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Review

Impact of urban atmospheric pollution on coronary disease

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Review

Recent epidemiological findings have suggested that urban atmospheric pollution may have adverse effects on the cardiovascular system as well as on the respiratory system. We carried out an exhaustive search of published studies investigating links between coronary heart disease and urban atmospheric pollution. The review was conducted on cited articles published between 1994 and 2005 and whose main objective was to measure the risk of ischaemic heart diseases related to urban pollution. Of the 236 references identified, 46 epidemiological studies were selected for analysis on the basis of predefined criteria. The studies were analysed according to short-term effects (time series and case-crossover designs) and long-term effects (case–control and cohort studies). A link between coronary heart disease and at least one of the pollutants studied (PM_{10}, O_3, NO_x, CO, SO_2) emerged in 40 publications. Particulate matter, nitrogen oxides, and carbon monoxide were the pollutants most often linked with coronary heart disease. The association was inconstant for O_3. Although the mean mortality or morbidity risk related to urban atmospheric pollution is low compared with that associated with other better-known risk factors, its impact on health is nevertheless major because of the large number of people who are exposed. This exhaustive review supports the possibility that urban pollution is indeed an environmental cardiovascular risk factor and should be considered as such by the cardiologists.

Introduction

Urban atmospheric pollution is considered as a major problem of environmental health.[1,2] At the present time, motor vehicle emissions are the main source of urban pollution than other sources such as heating and industrial activities.[3] Current pollutants are particulate matter (PM), emitted mainly by diesel engines, primary gaseous pollutants [nitrogen oxides (NO_x) and volatile organic compounds], and secondary pollutants due to the action of ultraviolet light, nitrogen dioxide, and above all ozone (O_3).[4] Urban air quality monitoring networks measure gaseous pollutants in the trace state as well as increasingly small particles (PM 10 μm to PM 2.5 μm), providing reliable data for epidemiological studies in the general population.

Urban atmospheric pollution has a well-known impact on acute and chronic respiratory disease,[5] whereas its effect on cardio-respiratory diseases has been analysed more recently.[6–9] An association with cardiovascular diseases has been found in several studies of mortality[10–12] and morbidity.[13–15] Recently, recommendations have been issued in order to increase the awareness of cardiologists.[16]

More specifically, ischaemic heart diseases appear to be associated with urban atmospheric pollution in terms of mortality[17,18] and morbidity.[19] Exposure to fine particles[20] or to NO_x[21] and O_3[22] may even trigger the onset of acute coronary syndrome.

The aim of this work was to sum up present epidemiological knowledge on the relationship between ischaemic heart disease and urban atmospheric pollution in order to draw the attention of healthcare professionals, and in particular cardiologists, to what may be a new environmental factor of cardiovascular risk.

The originality of this review is that it presents the risk levels of pollutant exposure according to type of epidemiological study, after conversion of the units of measurement to allow comparisons. It also indicates the estimated risk in the general population.

Methods

The systematic review of the literature included all original scientific papers published between 1994 and December 2005 in French or

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English, concerning human studies and including the following key words: air pollution, air pollutants, myocardial ischaemia, myocardial infarction, coronary disease, coronary arteriosclerosis, ischaemic heart disease, and angina.

Our search was carried out using the MEDLINE, BDSP, WHOLIS, and PASCAL databases. We also searched the tables of contents of the following general medical journals and specialist journals in cardiology, public health, and environmental health: The Lancet, British Medical Journal, JAMA, New England Journal of Medicine, Circulation, Epidemiology, Revue d'Epidemiologie et Santé Publique, Environmental Health Perspectives, and the Journal of Occupational and Environmental Medicine.

After reading the titles and summaries, each investigator excluded papers which did not correspond to the field of interest initially defined or whose objective was not measurement of the risk of ischaemic heart disease (I20–I25 according to ICD-10) related to urban pollution. The literature search was carried out by two independent investigators, a librarian and a physician. The results of both searches were compared at the end of the selection process and were then refined by consensus. We also excluded studies whose methodology was not considered satisfactory (insufficient power, lack of precision in measurement of pollutants, health effects, or populations studied).

