examine the association between proximity to industrial facilities (15 types of industry) and the risk of non-Hodgkin lymphoma in four United States SEER registry areas. Cases included 1321 patients with non-Hodgkin lymphoma, and controls were 1057 people identified by random-digit dialling. The overall response rate was 59% for cases and 44% for controls. Residential history was queried by interviewer-administered questionnaire, and residential proximity to industrial facilities during a 10-year period before diagnosis or reference year was calculated. Analyses were limited to participants with more than 70% of their person-years during the 10-year exposure period with reliable residential information, which yielded 864 cases and 684 controls. Unconditional logistic regression was used to estimate odds ratios adjusting for age, sex, race, education level, and study site. Having lived within 3.2 km of any type of industrial facility was not associated with the risk of non-Hodgkin lymphoma (OR, 1.0; 95% CI, 0.8–1.2). There was no dose–response relationship in terms of the proximity or the number of years of residence. Increased risk of non-Hodgkin lymphoma was observed for living within 3.2 km of several industries, including lumber and wood products (OR, 1.4; 95% CI, 0.9–2.1), chemical (OR, 1.2; 95% CI, 0.9–1.6), petroleum (OR, 1.1; 95% CI, 0.8–1.5), and primary metal (OR, 1.3; 95% CI, 1.0–1.6) industries. However, the findings were inconsistent in terms of distance or duration of residence. [Although the study had a large sample size, it had inconsistent results and a low response rate.]

2.5 Childhood cancer

Initial interest in the hypothesis that air pollution causes childhood cancer was prompted by two independent case–control studies of wire configuration and electromagnetic fields near the homes of children with cancer, which considered proximity to high-density road traffic as a potential confounder. Both studies found positive associations with metrics of heavy traffic near the residence (Wertheimer & Leeper, 1979; Savitz et al. 1988, Savitz & Feingold 1989).

Subsequent studies of air pollution and childhood cancer have consisted primarily of ecological/geographical studies and case–control studies. Ecological/geographical studies have compared the density of childhood cancer cases, for example incidence and mortality rates, in areas with higher and low air pollution levels, estimated for example by proximity to industry

or density of streets and cars, providing mixed results (Knox, 1994; Lyons et al., 1995; Sans et al., 1995; Alexander et al., 1996; Knox & Gilman, 1997; Nordlinder & Järvholm, 1997; Gilman & Knox, 1998; Harrison et al., 1999; Reynolds et al., 2002, 2003; Visser et al., 2004; Knox, 2005a, b, 2006; Thompson et al., 2008; Whitworth et al., 2008). Ecological studies are not reviewed here because of the limitations for causal inference. Case–control studies have explored differences in various metrics of exposure to outdoor air pollution at addresses of childhood cancer cases and control children, for example traffic density, modelled concentrations, neighbouring automotive repair garages, petrol stations, and refuelling of a car.

Several studies that addressed parental occupational exposure to motor-vehicle-related exhausts and the risk of cancer in the offspring showed associations with childhood leukaemia (Colt & Blair, 1998; IARC, 2013). However, these studies were not reviewed in detail because the Working Group believed that the exposures assessed could be relevant to engine exhausts but were not informative for outdoor air pollution. Furthermore, the results were not consistent and several common methodological limitations were identified related to the quality of the exposure assessment (usually just a job title), the small number of exposed cases, multiple comparisons, and possible bias towards reporting of positive results.

2.5.1 Case–control studies

See Table 2.10 for results for all cancers combined, Table 2.11 for leukaemia, Table 2.12 for acute leukaemia, Table 2.13 for lymphoma, Table 2.14 for central nervous system (CNS) tumours, and Table 2.15 for other cancers. (Note that some studies reported data for several cancer sites.)

(a) All cancers combined

See Table 2.10.

Wertheimer & Leeper (1979) considered traffic at the residence as a potential confounder in their study of wire configuration and the risk of childhood cancer mortality in the Denver, Colorado, area, USA. No risk estimates for traffic were provided, but based on the given numbers an odds ratio of 1.6 (95% CI, 1.1–2.3) for all cancers combined in association with 5000 vehicles per day or more at a street within 40 m of the home could be calculated (Feychting et al., 1998). [This study was limited by its use of mortality as a surrogate for the incidence of childhood cancer because a large proportion of children with cancer (e.g. acute lymphoblastic leukaemia) survive their disease. Other limitations were that only a crude exposure estimate and only odds ratios for all cancer types combined were presented. The odds ratio was based not on counts of cases and controls but on counts of case and control addresses, where each child could contribute with both an address at birth and an address at diagnosis.]

Savitz et al. (1988) and Savitz & Feingold (1989) identified 328 cases of all types of childhood cancer from the Colorado Central Cancer Registry and area hospitals and used random-digit dialling to select 262 controls from the population (response rate, 75%), who were matched to cases by age, sex, and area. The amount of traffic at the address at the time of diagnosis was provided by Highway Planning authorities. The study reported an odds ratio of 3.1 (95% CI, 1.2–8.0) for all incident cancers combined. Further adjustment for several covariates in a subset of study participants had little effect on the risk estimates. [The Working Group noted several limitations to this study, including that the random-digit dialling method for selection of controls could potentially result in selection bias, that the exposure assessment was crude, and that there were small numbers of exposed cases for specific types of cancer.]

Table 2.10 Case–control studies of all childhood cancers combined and outdoor air pollution

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Savitz & Feingold (1989) Denver, Colorado, USA, 1976–1983	280	262	Population; random-digit dialling	Traffic counts at home address at time of diagnosis	All cancers	< 500 vehicles/day		1.0 (ref)	Matched by age, sex, and area	Incidence. 0–14 yr. Adjustment in a subset for sex, age, year of diagnosis, type of residence, location at birth, mother's age, father's education level, per capita income, and wire configuration had little effect on the risk estimates. Also see Savitz et al. (1988)
						≥ 500 vehicles/day	48	1.7 (1.0–2.8)		
						≥ 5000 vehicles/day	29	1.8 (0.9–3.3)		
						≥ 10 000 vehicles/day	18	3.1 (1.2–8.0)		
Feychting et al. (1998) Sweden	63	550	Population; randomly selected among children living within 300 m of high-voltage power lines	Modelled peak concentrations of NO_2 (99th percentile of 1-h means); based on latest address within the power line corridor	All cancers	≤ 39 μg/m³		1.0 (ref)	Matched by calendar time, geographical area, and residence near same power line	Incidence. Cases: 0–15 yr; identified among children living within 300 m of high-voltage power lines. Adjustment for electromagnetic fields and socioeconomic position did not materially change the results. Similar effects for boys and girls
						40–49 μg/m³	35	1.3 (0.4–4.3)		
						≥ 50 μg/m³	44	2.7 (0.9–8.5)		
						≥ 80 μg/m³	8	3.8 (1.2–12.1)		

Table 2.10 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Raaschou-Nielsen et al. (2001) Denmark, 1968–1991	1989	5506	Randomly selected from whole population	Traffic density and modelled NO_2 and benzene at home addresses from time of conception to time of diagnosis	Leukaemia, CNS tumours, and lymphoma (3 main types of childhood cancer together)	NO_2 (in 1000 ppb-days) during childhood*			Matched by sex, age, and calendar time. Adjustment for urban development, geographical region, type of residence, electromagnetic fields, mother's age, and birth order	Incidence. Cases: 0–14 yr. Cumulative air pollution exposure over addresses during childhood. Similar results for exposure of mother during pregnancy. *Cut-off points for exposure categories were set at the 50th, 90th, and 99th percentiles
						< 11.5	955	1.0 (ref)		
						11.5–29.4	679	1.1 (0.9–1.3)		
						29.4–57.8	145	1.1 (0.8–1.5)		
						≥ 57.8	17	1.2 (0.6–2.3)		
						Number of vehicles/ day during childhood (time-weighted average)				
						< 500	1142	1.0 (ref)		
						≥ 10 000	27	1.0 (0.7–1.6)		
Reynolds et al. (2004) California, USA, 1988–1997	4369	8730	Population; birth certificates	Road density (miles) and traffic density (vehicle miles travelled per square mile) within 152 m of address at time of birth	All cancers	Quartile 1		1.0 (ref)	Matched by age and sex. Adjustment for race and ethnicity. Little effect of further adjustment for mother's age, birth weight, neighbourhood income, or county-level benzene emissions	Incidence. Cases: 0–4 yr. Successful validation of the exposure assessment method reported
						Road density ≥ 90th percentile		0.87 (0.75–1.00)		
						Traffic density ≥ 90th percentile		0.92 (0.80–1.06)		

CI, confidence interval; CNS, central nervous system; CO, carbon monoxide; h, hour or hours; IQR, interquartile range; NO_2, nitrogen dioxide; NR, not reported; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; ref, reference; SES, socioeconomic status; yr, year.