Results were converted so that they could be presented in a uniform manner: pollutant concentrations were expressed in $\mu g/m^3$, except for carbon monoxide (CO) which was expressed as parts per million (ppm). The percentage of variation (PV) of the health variable, used as a risk indicator in certain studies, was converted to relative risk (RR) using the formula $RR = (PV/100) + 1$. All RRs in time series studies were calculated for an increase, depending on the pollutant considered, of $10\ \mu g/m^3$ [PM, NO_x, O_3, sulphur dioxide (SO_2)] or 1 ppm (CO). RR was considered as significant if the lower threshold of the confidence interval was ≥ 1. Particulate atmospheric pollution was represented by total suspended particles (TSP), black smoke (BS), fine particles of decreasing aerodynamic diameter (in μm: PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$, $PM_{0.1}$).

The various studies cited in the tables were analysed according to their epidemiological design (time series, case-crossover studies, cohort studies) and the health issue (mortality or morbidity). Because of the large number of pollutants and the different measurement conditions, and to avoid excessively large tables, the RRs and their measurement conditions are given only for statistically significant risks (risk confidence interval which does not contain the value 1). The population attributable fraction (PAF) was calculated by the method of Levin:[23] $PAF = P_e \times (RR - 1)/[P_e \times (RR - 1) + 1]$, where P_e is the proportion of the population exposed to pollution.

Results

Combined research by key words yielded 236 references in MEDLINE, which is the most exhaustive database. The other databases did not produce any references which were not included in MEDLINE. After reading the titles and abstracts, 45 articles were retained, one of which included two studies. The references of the selected articles yielded a further nine articles, but five of these were excluded because of incomplete results (two articles), lack of adjustment for meteorological factors (one article), or diagnostic codes not restricted to ischaemic heart diseases (two articles). Forty-six studies were finally selected which included 10 mortality studies, 32 morbidity studies, and four which analysed both: 98% of these studies were carried out when levels of the usual pollutants were below the WHO Air Quality Guidelines and the limits of the 1999 EU Directive.

Studies of short-term effects

Time series studies

Time series analyse the short-term relationships between atmospheric levels of pollutants and health data after adjustment for meteorological factors. They study short-term associations (less than 1 day to several days) between ambient levels of pollutants and health effects (mortality, morbidity) after adjustment for factors which vary with time (meteorological conditions, climate, short- and long-term time trends).[24] The lag periods between pollutant measurement and health effects range from less than 1 day to 1 week.

Mortality studies

Table 1 shows mortality.[18,25–30] Excess risk of myocardial infarction or ischaemic heart disease related to increased particle level was demonstrated in five of the seven studies, whatever the particulate index: TSP,[25] PM_{10},[26,31] $PM_{2.5}$,[28] and sulphates.[18] One of three studies found that this risk was associated with increased concentrations of nitrogen dioxide (NO_2),[30] ozone,[30] and CO,[32] respectively. Increase in SO_2[27,30] was related to increased mortality in half the studies, notably after adjustment for the concentration of PM_{10} and CO.[27] Neither the interval between exposure and death nor the mean pollution level appeared to be determinant factors of risk level for PM and other pollutants in this type of study.

Morbidity studies

Table 2 presents the 23 time series studies[13,19,21,30–50] in the same way as *Table 1*, with the addition of the patients' age.

Of the 20 studies which tested an increase in particular pollution, nine reported an increased risk of hospital admissions for ischaemic heart disease or myocardial infarction.[13,30,32–34,36,38,47] Measurement of PM_{10} concentration was the indicator most often studied. A dose–effect relation (quartiles) was found in one study[33] and exclusion of days when pollution was above recommended limits did not modify the association. Five of these studies, grouped together in a meta-analysis,[51] revealed an RR of hospital admission for ischaemic heart disease of 1.007 (95% CI 1.004–1.010) for a PM_{10} increase of $10\ \mu g/m^3/24$ h. The studies demonstrated a significant risk which particularly affected patients aged 65 and over. One study[34] showed a risk level well above the other studies but it concerned only a subgroup of ischaemic heart diseases (ICD: I24) and the base levels of pollution measured were high.

Among gaseous pollutants, NO_x are those whose increase is most often related to increased hospital admissions,[21,30,34,36,38,39,41,44,47] consultations,[19] and emergency department referrals[43] for myocardial infarction, angina, or ischaemic heart disease. Patient age and morbidity indicators did not seem to differ between studies which did or did not reveal significant RR. The association remained significant when levels of PM_{10},[47] O_3,[36] and all pollutants[34,39] were taken into account.

Results were also divergent for O_3: the risk of ischaemic heart disease related to elevated O_3 levels was significantly increased in four studies[34,35,46,47] and reduced in three.[31,34,46] It is interesting to observe that two studies[34,46] found a similar divergence of risk, the RR being elevated for a 2-day lag and reduced for shorter lag

Table 1 Mortality time series studies

Reference	City (year)	Mean daily death	Pollutant	Lag (days)	Mean ($\mu g/m^3$/24 h)	Median ($\mu g/m^3$/24 h)	RR (95% CI) for ↑ 10 $\mu g/m^3$ of pollutant (↑ 1 ppm for CO)
Myocardial infarction: ICD-10: I21							
Rossi *et al.*[25]	Milan (1980–1989)	31.9	TSP	3 or 4	142		1.01 (1.00–1.02)
Braga *et al.*[26]	10 US cities (1986–1993)	0.9–15.2	PM_{10}	0–1	33		1.007 (1.00–1.01)
Sharovsky *et al.*[27]	Sao Paulo (1996–1998)	15.3	SO_2	0–3	18.9		1.03 (1.00–1.06)[a]
			PM_{10}, CO				NS
Ischaemic heart diseases: ICD-10: I20—I24							
Schwartz *et al.*[28]	Six US cities (1979–1987)	1.2–17.9	$PM_{2.5}$	0–1	18	14.7	1.02 (1.01–1.03)
			PM_{10}, $PM_{10-2.5}$, sulphates, H+				NS
Goldberg *et al.*[18]	Montreal (1984–1993)	15.7	Particular sulphates	0–2	4.1	3.1	1.08 (1.01–1.11)
			TSP, PM_{10}, $PM_{2.5}$				NS
			NO_2, O_3, SO_2, CO				NS
Hoek *et al.*[29]	The Netherlands (1986–1994)	62	CO	0–6		0.39 ppm	1.05 (1.00–1.09)
			BS, PM_{10}, NO_2, O_3, SO_2				NS
Wong *et al.*[30]	Hong Kong (1995–1998)	98.7–121	PM_{10}	0–3	51.5	46	1.01 (1.00–1.02)
			NO_2	1	56.4	54.2	1.02 (1.01–1.04)[a]
			O_3	3	33.9/8 h	29.3/8 h	1.009 (1.000–1.02)
			SO_2	1	16.7	14	1.03 (1.01–1.04)

H+, acid aerosol.
[a]RR remains significant after adjustment for other pollutant(s).

periods between a measured increase in pollution and the onset of ischaemic heart disease.

An increase in SO_2 was associated in more than one-third of the studies with increased doctors' house calls[38] and hospital admissions[30,33,36,38,39,45] for myocardial infarction, angina, or ischaemic heart disease. The association persisted when other pollutants were taken into consideration: BS,[36,45] PM_{10},[45] NO_2, and CO.[36]

Excess hospital admissions for ischaemic heart disease were associated with elevated CO in over half the studies (nine of 16).[33,36–38,41,44,47,48,50] This association, affecting all age groups, was not modified after adjustment for O_3,[36,48] PM_{10},[48] or the three pollutants SO_2, O_3, and PM_{10} analysed together.[48]

Volatile organic compounds, mainly traffic-related, were analysed in only one study: elevated concentrations were associated with increased emergency department visits for ischaemic heart disease.[19]

Case-crossover studies

The case-crossover studies were based on an original methodology[52] where, for each case, exposure during an at-risk period before the health event was compared with a distribution of exposures during a reference period.[53]