(b) Childhood leukaemia and lymphoma

See Table 2.11, Table 2.12, and Table 2.13.

Savitz et al. (1988) and Savitz & Feingold (1989) (see description in Section 2.5.1a) reported odds ratios of 3.1 (95% CI, 1.2–8.0) for all cancers combined and 4.7 (95% CI, 1.6–13.5) for leukaemia in association with 10 000 vehicles or more per day, compared with fewer than 500 vehicles per day, and 0.7 (95% CI, 0.2–3.0) for lymphoma.

A total of 142 cases of all types of childhood cancer were identified in the Swedish Cancer Registry among 127 000 children living within 300 m of transmission lines in Sweden (Feychting et al., 1998). Among the children living within the power line corridor, identified by the Swedish Population Registry, 550 controls were randomly selected and matched to cases by calendar time, geographical area, and residence near the same power line. The study used information on traffic density, street type, traffic speed, street width, and distance between the house and the street to model NO_2 at the latest home addresses within the power line corridor. The study noted elevated risk of incident childhood cancers among children living at addresses with high concentrations of NO_2. When NO_2 concentrations of 50 μg/m^3 or more were compared with concentrations of less than 40 μg/m^3, the odds ratios were 2.7 (95% CI, 0.9–8.5) for all cancers combined, 2.7 (95% CI, 0.3–20.6) for leukaemia, and 5.1 (95% CI, 0.4–61.2) for CNS tumours; NO_2 concentrations of 80 μg/m^3 or more were associated with an odds ratio for all cancers of 3.8 (95% CI, 1.2–12.1). There was indication of a linear exposure–response relationship. Further adjustment for electromagnetic fields and socioeconomic position had little impact on the results. [A strength of this study was the use of an air pollution model. Limitations included imprecise risk estimates due to the relatively few cases and no validation of the exposure model (i.e. no comparison between modelled and measured concentration).]

In a population-based study, Raaschou-Nielsen et al. (2001) identified 1989 cases of leukaemia, lymphoma, and CNS tumours in the Danish Cancer Registry and randomly selected 5506 controls from among the whole Danish childhood population using the Danish Population Registry. Controls were matched to cases by sex, age, and calendar time. The residential history of each child was traced from 9 months before birth to the time of diagnosis. NO_2 and benzene concentrations were calculated from a validated model based on traffic and the configuration of the street and buildings at the address, emission factors of the Danish car fleet, meteorological variables, and the background air pollution concentration. The analyses adjusted for urban development, geographical region, type of residence, electromagnetic fields, mother's age, and birth order. For exposure to NO_2 between the 90th and 99th percentile or above the 99th percentile compared with below the 50th percentile, the respective relative risks were 1.1 (95% CI, 0.8–1.5) and 1.2 (95% CI, 0.6–2.3) for all three cancer types combined, 1.3 (95% CI, 0.8–2.3) and 0.4 (95% CI, 0.1–1.3) for leukaemia, 0.8 (95% CI, 0.5–1.5) and 1.0 (95% CI, 0.3–3.1) for CNS tumours, and 1.8 (95% CI, 0.7–4.3) and 4.7 (95% CI, 1.2–17.6) for lymphomas. The results also indicated no associations with exposure to benzene concentrations or traffic density either in utero or during childhood. [The Working Group noted several strengths of this study, including the large sample size, assessment of cumulative exposure over all addresses during pregnancy and childhood, successful validation of the exposure assessment method, and a low potential for bias.]

Langholz et al. (2002) evaluated the amount of traffic near the residence of children (0–10 years) who developed leukaemia (n = 212) and controls (n = 202) from an earlier study of electromagnetic fields (London et al., 1991) in the Los Angeles area, which has some of the heaviest traffic loads in the USA. Cases were ascertained

by the Los Angeles County Cancer Surveillance Programme, and controls, matched to cases by age and sex, were either friends or identified by random-digit dialling. Exposure was assessed as a distance-weighted metric of the total amount of traffic within 457 m (1500 feet) of the home address where the child had lived for the longest time. Although an increased risk of leukaemia was observed in the upper quintile compared with the lowest quintile (RR, 1.4; 95% CI, 0.7–3.0; adjustment for wire coding), no exposure–response association was observed; the second quintile was associated with the highest risk. Further adjustment for magnetic fields and other variables had little impact on the results. (The "other variables" were not specified in the article, which referred to an Interim Report from the Electric Power Research Institute; EPRI EN-7464.) [Several weaknesses were noted, including the selection of controls and friends, which could lead to selection bias, and the use of a crude exposure measure.]

A small study of leukaemia incidence was undertaken in Varese, Italy (Crosignani et al., 2004). A total of 120 cases were identified in the population-based Lombardy Cancer Registry, and 480 population controls were selected from the population-based Health Service Archives and matched to cases by age and sex. Benzene concentration at the address at diagnosis was calculated on the basis of traffic density on surrounding roads and the distances from the home address to roads with heavy traffic. When benzene concentrations of more than 10 μg/m^3 were compared with concentrations of less than 0.1 μg/m^3, the relative risk was 3.9 (95% CI, 1.4–11.3; 7 exposed cases; adjusted for socioeconomic status of the municipality) and there was a trend across the three exposure categories. [The exposure model was a strength of the study. Limitations included a small number of cases and the lack of validation of the exposure model.]

A large, state-wide study in California, USA, evaluated risk relationships for incident cancers among young children (0–4 years) (Reynolds et al., 2004). A total of 4369 cases of all types of cancer were identified in the population-based Californian Cancer Registry, and 8730 population controls were selected using birth certificates. Controls were matched to cases by age and sex. Road and traffic density was assessed within 152 m of the address at the time of birth. For leukaemia, the odds ratio was 0.79 (95% CI, 0.63–1.00) in association with road density and 0.92 (95% CI, 0.73–1.15) in association with traffic density, for the upper 10% compared with the lowest quartile. Similarly, no association was found for all cancers combined or for CNS tumours. Thus, the study found no evidence for an association with traffic near the mother's residence at the time of the child's birth, after adjustment for race and ethnicity. Further adjustment for mother's age, birth weight, neighbourhood income, or county-level benzene emissions had little effect on the results. The exposure assessment method was successfully validated against benzene measurements. [Strengths of this study are that it was large and state-wide, that it had a low potential for bias, and that the exposure assessment method was successfully validated.]

Von Behren et al. (2008) studied the incidence of acute lymphocytic leukaemia among children in northern and central California, USA, in association with traffic load at the residence at the time of birth, at the time of diagnosis, and a time-weighted average over all addresses during childhood. A total of 310 cases were recruited at hospitals, and 396 population controls were selected from birth certificates and matched to cases by age, sex, Hispanic ethnicity, mother's race, and county of birth. Exposure was defined as the total number of vehicle miles travelled within 152 m of the residence. After adjustment for household income, for the upper quartile of exposure compared with the "no road traffic" category, the odds ratio was 1.1 (95% CI, 0.7–1.8) for the address at birth, 1.2 (95% CI, 0.8–1.8) for the address at diagnosis, and 1.2 (95% CI, 0.7–2.1)

for all addresses. The exposure assessment method was successfully validated against measurements. [Strengths of this study include the use of all addresses in the exposure assessment and the validation of the exposure measurements.]