The seven case-crossover studies[20,22,54–58] are presented in *Table 3*. RRs related to pollutants were not significant in the two studies in which cardiac arrest was the health effect assessed. The observed RRs for myocardial infarction were much higher in this study design than in time series studies analysing this health effect (*Table 2*). Increased levels of TSP[54] and $PM_{2.5}$[20] were associated with increased risk of myocardial infarction in two of the studies which analysed particulate pollution. The risk associated with TSP persisted after taking CO or NO_2 levels into account.[54]

The pollutants NO_2, CO, and O_3 were each associated with risk of myocardial infarction in only one of the four studies. A recent study focused on out-of-hospital coronary deaths[58] found a significant risk of mortality associated with an interquartile range variation of particle number concentration, PM_{10} and CO; the risk was higher for a short lag time (0–1 day) than for a longer period.

Studies of long-term effects

Case—control studies

A case–control study of 448 men aged 25–64 years matched with 1777 controls found, after adjustment for cardiovascular risk factors, a higher risk of myocardial infarction [OR = 1.43 (95% CI 1.04–1.96)] in men who were exposed to mean annual levels of NO_2 ranging between 17 and 19 $\mu g/m^3$ compared with those exposed to concentrations lower than 17 $\mu g/m^3$.[59]

Cohort studies

A North American cohort study of 319 000 persons aged over 30 followed for 16 years[17] and a Norwegian cohort study of 16 209 men aged 40–49 followed for 24 years[60] examined the impact of urban ambient pollution on coronary disease after adjustment for conventional cardiovascular risk factors. The first study found an adjusted RR of mortality from ischaemic heart diseases of 1.18 (95% CI 1.14–1.23) for a long-term increase in average $PM_{2.5}$ concentration of

Table 2 Morbidity time series studies

Reference	City (year)	Daily admissions	Pollutant	Disease[a]	Age	Lag (days)	Mean $\mu g/m^3$/24 h	Median $\mu g/m^3$/24 h	RR (95% CI) for ↑ 10 $\mu g/m^3$ pollutant (↑ 1 ppm for CO)
Schwartz[33]	Detroit (1986–1989)	15.7	PM_{10}	IC	65+	0	48	43	1.006 (1.00–1.01)[b]
			SO_2	IC	65+	0	68[c]	61[c]	1.003 (1.00–1.01)
			CO	IC	65+	0	2.38 ppm[c]	2.12 ppm[c]	1.008 (1.00–1.01)
			O_3	IC	65+				NS
Pönkä and Virtanen[34]	Helsinki (1987–1989)	11.6	TSP	OIC	All	3	76		1.22 (1.03–1.46)[d]
			NO	IC	All	1	91		1.12 (1.05–1.18)[d]
			NO_2	AP	All	6	39		1.26 (1.02–1.57)[d]
			NO_2	AP	All	7	39		0.77 (0.64–0.92)[d]
			O_3	IC	All	1	22		0.86 (0.80–0.93)[d]
			O_3	IC	All	2	22		1.14 (1.04–1.24)[d]
			SO_2	IC	All				NS
Medina *et al.*[35]	Paris (1991–1995)	1[e]	O_3	MI + AP	All	3	34[f]		1.05 (1.01–1.09)[g]
			SO_2	MI + AP	All	3	19		1.06 (1.02–1.09)
			BS, PM_{13}, NO_2	MI + AP	All				NS
Poloniecki *et al.*[36]	London (1987–1994)	26.7	BS	MI	All	1		12	1.02 (1.01–1.04)[b,h]
			NO_2	MI	All	1		67	1.007 (1.00–1.01)[b,h]
			SO_2	MI	All	1		16	1.008 (1.00–1.01)[b,h]
			CO	MI	All	1		0.9 ppm	1.02 (1.01–1.04)[b,h]
			O_3	MI	All				NS
Yang *et al.*[37]	Reno (1989–1994)	6	CO	IC	All	0	3.09 ppm[c]		1.03 (1.02–1.04)
Atkinson *et al.*[38]	London (1992–1994)	37.6	BS	IC	65+	3	13	11	1.018 (1.00–1.03)
			PM_{10}	IC	65+	0	29	25	1.010 (1.00–1.02)
			NO_2	IC	65+	0	96[c]	90[c]	1.004 (1.00–1.01)
			SO_2	IC	65+	0	21	20	1.017 (1.00–1.03)
			CO	IC	65+	3	0.8 ppm	0.7 ppm	1.028 (1.00–1.05)
			O_3	IC	65+				NS
Burnett *et al.*[39]	Toronto (1980–1994)	24	NO_2	IC	All	0–1	48.1		1.02[b,i]
			SO_2	IC	All	0–2	14.2		1.007[i]
			PM_{10}, $PM_{10-2.5}$	IC	All				NS
			$PM_{2.5}$, O_3, CO	IC	All				NS
Wong *et al.*[40]	Hong Kong (1994–1995)	101	PM_{10}, NO_2, O_3, SO_2	IC					NS
Linn *et al.*[41]	Los Angeles (1992–1995)	1.2	NO_2	MI	30+	0	64.94		1.006 (1.00–1.01)
			CO	MI	30+	0	1.5 ppm		1.041 (1.02–1.06)
			PM_{10}, O_3	MI	30+				NS
Anderson *et al.*[42]	Birmingham (1994–1996)	28	PM_{10}, 10–2.5, BS	IC					NS
			Sulphates						NS
			NO_2, O_3, SO_2, CO						NS
Eilstein *et al.*[21]	Strasburg (1984–1989)	0.68	NO	MI	All	5	153[c]		1.007 (1.00–1.01)
			NO_2	MI	All	5	94[c]		1.02 (1.00–1.03)[h]
			PM13, O_3, CO, SO_2	MI	All				NS
Lippmann *et al.*[32]	Detroit (1992–1994)	–	PM_{10}	IC	65+	2	31	28	1.02 (1.00–1.03)[b]
			$PM_{10-2.5}$	IC	65+	2	13	12	1.041 (1.01–1.07)[b]
			TSP, $PM_{2.5}$, sulphates, H+, NO_2, O_3, SO_2, CO	IC	65+				NS