Steffen et al. (2004) identified 280 cases of acute leukaemia at hospitals in France and used 285 children hospitalized for acute pathologies as controls. Controls were matched to cases by age, sex, ethnic origin, hospital centre, and urban or rural setting. Mothers of case and control children were interviewed about heavy-traffic roads near addresses during childhood, neighbouring automotive repair garages or petrol stations, and many other potential risk factors. The odds ratios were 4.0 (95% CI, 1.5–10.3) for living neighbouring a repair garage or petrol station and 1.3 (95% CI, 0.6–2.9) for living near a motorway. Adjustment for family history of solid tumours or haematological neoplasms, early infections, day-care attendance, breastfeeding, and high-traffic roads did not modify the association. [Several limitations of the study were noted, including potential selection bias resulting from the use of hospital-based controls, potential recall bias resulting from the interview-based exposure assessment, and the lack of certainty as to how the crude exposure measures relate to air pollution exposure.]

Brosselin et al. (2009) further investigated the hypothesis of an association between acute leukaemia and residence near petrol stations and automotive repair garages in a new independent nationwide study in France including 765 cases of acute leukaemia from hospitals and 1681 controls selected from national telephone lists (landlines only). Mothers of case and control children were interviewed about proximity of the home to automotive repair garages, petrol stations, and other businesses, and many other potential risk factors during childhood. The study showed an increased risk for living neighbouring a repair garage or petrol station (OR, 1.6; 95% CI, 1.2–2.2) after adjustment for age, sex, number of children in the household, degree of urban development, and type of housing. [A strength of the study is its large sample size. Limitations include potential recall bias resulting from the interview-based exposure assessment, the use of a crude exposure measure, and potential selection bias due to the fact that lists of landline telephones would probably not cover the total base population. This study overlaps with Amigou et al. (2011).]

Amigou et al. (2011) assessed the association between acute leukaemia and traffic or NO_2 near the residence using many of the same methods as Brosselin et al. (2009) but applying objective approaches for NO_2 assessment in local 4 km^2 grids, proximity to roads, and road density within 500 m of the address at diagnosis. Controls were matched to cases by age and sex, and the results were adjusted for socioeconomic status. The study found positive associations between all three measures for air pollution and acute leukaemia; the odds ratios were 2.0 (95% CI, 1.0–3.6) for a high score on the index for proximity to main roads compared with the unexposed category, 2.2 (95% CI, 1.1–4.2) for a high score on the index for heavy-traffic roads within 500 m compared with the unexposed category, and 1.2 (95% CI, 1.0–1.5) for traffic-related NO_2 of 16.2 $\mu g/m^3$ or more compared with less than 12.2 $\mu g/m^3$. Further adjustment for degree of urban development, type of housing, birth order, infections, pesticide use, and parental smoking did not change the results. [The large sample size is a strength of this study. Limitations include potential selection bias resulting from the fact that lists of landline telephones would probably not cover the total base population, the use of crude exposure measures, and the lack of validation of the NO_2 model.]

Associations of childhood leukaemia with several indicators of exposure to air pollution were reported in several papers from Taiwan, China. Weng et al. (2008b) studied leukaemia mortality in association with the same industry index at the municipality level (405 cases and

405 controls), petrol-station density, defined as number of petrol stations divided by the area of the municipality (729 cases and 729 controls) (Weng et al., 2009), and NO_2 measured at monitoring stations in 64 municipalities (308 cases and 308 controls) (Weng et al., 2008a). Controls were selected from among all people who had died due to non-neoplastic, non-respiratory diseases and were matched to cases by sex, year of birth, and year of death. Results were adjusted for the urbanization level of the municipality. Among those aged 0–19 years, the odds ratio was 1.75 (95% CI, 1.00–3.06) for the highest quartile of 226 more-rural municipalities compared with the lowest quartile of scores for the petrochemical air pollution index and 1.26 (95% CI, 0.70–2.26) for the non-petrochemical industry index (Weng et al., 2008b). The two industrial indices were mutually adjusted. [Limitations of the study are the use of mortality and the uncertainty as to how the air pollution indices relate to concentrations at participants' addresses since no validation is presented.]

The highest tertile of the municipality petrol-station density index was associated with a significantly higher risk of death due to leukaemia among children aged 0–14 years (OR, 1.91; 95% CI, 1.29–2.82) (Weng et al., 2009). [The study is large but is limited by the use of mortality and the uncertainty as to how the petrol-station density index relates to concentrations at participants' addresses since no validation is presented.]

A related paper (Weng et al., 2008a) reported leukaemia mortality among children aged 0–14 years to be associated with the highest tertile of annual mean concentrations of NO_2 at municipal monitoring stations compared with the lowest tertile of municipalities (OR, 2.29; 95% CI, 1.44–3.64). [This study is limited by the use of mortality, the lack of information on location (street or background) of the monitoring stations, and the uncertainty as to how the concentrations monitored in the different municipalities reflect population exposure.]

In another study from Taiwan, China, Yu et al. (2006) studied incidence of leukaemia among children aged 0–19 years in metropolitan Kaohsiung. Cases (n = 131) were identified at the large hospitals in the area, and controls were selected from a population registry and matched to cases by age and sex. Assessment of exposure to petrochemical air pollution was improved over previous methods by using an exposure opportunity score based on the assessment of all addresses held for more than 1 year for distance to petrochemical plant(s), prevailing wind direction, and multiple sources of petrochemical pollution. The odds ratios for an association with the exposure opportunity score were 1.04 (95% CI, 0.79–1.38) for all leukaemias and 1.21 (95% CI, 0.89–1.65) for acute lymphocytic leukaemia. Further adjustment for parental occupation in the petrochemical industry had little impact on the results. [This study is limited by the small sample size. The Working Group noted that although the exposure assessment method is more sophisticated compared with the simple petrochemical index used in other studies, it is uncertain how the exposure opportunity score relates to concentrations at participants' addresses since no validation is presented.]

In Australia, Bailey et al. (2011) studied parental non-occupational refuelling of a car the year before and during pregnancy, as a surrogate for exposure to benzene, a potential risk factor for childhood acute lymphoblastic leukaemia. A total of 389 cases were ascertained from the Australian paediatric oncology centres, and population controls were selected using random-digit dialling. Information about exposure was collected by questionnaire. The odds ratios for acute lymphoblastic leukaemia in the offspring were 0.82 (95% CI, 0.57–1.20) for refuelling by the mother (ever vs never) and 1.56 (95% CI, 0.65–3.77) for refuelling by the father (ever vs never) after adjustment for age, sex, state, and education level. Further adjustment for income, ethnicity, birth order, parental age, birth defects,

and paternal smoking had little impact on the results. [The Working Group noted that the use of random-digit dialling for selection of controls could lead to selection bias, the assessment of exposure by questionnaire could lead to recall bias, the exposure measures were crude, and there was uncertainty as to how these related to the exposure of participants.]

In the Emilia-Romagna region, in northern Italy, Vinceti et al. (2012) identified 83 incident cases of acute leukaemia among children aged 0–14 years in the population-based cancer registry of the Italian Association of Paediatric Haematology and Oncology and selected 332 population controls individually matched to cases by sex, year of birth, and province of residence. Traffic-related benzene and PM_{10} concentrations were estimated by the CALINE4 dispersion model at the addresses at the time of diagnosis. Modelled concentrations were validated against those measured at fixed-site monitoring stations. For the highest compared with the lowest exposure categories, the odds ratios were 1.8 (95% CI, 0.9–3.7) for benzene and 1.8 (95% CI, 0.8–3.9) for PM_{10}. Stronger, statistically significant results were found for children younger than 5 years. [A strength of this study was the use of a validated exposure model. A limitation was the small sample size, resulting in wide confidence intervals.]

In a nationwide case–control study in Italy, Badaloni et al. (2013) studied leukaemia among children aged 0–10 years in association with traffic and air pollutants at the residence. A total of 747 eligible cases from 14 out of 20 Italian regions were identified through the national childhood cancer registry of the Italian Association of Paediatric Haematology and Oncology and the National Paediatric Oncology Task Force, and 1509 controls were randomly selected from the population and matched to cases by birth data, sex, and region; 91% of the cases and 69% of the controls participated. Information about residential history and individual-level potential confounders was collected by face-to-face interviews. $PM_{2.5}$ concentration was estimated by a national dispersion model with 4 km × 4 km resolution. Concentrations of NO_2, PM_{10}, and ozone were estimated by land-use regression models with 100 m × 100 m resolution. Increased risks for leukaemia were not found regardless of the exposure measure applied: the odds ratio for the highest quartile compared with the lowest quartile was 0.85 (95% CI, 0.61–1.18) for NO_2 and 1.00 (95% CI, 0.70–1.41) for PM_{10}. Similar negative results were found in several sensitivity analyses. [Strengths of this study include the large sample size, the nationwide coverage, and a detailed exposure assessment that was successfully validated. However, this study may be affected by selection bias due to the large difference in participation rate between cases and controls.]