Ye *et al.*[43]	Tokyo (July–August, 1980–1995)	2–3.6	NO_2	MI	65+	0	48.5		1.03 (1.01–1.05)
		2.2–4.1		AP	65+	0	48.5		1.04 (1.03–1.05)
			$PM1_0$, O_3, CO, SO_2						NS
Le Tertre *et al.*[13]	Europe (1990–1996)	4–7	BS	IC	65+	0–1	20		1.01 (1.01–1.02)[b]
			PM_{10}	IC	65+	0–1	36		1.01 (1.00–1.01)[b]
Mann *et al.*[44]	Los Angeles (1988–1995)	1	NO_2	MI	All	0	71	66.4	1.01 (1.01–1.02)
		2.2		IC	All	0	71	66.4	1.009 (1.01–1.01)
		0.5		OIC	All	0	71	66.4	1.009 (1.00–1.01)
			CO	MI	All	0	2.07 ppm[f]	1.70 ppm[f]	1.03 (1.02–1.05)
				IC	All	0	2.07 ppm[f]	1.70 ppm[f]	1.02 (1.02–1.03)
				OIC	All	0	2.07 ppm[f]	1.70 ppm[f]	1.02 (1.01–1.03)
			PM_{10}, O_3						NS
Sunyer *et al.*[45]	Europe (1990–1996)	4–60	SO_2	IC	<65	0–1	16.7		1.006 (1.00–1.01)[b]
		28–81		IC	65+	0–1	16.7		1.012 (1.01–1.02)
Wong *et al.*[31]	London (1995–1997)	5.9–7.6	PM_{10}	IC	All	0–1	28.5	24.8	1.01 (1.00–1.02)
			NO_2	IC	All	0–1	64.3	61.2	1.01 (1.00 –1.01)
			O_3	IC	All	0–1	34.9[j]	32[j]	0.99 (0.98–0.99)
			SO_2	IC	All	0–1	23.7	20.6	1.02 (1.01–1.03)
Koken *et al.*[46]	Denver (July–August, 1993–1997)	0.51	O_3	MI	65+	0	50	50.4	0.90 (0.85–0.96)
		0.23		CIC	65+	2	50	50.4	1.06 (1.02–1.10)
			PM_{10}, NO_2, CO, SO_2						NS
Lee *et al.*[47]	Seoul (1997–1999)	4.4	PM_{10}	IC	65+	5	64	59.1	1.01 (1.00–1.022)
			NO_2	IC	65+	5	60	58.6	1.03 (1.01–1.046)[b]
			O_3	IC	65+	3	72[c]	63.2[c]	1.02 (1.01–1.032)[b]
			CO	IC	65+	5	1.6 ppm[c]	1.8 ppm[c]	1.07 (1.01–1.13)
			SO_2	IC	65+				NS
Lin *et al.*[48]	Sao Paulo (1994–1995)	3.7	CO	MI + AP	45–80	0–1	5.12 ppm[j]		1.02 (1.00–1.04)[b]
			PM_{10}, O_3, SO_2	MI + AP	45–80				NS
Metzger *et al.*[19]	Atlanta (1993–2000)	11.7	NO_2	IC	All	0–3		84[c]	1.008 (1.00–1.01)
			VOC[k]	IC	All	0–3		29 ppb	1.06 (1.01–1.1)[l]
			PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$	IC	All				
			O_3, CO, SO_2						NS
Zanobetti and Schwartz[49]	21 US cities (1986–1999)	26.1/city	PM_{10}	MI	All	0–2	27		1.006 ((1.00–1.01)
Hosseinpoor *et al.*[50]	Teheran (1996–2001)	23.4	1CO adjusted on NO_2, O_3, PM_{10}	AP	All	1	9.8 ppm		1.009 (1.00–1.02)