(c) Other childhood cancers

Data for childhood CNS tumours are presented in Table 2.14; data for other childhood cancers are presented in Table 2.15.

Associations of childhood CNS tumours with indicators of exposure to air pollution were investigated in the previously cited studies by Savitz & Feingold (1989) and Feychting et al. (1998). No significant association was found.

In a large study in Los Angeles County, California, USA, Ghosh et al. (2013) investigated incident cancer among children aged 0–5 years in association with exposure to NO, NO_2, and NO_x during pregnancy. A total of 4015 cases of all types of cancer diagnosed between 1988 and 2008 were identified in the California Cancer Registry that could be linked to birth certificates (11% of identified cases could not be linked and were excluded), and 80 658 population controls were selected using birth certificates. Land-use regression models were successfully validated and used to calculate the annual mean levels of NO, NO_2, and NO_x at the address at birth. Monthly variation was estimated from data from

the nearest monitoring station. Risk of childhood cancer was analysed per linear increase of 25 ppb during pregnancy. Among 19 types of childhood cancer assessed, only rare bilateral retinoblastoma showed a statistically significant result for exposure during the third trimester. For acute lymphoblastic leukaemia, the odds ratios were 1.08 (95% CI, 1.01–1.16) for NO_x, 1.23 (95% CI, 0.98–1.53) for NO_2, and 1.09 (95% CI, 1.01–1.18) for NO. For acute myeloid leukaemia, the odds ratios were 0.88 (95% CI, 0.73–1.07) for NO_x, 0.71 (95% CI, 0.39–1.30) for NO_2, and 0.84 (95% CI, 0.65–1.09) for NO. The results were adjusted for sex, year of birth, mother's age, race/ethnicity, education level, parity, prenatal care, insurance type, and socioeconomic score of the census block. Further adjustment for prenatal care, mother's birthplace, father's race, father's education level, child's birth weight, and birth season had little impact on the results. [Strengths of this study include the large sample size and the validated exposure assessment method. Limitations include the possibility of chance findings resulting from multiple testing and the potential for selection bias if the 11% of cases that were excluded differed from the included cases with respect to air pollution exposure.]

Heck et al. (2013) used the California Cancer Registry to identify incident childhood (0–5 years) cancer cases born and diagnosed in 1998–2007; 3590 cases (89%) that could be matched to California birth certificates were included, and 80 224 controls were randomly selected directly from the California birth rolls. Concentrations of CO, NO_x, and $PM_{2.5}$, considered markers of the traffic-related air pollution mix, were modelled by the validated CALINE4 dispersion model. The exposure metrics assessed included residence of the child within 8 km of a fixed-site monitoring station, $PM_{2.5}$ concentrations from these monitors, and traffic density within 500 m of the residence. The analyses were adjusted for year of birth, parental race/ethnicity, mother's education level, mother's county of birth, method of payment for prenatal care, and neighbourhood socioeconomic status index. Among the 16 different types of childhood cancer assessed, the odds ratios for an IQR increase in exposure during pregnancy of CO and $PM_{2.5}$, respectively, were 1.05 (95% CI, 1.01–1.10) and 1.10 (95% CI, 0.92–1.30) for acute lymphoblastic leukaemia, 1.16 (95% CI, 1.02–1.33) and 1.46 (95% CI, 0.70–3.06) for bilateral retinoblastoma, and 1.26 (95% CI, 1.12–1.41) and 0.77 (95% CI, 0.36–1.68) for germ cell tumours of the teratoma type. The odds ratios for acute lymphoblastic leukaemia in association with CO were similar for Los Angeles County (1.06; 95% CI, 1.00–1.12) and the rest of the state (1.08; 95% CI, 0.99–1.17). For acute myeloid leukaemia, the odds ratios for an IQR increase in exposure during pregnancy were 0.85 (95% CI, 0.73–0.98) for CO and 0.85 (95% CI, 0.57–1.27) for $PM_{2.5}$. There was some consistency with the results presented by Ghosh et al. (2013) since both studies showed increased risk of acute lymphoblastic leukaemia and retinoblastoma and decreased risk of acute myeloid leukaemia. [About one third of the study population overlapped with that investigated by Ghosh et al. (2013) (Julia Heck, personal communication), and the results from these two studies are therefore not independent, except for the acute lymphoblastic leukaemia result for California excluding Los Angeles County, where no overlap in study population existed. Strengths of this study include the large sample size, the statewide enrolment, and a validated exposure model. Limitations include the possibility of chance findings resulting from multiple testing, the small numbers of rare cancers, and the potential for selection bias if the 11% of cases that could not be matched to birth certificates differed from the included cases with respect to air pollution exposure.]

Table 2.11 Case–control studies of childhood leukaemia and outdoor air pollution

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Savitz & Feingold (1989) Denver, Colorado, USA, 1976–1983	328	262	Population; random-digit dialling	Traffic counts at home address at time of diagnosis	Leukaemia	≥ 500 vehicles/day ≥ 5000 vehicles/day ≥ 10 000 vehicles/day	17 13 8	2.1 (1.1–4.0) 2.7 (1.3–5.9) 4.7 (1.6–13.5)	Matched by age, sex, and area	Incidence. 0–14 yr. Adjustment in a subset for sex, age, year of diagnosis, type of residence, location at birth, mother's age, father's education level, per capita income, and wire configuration had little effect on the risk estimates
Feychting et al. (1998) Sweden	142	550	Population; randomly selected from among children living within 300 m of high-voltage power lines	Modelled peak concentrations of NO_2 (99th percentile of 1-h means). Based on latest address within the power line corridor	Leukaemia	40–49 μg/m³ ≥ 50 μg/m³	7 9	1.7 (0.2–14.6) 2.7 (0.3–20.6)	Matched by calendar time, geographical area, and residence near same power line	Incidence. Cases: 0–15 yr; identified among children living within 300 m of high-voltage power lines. Similar effects for boys and girls

Table 2.11 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Raaschou-Nielsen et al. (2001) Denmark, 1968–1991	1989	5506	Randomly selected from whole population	Traffic density and modelled NO_2 and benzene at home addresses from time of conception to time of diagnosis	Leukaemia, CNS tumours, and lymphoma	NO_2 (in 1000 ppb-days) during childhood*			Matched by sex, age, and calendar time. Adjustment for urban development, geographical region, type of residence, electromagnetic fields, mother's age, and birth order	Incidence. Cases: 0–14 yr. Cumulative air pollution exposure over addresses during childhood. Similar results for exposure of mother during pregnancy. Successful validation of the exposure assessment method was reported *Cut-off points for exposure categories were set at the 50th, 90th, and 99th percentiles
						< 11.5	585	1.0 (ref)		
						11.5–29.4	237	0.9 (0.7–1.3)		
						29.4–57.8	58	1.3 (0.8–2.3)		
						≥ 57.8	3	0.4 (0.1–1.3)		
						Number of vehicles/ day during childhood (time-weighted average)				
						< 500	566	1.0 (ref)		
						≥ 10 000	14	1.1 (0.6–2.2)		
Langholz et al. (2002) Los Angeles County, California, USA, 1978–1984	212	202	Population; a friend, or selected by random-digit dialling	Sum of traffic counts (vehicles/ day) at all streets within 457 m of home address at which the child had resided the longest; a distance-weighted metric was used	Leukaemia	< 2301	35	1.0 (ref)	Matched by age and sex. Adjustment for wire coding	Incidence. Cases: 0–10 yr. Quintiles were used for cut-off points between exposure categories. Overlaps with London et al. (1991)
						2301–5997	45	1.6 (0.8–3.6)		
						5997–13 264	43	1.1 (0.5–2.4)		
						13 264–28 497	43	1.1 (0.5–2.2)		
						≥ 28 497	46	1.4 (0.7–3.0)		

Table 2.11 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Crosignani et al. (2004) Province of Varese, Italy, 1978–1997	120	480	Population; Health Service archives	Modelled concentration of benzene (μg/m³) outside the residence at time of diagnosis	Leukaemia	< 0.1 0.1–10 > 10	88 25 7	1.0 (ref) 1.5 (0.9–2.5) 3.9 (1.4–11.3)	Matched by age and sex. Adjustment for SES of the municipality	Incidence. Cases: 0–14 yr. P_{trend} = 0.005
Reynolds et al. (2004) California, USA, 1988–1997	4369	8730	Population; birth certificates	Road density (miles) and traffic density (vehicle miles travelled per square mile) within 152 m of address at time of birth	Leukaemia	Quartile 1 Road density ≥ 90th percentile Traffic density ≥ 90th percentile		1.0 (ref) 0.79 (0.63–1.00) 0.92 (0.73–1.15)	Matched by age and sex. Adjustment for race and ethnicity. Little effect of further adjustment for mother's age, birth weight, neighbourhood income, or county-level benzene emissions	Incidence. Cases: 0–4 yr.
Yu et al. (2006) Kaohsiung, Taiwan, China, 1997–2003	131	314	Population register	Exposure opportunity score based on distance to petrochemical plant(s), prevailing wind direction, and multiple petrochemical pollution sources. Based on all addresses held for >1 yr	Leukaemia	Log-linear analyses (i.e. relative risk per 1-unit increase in the log-transformed exposure opportunity score)		All leukaemias 1.04 (0.79–1.38)	Matched by age and sex. Adjustment for mother's educational status	Incidence. Cases: 0–19 yr.

Table 2.11 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Weng et al. (2008a) Taiwan, China, 1995–2005	308	308	Selected from among all who had died due to non-neoplastic, non-respiratory diseases	Mean NO_2 concentrations measured in 1995–2005 in 64 municipalities with monitoring stations. Residence at time of death was used	Leukaemia	≤ 20.9 ppb ≥ 26.3 ppb	88 117	1.00 (ref) 2.29 (1.44–3.64)	Matched by sex, year of birth, and year of death. Adjustment for urbanization level of municipality	Mortality. Cases: 0–14 yr. Location (street or background) of the monitoring stations is not described. Tertiles of NO_2 concentration used in analyses. P_{trend} < 0.001. Overlaps with Weng et al. (2008b)
Weng et al. (2008b) Taiwan, China, 1995–2005	405	405	Selected from among all who had died due to non-neoplastic, non-respiratory diseases	Number of workers in, respectively, petrochemical industry and non-petrochemical manufacturing divided by the total population of the municipality. Residence at time of death was used	Leukaemia	Petrochemical air pollution index ≤ 25th percentile > 75th percentile Non-petrochemical air pollution index ≤ 25th percentile > 75th percentile	 96 116 88 109	 1.00 (ref) 1.75 (1.00–3.06) 1.00 (ref) 1.26 (0.70–2.26)	Matched by sex, year of birth, and year of death. Adjustment for urbanization level of municipality. Results for petrochemical air pollution were adjusted for non-petrochemical air pollution and vice versa	Mortality. Cases: 0–19 yr. Study included 226 more-rural municipalities out of 361 municipalities of Taiwan, China. Overlaps with Weng et al. (2008a)

Table 2.11 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Weng et al. (2009) Taiwan, China, 1996–2006	729	729	Selected from among all who had died due to non-neoplastic, non-respiratory diseases	Petrol-station density of municipality (i.e. number of petrol stations divided by the area of the municipality). Residence at time of death was used	Leukaemia	Lowest tertile Highest tertile	179 312	1.00 (ref) 1.91 (1.29–2.82)	Matched by sex, year of birth, and year of death. Adjustment for urbanization level of municipality	Mortality. Cases: 0–14 yr.
Badaloni et al. (2013) Italy, 1998–2001	620	957	Population	(i) Distance to main roads and length of main roads within 100 m; (ii) $PM_{2.5}$ from national dispersion model (4 km × 4 km resolution); (iii) NO_2, PM_{10}, and O_3 from LUR models (100 m × 100 m resolution). Birth address used for primary analyses	Leukaemia	Distance from main road > 150 m 50–149 m < 50 m Main road distance < 100 m No main roads 1st tertile 2nd tertile 3rd tertile	 209 190 221 296 122 94 108	 1.00 1.05 (0.80–1.36) 0.80 (0.62–1.02) 1.00 1.07 (0.80–1.41) 0.69 (0.51–0.92) 0.91 (0.68–1.21)	Age, sex, region, and parental education level	Incidence. Cases: 0–10 yr.

Table 2.11 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Badaloni et al. (2013) Italy, 1998–2001 (cont.)						NO_2				
						1st quartile	158	1.00		
						2nd quartile	160	1.09 (0.81–1.46)		
						3rd quartile	161	1.03 (0.76–1.39)		
						4th quartile	141	0.85 (0.61–1.18)		
						$PM_{2.5}$				
						1st quartile	155	1.00		
						2nd quartile	171	1.18 (0.88–1.59)		
						3rd quartile	136	0.75 (0.54–1.04)		
						4th quartile	158	1.00 (0.72–1.39)		

CI, confidence interval; CNS, central nervous system; h, hour or hours; LUR, land-use regression; NO_2, nitrogen dioxide; O_3, ozone; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; ref, reference; SES, socioeconomic status; yr, year.

Table 2.12 Case–control studies of childhood acute leukaemia and outdoor air pollution

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Steffen et al. (2004) Nancy, Lille, Lyon, and Paris, France, 1995–1999	280	285	Hospital; among children with acute pathologies	Interview with mothers about heavy-traffic road within 50 m of the residence, neighbouring automotive repair garage or petrol station, etc. All addresses until diagnosis were used	Acute leukaemia	Motorway < 50 m No Yes Neighbouring business No Yes, repair garage or petrol station	 14 249 17	 1.0 (ref) 1.3 (0.6–2.9) 1.0 (ref) 4.0 (1.5–10.3)	Matched by age, sex, ethnic origin, hospital centre, and urban or rural setting	Incidence. Cases: 0–14 yr.
Yu et al. (2006) Kaohsiung, Taiwan, China, 1997–2003	131	314	Population register	Exposure opportunity score based on distance to petrochemical plant(s), prevailing wind direction, and multiple petrochemical pollution sources. Based on all addresses held for > 1 yr	Acute lymphocytic leukaemia	Log-linear analyses (i.e. relative risk per 1-unit increase in the log-transformed exposure opportunity score)		1.21 (0.89–1.65)	Matched by age and sex. Adjustment for mother's educational status	Incidence. Cases: 0–19 yr.

Table 2.12 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Von Behren et al. (2008) Northern and central California, USA, 1995–2002	310	396	Population; birth certificate files	Vehicle miles travelled within 152 m of the address at birth, the address at diagnosis, and a time-weighted average over all addresses during childhood. Based on all addresses during childhood	Acute lymphocytic leukaemia	*Address at birth* No road traffic ≥ 75th percentile *Address at diagnosis* No road traffic ≥ 75th percentile *All addresses* No road traffic ≥ 75th percentile	 93 56 129 70 63 52	 1.0 (ref) 1.1 (0.7–1.8) 1.0 (ref) 1.2 (0.8–1.8) 1.0 (ref) 1.2 (0.7–2.1)	Matched by age, sex, Hispanic ethnicity, mother's race, and county of birth. Adjustment for household income	Incidence. Cases: 0–14 yr.
Brosselin et al. (2009) France, 2003–2004	765	1681	Population; French national telephone directory	Interview with mothers about proximity of the home to automotive repair garages, petrol stations, other businesses, etc. All addresses until diagnosis were used	Acute leukaemia	Address next to automotive repair garage or petrol station Never Ever	 689 76	 1.0 (ref) 1.6 (1.2–2.2)	Adjustment for age, sex, number of children in the household, degree of urban development, and type of housing	Incidence. Cases: 0–14 yr. Overlaps with Amigou et al. (2011)