[a]MI, myocardial infarction (ICD-10: I21); AP, angina pectoris (ICD-10: I20); IC, ischaemic cardiopathy (ICD-10: I20-I24); OIC, other ischaemic cardiopathy (ICD-10: I24); CIC, chronic ischaemic cardiopathy (ICD-10: I25).
[b]Risk remains significant after adjustment for other pollutant(s).
[c]Hourly maximum.
[d]RR calculated for a pollutant variation of a factor of 2.7 (1 logarithmic unit) and in a model including the five pollutants.
[e]House calls.
[f]Eight hours maximum.
[g]Adjustment on many climatic parameters.
[h]Winter season.
[i]Significant result according to the test used.
[j]Eight hours.
[k]VOC, volatile organic compounds.
[l]Risk calculated for an increase of 15 parts per billion (ppb).

Table 3 Case-crossover analyses

Reference	City (year)	Age	Cases	Pollutant	Lag (days)	Mean ($\mu g/m^3$/24 h)	Δ[a] ($\mu g/m^3$/24 h)	OR (95% CI)
Myocardial infarction								
Peters *et al.*[20]	Boston (1995–1996)	All	772	$PM_{2.5}$	1–3[b]	12.1	+25	1.48 (1.09–2.02)
				PM_{10}, NO_2, O_3 SO_2, CO	1–2	12.1	+20	1.62 (1.13–2.34) NS
D'Ippoliti *et al.*[54]	Rome (1995–1997)	>18	6531	TSP	0–2	66.9	+10	1.03 (1.00–1.05)[c]
				NO_2	0–2	86.4	+10	1.02 (0.99–1.05)
				CO	0–2	3.7 ppm	+1 ppm	1.04 (1.00–1.09)
				SO_2				NS
Sullivan *et al.*[55]	King County (1988–1994)	All	5793	PM_{10}, $PM_{2.5}$, SO_2, CO				NS
Ruidavets *et al.*[22]	Toulouse (1997–1999)	35–64	635	O_3	0 or 1	74.8[d]	+5	1.05 (1.01–1.08)
				NO_2, SO_2				NS
Cardiac arrest								
Levy *et al.*[56]	King County (1988–1994)	25–75	362	PM_{10}, $PM_{2.5}$, CO, SO_2				NS
Sullivan *et al.*[57]	King County (1985–1994)	All	1206	PM_{10}, $PM_{2.5}$, CO, SO_2				NS
Out-of-hospital coronary death								
Forastiere *et al.*[58]	Rome (1998–2000)	All	5144	PM_{10}	0	52.1	Inter-quartile	1.05 (1.00–1.09)
				C0	0	2.1 ppm	Inter-quartile	1.06 (1.00–1.12)

[a]Corresponds to pollutant variations with significant excess risk.
[b]Hours.
[c]Risk remains significant after adjustment for other pollutant(s).
[d]Eight hours maximum.