Table 2.12 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Amigou et al. (2011) France, 2003–2004	762	1681	Population; national telephone lists (landlines)	Traffic indicators: indices based on function classes of roads within 500 m of the residence. NO_2: national smoothed maps of NO_2 in 4 km^2 grids, modelled from road, transportation, and emission data. Inverse-distance-weighted average of concentrations at grid-square centres within 3 km of each address. Address at diagnosis was used	Acute leukaemia	Index for proximity to main roads			Matched by age and sex. Adjustment for SES	Incidence. Cases: 0–14 yr. Results persisted after exclusion of children with Down syndrome, those having lived closed to a gas station, and with poor precision in geocoding of the address. Overlaps with Brosselin et al. (2009)
						Unexposed	282	1.0 (ref)		
						High	22	2.0 (1.0–3.6)		
						Index for length of heavy-traffic roads within 500 m				
						Unexposed	547	1.0 (ref)		
						High	19	2.2 (1.1–4.2)		
						Traffic-related NO_2				
						< 12.2 µg/m	337	1.0 (ref)		
						≥ 16.2 µg/m^3	204	1.2 (1.0–1.5)		

Table 2.12 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Bailey et al. (2011) Australia, 2003–2007	389	876	Population; random-digit dialling	Information about frequency of refuelling a vehicle the year before and during pregnancy	Acute lymphocytic leukaemia	Refuelling of vehicle by mother in the year before or during pregnancy			Adjustment for age, sex, state, and education level	Incidence. Cases: 0–14 yr. No associations appeared in subanalyses by frequency of refuelling and type of fuel (petrol, diesel, liquefied petroleum gas).
						Never		1.00 (ref)		
						Ever		0.82 (0.57–1.20)		
						Refuelling of vehicle by father in the year before pregnancy				
						Never		1.00 (ref)		
						Ever		1.56 (0.65–3.77)		
Vinceti et al. (2012) Emilia-Romagna region, northern Italy, 1998–2009	83	332	Population; registry	CALINE4 dispersion model estimating exposure to benzene and PM_{10} from road traffic. Based on address at diagnosis	Acute leukaemia	Average benzene level ($\mu g/m^3$)			Matched by sex, year of birth, and province of residence	Incidence. Cases: 0–14 yr. Linear trends were not statistically significant. Stronger (and statistically significant) associations for children < 5 yr
						< 0.10	16	1.0 (ref)		
						0.10–0.25	18	1.1 (0.5–2.3)		
						0.25–0.50	17	1.2 (0.5–2.7)		
						> 0.50	32	1.8 (0.9–3.7)		
						Average PM_{10} level ($\mu g/m^3$)				
						< 2.5	18	1.0 (ref)		
						2.5–5.0	16	1.1 (0.5–2.3)		
						5.0–7.5	21	1.6 (0.8–3.4)		
						> 7.5	28	1.8 (0.8–3.9)		

Table 2.12 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Ghosh et al. (2013) Los Angeles County, California, USA, 1988–2008	4015	80 658	Population; birth records	Modelled NO, NO_2, and NO_x at address at birth. Monthly variation was estimated from data from the nearest monitoring station to create "seasonalized" exposure measures for the pregnancy period and for each trimester	Acute lymphoblastic leukaemia (n = 1346)	Linear analyses per 25 ppb increment during pregnancy (seasonalized exposure measure)			Adjustment for sex, year of birth, mother's age, race/ethnicity, education level, parity, prenatal care, insurance type, and socioeconomic score of the census block	Incidence. Cases: 0–5 yr. Among analyses of 15 other types of childhood cancer, only bilateral retinoblastoma showed a statistical significant result, and only so for exposure during the third trimester. No association was found with acute lymphoblastic leukaemia (ALL) when using the unseasonalized exposure measure.
						NO		1.09 (1.01–1.18)		
						NO_2		1.23 (0.98–1.53)		
						NO_x		1.08 (1.01–1.16)		
					Acute myeloid leukaemia (n = 217)					
						NO		0.84 (0.65–1.09)		
						NO_2		0.71 (0.39–1.30)		
						NO_x		0.88 (0.73–1.07)		

Table 2.12 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Heck et al. (2013) California, USA, 1998–2007	3590	80 224	Population; randomly selected from California birth rolls	Exposure estimated during pregnancy and during first year of life. CO estimated with dispersion model using traffic < 1.5 km as input. $PM_{2.5}$ during pregnancy estimated from central monitors within 8 km. Traffic density within 500 m of the residence was estimated. Birth address used in exposure assessment	Acute lymphoblastic leukaemia	CO	1280	1.05 (1.01–1.10)	Year of birth, parental race/ethnicity, mother's education level, mother's county of birth, method of payment for prenatal care, and neighbourhood SES index	Incidence, 0–5 yr, statewide study. High correlations between air pollution during all trimesters; only results for 1st trimester presented. Results were provided for 16 types of childhood cancer. Only types showing significant results in the fully adjusted model are shown in this table
						$PM_{2.5}$	397	1.10 (0.92–1.30)		
						Traffic density	1243	1.03 (1.00–1.07)		
					Acute myeloid leukaemia	CO	229	0.85 (0.73–0.98)		
						$PM_{2.5}$	82	0.85 (0.57–1.27)		
						Traffic density	224	0.89 (0.79–1.00)		

CI, confidence interval; CO, carbon monoxide; NO, nitrogen oxide; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 μm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; ref, reference; SES, socioeconomic status; yr, year.

Table 2.13 Case–control studies of childhood lymphoma and outdoor air pollution

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Savitz & Feingold (1989) Denver, Colorado, USA, 1976–1983	328	262	Population; random-digit dialling	Traffic counts at home address at time of diagnosis	Lymphoma	≥ 500 vehicles/day	2	0.7 (0.2–3.0)	Matched by age, sex, and area	Incidence. 0–14 yr. Adjustment in a subset for sex, age, year of diagnosis, type of residence, location at birth, mother's age, father's education level, per capita income, and wire configuration had little effect on the risk estimates
Raaschou-Nielsen et al. (2001) Denmark, 1968–1991	1989	5506	Randomly selected from whole population	Traffic density and modelled NO_2 and benzene at home addresses from time of conception to time of diagnosis	Leukaemia, CNS tumours, and lymphoma	NO_2 (in 1000 ppb-days) during childhood*			Matched by sex, age, and calendar time. Adjustment for urban development, geographical region, type of residence, electromagnetic fields, mother's age, and birth order	Incidence. Cases: 0–14 yr. Cumulative air pollution exposure over addresses during childhood. Similar results for exposure of mother during pregnancy. *Cut-off points for exposure categories were set at the 50th, 90th, and 99th percentiles
						< 11.5	75	1.0 (ref)		
						11.5–29.4	134	1.7 (1.0–3.0)		
						29.4–57.8	30	1.8 (0.7–4.3)		
						≥ 57.8	8	4.7 (1.2–17.6)		
						Number of vehicles/day during childhood (time-weighted average)				
						< 500	152	1.0 (ref)		
						≥ 10 000	3	1.3 (0.4–4.8)		

Table 2.13 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Ghosh et al. (2013) Los Angeles County, California, USA, 1988–2008	4015	80 658	Population; birth records	Modelled NO, NO_2, and NO_x at address at birth. Monthly variation was estimated from data from the nearest monitoring station to create "seasonalized" exposure measures for the pregnancy period and for each trimester	Non-Hodgkin lymphoma (n = 109)	Linear analyses per 25 ppb increment during pregnancy (seasonalized exposure measure) NO_x		0.98 (0.75–1.27)	Adjustment for sex, year of birth, mother's age, race/ethnicity, education level, parity, prenatal care, insurance type, and socioeconomic score of the census block	Incidence. Cases: 0–5 yr.

CI, confidence interval; CNS, central nervous system; NO, nitrogen oxide; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; ref, reference.