10 $\mu g/m^3$ and the second an adjusted RR of 1.08 (95% CI 1.03–1.12) for a mean 5-year increase in NO_x concentration of 10 $\mu g/m^3$.

The risk of hospital cardiac re-admissions for myocardial infarction associated with air pollution has recently been analysed in the HEAPSS cohort among 22 006 survivors of first myocardial infarction.[61] During the 10 years of follow-up, 6655 cardiac re-admissions were found to be associated with same day concentration of PM_{10} [RR = 1.021 (1.004–1.039)] per 10 $\mu g/m^3$. Similar effects were also found for CO, O_3, and NO_2.

A recent study[62] has re-analysed the data of the American Cancer Society Cohort of 22 095 patients, which originally estimated risk for PM_{2-5} and O_3 exposure in the urban population. This study also included 44 potential individual confounding factors including lifestyle, dietary, occupational and educational factors, and contextual variables such as air-conditioning related to indoor pollution levels. The RRs of death from ischaemic heart disease, expressed as 10 $\mu g/m^3$ exposure differences in PM_{2-5}, were RR = 1.49 [1.20–1.85] for PM_{2-5} only, RR = 1.39 (1.20–1.73) including 44 individual covariates and RR = 1.26 (1.005–1.60) including individual and contextual variables.

The risk of mortality from coronary heart disease related to pollution by PM_{10} particulates was compared in men and in women in a cohort of 6338 participants followed for 22 years (Adventist Health Study).[63] The RR, adjusted for age, educational level, and smoking status, was higher in women: RR = 1.22 (1.06–1.40) than in men: RR = 0.94 (0.80–1.11). This excess risk was also found for $PM_{2.5}$ particulates. Of two studies[64,65] which were not conducted according to usual epidemiological methods, one demonstrated excess mortality risk from ischaemic heart disease [RR = 1.18 (95% CI 1–1.39)] associated with a pollution peak of NO_x.

Considering that pollution levels are lower in small cities or rural areas,[66] if we assume that 45% of the French population lives in cities of more than 100 000 inhabitants and that average morbidity risk level observed in time series in this review is close to RR $\approx$ 1.02 (short-term exposure), we can estimate that 0.89% of myocardial infarction may be attributed to an increase in urban gaseous or particulate pollution of 10 $\mu g/m^3$/24 h (PAF calculation). Considering mortality from ischaemic heart diseases in cohort studies (long-term exposures), with observed average morbidity risk level close to RR $\approx$ 1.20, we can also estimate with the same formula that 8.25% of ischaemic heart deaths may be attributed to the same increase of urban gaseous or particulate pollution.

Discussion

This review of the literature highlights the association between ischaemic heart disease and urban air pollution: these findings were constant whatever the pollutants, type of investigation (time series, case-crossover studies, cohorts), or methods used (populations and areas studied, health indicators, mean pollutant concentrations, type of particular pollution, time lag between exposure and effect). In time series, adjustment was also always carried out for meteorological parameters (temperature, humidity) which may be related to coronary events.[67] The results of cohort studies were adjusted for known risk factors for coronary heart disease (smoking, diabetes, dyslipidaemia, arterial hypertension). It is important to consider study

design when interpreting data: time series and case-crossover studies analyse short-term exposure, whereas case–control and cohort studies analyse the long-term effects of exposure. This may explain the observed differences of risk level between studies.