Table 2.14 Case–control studies of childhood central nervous system tumours and outdoor air pollution

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Savitz & Feingold (1989) Denver, Colorado, USA, 1976–1983	328	262	Population; random-digit dialling	Traffic counts at home address at time of diagnosis	CNS tumours	≥ 500 vehicles/day	9	1.7 (0.8–3.9)	Matched by age, sex, and area	Incidence. 0–14 yr.
Feychting et al. (1998) Sweden	142	550	Population; randomly selected from among children living within 300 m of high-voltage power lines	Modelled peak concentrations of NO_2 (99th percentile of 1-h means). Based on latest address within the power line corridor	CNS tumours	40–49 µg/m³ ≥ 50 µg/m³	6 11	1.0 (0.1–12.7) 5.1 (0.4–61.2)	Matched by calendar time, geographical area, and residence near same power line	Incidence. Cases: 0–15 yr; identified among children living within 300 m of high-voltage power lines. Similar effects for boys and girls

Table 2.14 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Raaschou-Nielsen et al. (2001) Denmark, 1968–1991	1989	5506	Randomly selected from whole population	Traffic density and modelled NO_2 and benzene at home addresses from time of conception to time of diagnosis	CNS tumours	NO_2 (in 1000 ppb-days) during childhood*			Matched by sex, age, and calendar time. Adjustment for urban development, geographical region, type of residence, electromagnetic fields, mother's age, and birth order	Incidence. Cases: 0–14 yr. Cumulative air pollution exposure over addresses during childhood.
						< 11.5	295	1.0 (ref)		
						11.5–29.4	308	1.1 (0.8–1.5)		
						29.4–57.8	57	0.8 (0.5–1.5)		
						≥ 57.8	6	1.0 (0.3–3.1)		
						Number of vehicles/ day during childhood (time-weighted average)				
						< 500	424	1.0 (ref)		
						≥ 10 000	10	0.9 (0.4–1.8)		
						Road density				
						≥ 90th percentile		1.03 (0.75–1.43)		
						Traffic density				
						≥ 90th percentile		1.22 (0.87–1.70)		

Table 2.14 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Liu et al. (2008b) Taiwan, China, 1995–2005	340	340	Selected from among all who had died due to non-neoplastic, non-respiratory diseases	Number of workers in, respectively, petrochemical industry and non-petrochemical manufacturing divided by the total population of the municipality. Residence at time of death	Brain	Petrochemical air pollution index Lowest tertile Highest tertile Non-petrochemical air pollution index Lowest tertile Highest tertile	 93 127 94 129	 1.00 (ref) 1.65 (1.00–2.73) 1.00 (ref) 1.41 (0.84–2.38)	Matched by sex, year of birth, and year of death. Adjustment for urbanization level of municipality. Results for petrochemical air pollution were adjusted for non-petrochemical air pollution and vice versa	Mortality. Cases: 0–29 yr. About half of cases were < 15 yr. Municipalities divided into tertiles
Ghosh et al. (2013) Los Angeles County, California, USA, 1988–2008	4015	80 658	Population; birth records	Modelled NO, NO_2, and NO_x at address at birth. Monthly variation was estimated from data from the nearest monitoring station to create "seasonalized" exposure measures for the pregnancy period and for each trimester	CNS tumours (n = 709)	Linear analyses per 25 ppb increment during pregnancy (seasonalized exposure measure) NO_x		0.96 (0.87–1.07)	Adjustment for sex, year of birth, mother's age, race/ethnicity, education level, parity, prenatal care, insurance type, and socioeconomic score of the census block	Incidence. Cases: 0–5 yr.

CI, confidence interval; CNS, central nervous system; h, hour or hours; IQR, interquartile range; NO, nitrogen oxide; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; PAHs, polycyclic aromatic hydrocarbons; ref, reference; yr, year.

Table 2.15 Case–control studies of other childhood cancers and outdoor air pollution

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Heck et al. (2013) California, USA, 1998–2007	3590	80 224	Population; randomly selected from California birth rolls	Exposure estimated during pregnancy and during first year of life. CO estimated with dispersion model using traffic < 1.5 km as input. $PM_{2.5}$ during pregnancy was estimated from central monitors within 8 km. Traffic density within 500 m of the residence was estimated. Birth address used in exposure assessment	Bilateral retinoblastoma	CO	87	1.16 (1.02–1.33)	Year of birth, parental race/ethnicity, mother's education level, mother's county of birth, method of payment for prenatal care, and neighbourhood SES index	Incidence, 0–5 yr, statewide study.
						$PM_{2.5}$	22	1.46 (0.70–3.06)		
						Traffic density	81	1.09 (0.97–1.24)		
					Germ cell tumours of the teratoma type	CO	72	1.26 (1.12–1.41)		
						$PM_{2.5}$	23	0.77 (0.36–1.68)		
						Traffic density	71	1.16 (1.04–1.30)		

CI, confidence interval; CO, carbon monoxide; IQR, interquartile range; NO_2, nitrogen dioxide; PAHs, polycyclic aromatic hydrocarbons; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 μm; SES, socioeconomic status; yr, year.

Table 2.16 Cohort studies of outdoor air pollution and risk estimates for cancers of the bladder, breast, colon, stomach, brain, and pancreas

Reference, study, location and period	Exposure	Relative risk (95% CI)					
		Bladder	Breast	Colon	Stomach	Brain	Pancreas
North America							
Harvard Six Cities Study							
McKean-Cowdin et al. (2009) USA	$PM_{2.5}$					0.91 (0.74–1.11)	
	PM_{10}					0.92 (0.82–1.03)	
	SO_2					0.82 (0.67–0.99)	
	NO_2					0.88 (0.81–0.96)	
	CO					0.81 (0.68–0.95)	
	O_3					1.02 (0.75–1.41)	
AHSMOG							
Beeson et al. (1998) USA	TSP > 200 µg/m³		1.51 (0.92–2.47)				
Mills et al. (1991) USA	TSP > 200 µg/m³		1.51 (0.92–2.47)				
Paradis et al. (1989) Canada	Bus drivers (SMR)	0.54 (0.15–1.38)					
Europe							
Raaschou-Nielsen et al. (2011b) Denmark	NO_x	1.32 (0.80–2.19)	1.16 (0.89–1.51)	0.93 (0.60–1.46)	0.65 (0.21–2.02)	2.28 (1.25–4.19)	0.64 (0.24–1.71)
	Major street within 50 m	0.94 (0.60–1.48)	0.98 (0.78–1.22)	0.89 (0.41–1.95)	0.92 (0.42–1.98)	1.89 (1.07–3.36)	0.79 (0.38–1.63)
	Per 10^4 vehicle-km/day traffic load within 200 m of the residence	1.09 (0.87–1.35)	0.98 (0.88–1.10)	0.99 (0.66–1.47)	1.00 (0.70–1.48)	1.27 (0.93–1.75)	0.73 (0.49–1.09)
Visser et al. (2004) Netherlands; SIR	TIS ≥ 10 000	1.05 (0.87–1.20)	1.00 (0.91–1.09)				
	10 000 ≤ TIS < 20 000	1.16 (0.93–1.43)	0.98 (0.86–1.12)				
	TIS ≥ 20 000	0.87 (0.66–1.12)	1.01 (0.89–1.15)				

Table 2.16 (continued)

Reference, study, location and period	Exposure	Relative risk (95% CI)					
		Bladder	Breast	Colon	Stomach	Brain	Pancreas
Ranzi et al. (2011) Italy	Heavy metal concentrations from incinerators, quartiles; lowest quartile used as a reference						
	Incidence in men						
	Smoking not adjusted for						
	Second quartile (0.5–1 ng/m³)	0.83 (0.53–1.29)			1.18 (0.69–2.00)		
	Third quartile (1–2 ng/m³)	0.76 (0.48–1.18)			1.47 (0.89–2.42)		
	Highest quartile (> 2 ng/m³)	0.78 (0.43–1.42)			1.24 (0.64–2.40)		
	Incidence in women						
	Second quartile (0.5–1 ng/m³)	1.49 (0.55–4.01)	0.89 (0.68–1.17)		1.02 (0.57–1.81)		
	Third quartile (1–2 ng/m³)	0.85 (0.27–2.68)	0.78 (0.59–1.03)		1.54 (0.91–2.63)		
	Highest quartile (> 2 ng/m³)	2.30 (0.73–7.24)	0.76 (0.51–1.13)		1.09 (0.49–2.44)		
Balarajan & McDowall (1988) United Kingdom	Professional drivers (SMR)	1.05			1.30 ($P < 0.05$)		
Forastiere et al. (1994) Italy	Urban police officers, male [SMR (no adjustment)]	1.27 (0.67–2.1)	14.36 (1.73–51)	1.47 (0.84–2.30)	1.09 (0.70–1.60)	0.52 (0.13–1.20)	0.87 (0.35–1.70)
Soll-Johanning et al. (1998) Denmark	Bus drivers and tramway employees, male	1.4 (1.2–1.6)			1.0 (0.8–1.3)		
	Retrospective cohort						
	Bus drivers and tramway employees, female	1.3 (0.2–4.7)	1.1 (0.8–1.6)				
	SIR (no adjustment)						
Guo et al. (2004) Finland	Exposure to diesel exhausts, highest quartile vs none; men	0.97 (0.77–1.21)					
	Exposure to gasoline exhausts, highest quartile vs none; men	0.93 (0.71–1.23)					
Soll-Johanning & Bach (2004) Denmark	Mail carriers, male (SIR)	0.98 (0.82–1.16)					
	Mail carriers, female (SIR)		0.84 (0.48–1.37)				
Petersen et al. (2010) Denmark	Bus drivers (SIR)	1.6 (1.2–2.0)					

Table 2.16 (continued)

Reference, study, location and period	Exposure	Relative risk (95% CI)					
		Bladder	Breast	Colon	Stomach	Brain	Pancreas
Rafnsson & Gunnarsdóttir (1991) Iceland	Truck drivers (SMR)	1.02 (0.21–2.97)		1.25 (0.50–2.58)	0.92 (0.55–1.43)	1.40 (0.29–4.10)	1.50 (0.65–2.96)
Gubéran et al. (1992) Switzerland	*Men only* Professional drivers; mortality (SMR)	1.43 (0.80–2.36)		0.92 (0.50–1.56)	1.79 (1.17–2.63)		0.91 (0.43–1.71)
	Professional drivers; incidence (SIR)	1.25 (0.74–1.99)		1.11 (0.67–1.74)	2.33 (1.56–3.36)		
Lagorio et al. (1994) Italy	Service station attendants (SMR)	1.20 (0.52–2.36)	1.04 (0.18–3.28)	1.02 (0.44–2.01)	0.60 (0.26–1.18)		0.76 (0.21–1.95)
Pukkala & Pönkä (2001) Finland	Households built close to a former industrial and household waste dump (SIR)		1.12 (0.60–1.91)			1.55 (0.42–3.97)	1.52 (0.61–3.13)

CI, confidence interval; CO, carbon monoxide; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; O_3, ozone; PM_{10}, particulate matter with particles of aerodynamic diameter < 10 µm; $PM_{2.5}$, particulate matter with particles of aerodynamic diameter < 2.5 µm; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SO_2, sulfur dioxide; TIS, traffic intensity score; TSP, total suspended particles.

2.6 All cancers combined and cancers of other sites

Few studies have reported the association between exposure to air pollution and all cancers combined or cancers at sites other than the lung, bladder, breast, or haematopoietic system, or childhood cancers. The sparse data limit a formal evaluation. Furthermore, the interpretation of all cancer sites combined is difficult because different cancer sites have different etiologies and different potential confounders.

2.6.1 All cancers combined

The group of studies that investigated all cancer sites combined have different designs, including ecological studies (Nasca et al., 1980; Robertson, 1980; Howe, 2005; Visser et al., 2005; García-Pérez et al., 2013) and cohort studies (Forastiere et al., 1994; Soll-Johanning et al., 1998; Pukkala & Pönkä, 2001; Soll-Johanning & Bach, 2004; Ranzi et al., 2011). These studies focused on different sources, such as "general urban mixture of air pollutants," as well as specific point sources, such as waste disposal facilities, industries, and airports. [The Working Group noted that combining all cancer sites in studies that assessed air pollution renders them uninterpretable due to the different etiologies and the lack of control for the appropriate potential confounders.]

2.6.2 Cancers of other sites

(a) Case–control studies

Liu et al. (2008b) investigated the relationship between petrochemical air pollution and brain cancer death in Taiwan, China, using a matched case–control study (see Table 2.14). Cases were 340 deaths from brain cancer (ICD-9 code: 191) aged 29 years or younger registered between 1995 and 2005. About half of the cases were younger than 15 years. A total of 340 controls were selected from among all people who had died due to non-neoplastic, non-respiratory diseases in the same period and were pair-matched to cases by sex, year of birth, and year of death. A surrogate measure of exposure to petrochemical air pollution was defined as the proportion of workers working in the petrochemical manufacturing industry per municipality. Subjects were assigned to tertiles of the petrochemical air pollution index according to their residential municipality. Conditional logistic regression models were used with adjustment for age, sex, urbanization level of residence, and non-petrochemical air pollution exposure level. The odds ratio for living in a municipality with high petrochemical air pollution index compared with low index was 1.65 (95% CI, 1.00–2.73). A dose–response relationship was observed, with increasing exposure to petrochemical air pollutants in a residential municipality associated with a greater odds ratio (P-value from test for trend < 0.01). [Limitations of the study are the use of mortality, an indirect measure of air pollution, and the lack of adjustment for other potential confounding factors, such as exposure to ionizing radiation.]

Chiu et al. (2011) conducted a matched case–control study to examine the association between petrol-station density and death from gastric cancer in Taiwan, China. Cases included 358 deaths from gastric cancer (ICD-9 code: 151), aged 50–69 years, registered from 2004 to 2008. Control subjects were 358 non-cancer or gastrointestinal disorder-related deaths, pair-matched by sex, year of birth, and year of death. Petrol-station density was calculated by summing the total number of petrol stations in each municipality, divided by the total area (km^2). Participants were assigned to tertiles of exposure according to levels of petrol-station density within their residential municipality. Conditional logistic regression models were applied with adjustment for marital status and urbanization level. The adjusted odds ratio for living in a municipality

with high petrol-station density compared with low petrol-station density was 1.26 (95% CI, 1.04–1.53). A dose–response relationship was observed, with increasing petrol-station density in a residential municipality related to a greater odds ratio (*P*-value from test for trend < 0.001). [Limitations of the study are the use of mortality, an indirect measure of air pollution, and the lack of adjustment for other potential confounding factors, such as smoking and diet.]

Parent et al. (2013) conducted a case–control study based on incident cases (803 cases) in Montreal, Canada, to estimate associations between exposure to modelled ground-level NO_2 concentration, a marker for traffic-related air pollution, and incidence of prostate cancer. For each increase of 5 ppb in NO_2, the odds ratio was 1.27 (95% CI, 1.03–1.58), adjusted for age, first-degree family history of prostate cancer, ancestry, attained level of education, and three ecological covariates from the 1996 Canadian census: percentage of adults who did not complete high school, median household income, and percentage of recent immigrants. [The study modelled ground-level NO_2 concentration as an estimator of traffic-related pollution.]

(b) Cohort studies

See Table 2.16.

Selected other cancer sites reported in cohort studies that assessed exposure to air pollution or occupations involving exposure to outdoor air pollution are summarized in Table 2.16. Mixed results were reported in several studies for colon cancer (Rafnsson & Gunnarsdóttir, 1991; Gubéran et al., 1992; Forastiere et al., 1994; Lagorio et al., 1994; Raaschou-Nielsen et al., 2011b). Of the cohort studies that assessed stomach cancer (Rafnsson & Gunnarsdóttir, 1991; Gubéran et al., 1992; Forastiere et al., 1994; Lagorio et al., 1994; Soll-Johanning et al., 1998; Raaschou-Nielsen et al., 2011b; Ranzi et al., 2011) and brain cancer (Rafnsson & Gunnarsdóttir, 1991; Gubéran et al., 1992; Forastiere et al., 1994; Pukkala & Pönkä, 2001; McKean-Cowdin et al., 2009; Raaschou-Nielsen et al., 2011b), many reported risk estimates greater than 1. All except two cohort studies reported a decreased risk of pancreatic cancer, although none of the associations reported were statistically significant (Raaschou-Nielsen et al., 2011b; Forastiere et al., 1994; Rafnsson & Gunnarsdóttir, 1991; Gubéran et al., 1992; Lagorio et al., 1994; Pukkala & Pönkä, 2001). A large cohort study (Raaschou-Nielsen et al. 2011b) in Denmark reported increased risks of cervical cancer associated with proximity to a major road at both 50 m (IRR, 4.36; 95% CI, 2.12–8.95) and 200 m (IRR, 1.70; 95% CI, 1.12–2.58) and exposure to NO_x (IRR, 2.45; 95% CI, 1.01–5.93, per 100 μg/m^3 increase in NO_x, adjusted for smoking, education level, and oral contraceptive use). [This study did not adjust for human papillomavirus (HPV) status, an important risk factor for cervical cancer. Chance findings are possible given the number of cancer sites considered.]

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