RR levels are generally lower in time series studies than in other epidemiological designs. This may be related to a number of parameters such as confounding factors, assessment of pollutant levels, or short-term or long-term exposure. Some recommendations for choosing a referent strategy with air pollution exposure data have been recently proposed for case-crossover studies;[68] they include a time-stratified approach.

The relationship between urban pollution and ischaemic heart disease seems to affect all age groups. There is little information as to whether certain populations such as elderly persons[10] and subjects with a history of heart failure or arrhythmia[44] or high plasma fibrinogen levels[69] may be more sensitive to the ischaemic effects of pollution. One study found that excess risk was constantly higher in women than in men, whatever the multivariate statistical model used;[63] this finding deserves to be confirmed by further studies. The risk appears to be higher in patients who had previously been hospitalized for cardiorespiratory diseases[49] or who had already had myocardial infarction.[61]

Numerous methodological factors hamper the comparability and power of the studies: difficulty of comparing risks for particles of different aerodynamic diameter which do not have the same health impact (on the respiratory tree in particular), absence of measurement of other traffic-related toxic compounds (PAHs, metallic organic compounds adsorbed onto ultrafine particles), extrapolation of measurements taken by fixed monitors which do not take into account the movement of individuals nor the level of indoor pollution.

Nevertheless, the associations found are in agreement with current hypotheses concerning the pathophysiological mechanisms of the effects observed. Most investigations concerned particles. Particles smaller than 10 μm are deposited in the airways when inhaled and $PM_{2.5}$ may reach the pulmonary alveoli and accumulate there. A consensus has been reached that adverse health impact is mainly due to fine particles ($PM_{2.5}$).[4,70] Ultrafine particles ($PM_{0.1}$), emitted notably by diesel engines and which account for most PM in an urban environment, may even pass directly into the blood circulation and have vascular effects.[71] Experimental and clinical studies in man have shown that particles cause an inflammatory reaction of the lung which is related as much to their physical parameters as to the oxidative stress generated by the organic and metallic compounds adsorbed onto their surface.[72,73] These compounds may then trigger a cascade of reactions: initial local production by macrophages and activated alveolar cells of pro-inflammatory cytokines, such as interleukin-6,[74] and increased expression of endothelin,[75] whose elevated systemic levels are associated with a poor cardiovascular prognosis.[76] This induced systemic inflammation may be reflected by elevated CRP[77] which is significantly and independently associated with the risk of coronary heart disease.[74,78] Other studies have shown increased levels of fibrinogen and platelets,[79] altered blood viscosity,[80] modification of the adhesive properties of red blood cells with peripheral sequestration, and altered vascular tone.[80]

A disturbance of cardiac autonomic nervous activity could be a complementary harmful mechanism: particular pollution has in fact been associated with decreased heart rate variability,[81–83] elevated pulse rate,[84] and increased incidence of cardiac arrhythmia.[85]

Among the gaseous pollutants, NO_x and O_3, which are powerful oxidating agents, may also trigger an inflammatory pulmonary,[86] then systemic reaction with an increase of blood coagulability, fibrinogen,[87] and platelets.[88] An arrhythmic[85] and vasoconstrictor effect[80] has also been demonstrated. The role of SO_2 itself in the effects observed is unclear. At the present time, its cardiovascular toxicity appears to be related above all to sulphates, pollutants which are combustion by-products and can be adsorbed onto the particular surface.[88]

CO, which binds very strongly to haemoglobin to form carboxyhaemoglobin, reduces the capacity of haemoglobin to transport oxygen and to deliver it to peripheral tissues, thus contributing to tissue hypoxia. It may also lead to the production of oxidizing agents.[89]

Traffic-related air pollution plays a major part in the exposure of the urban population to fine PM, NO_x, and CO. Ozone is formed for the most part by the interaction between solar radiation and primary pollutants (NO_x, CO, volatile hydrocarbons) which are present in exhaust fumes. Ozone levels increase at a distance from the points of emission, often in peripheral urban areas, which explains the widely different results observed.

The recent statement of the American Heart Association on air pollution and cardiovascular disease draws attention to the difficulty of obtaining homogeneous risk levels between studies, because of the very numerous factors which influence these observational studies. It stresses that our understanding of the biological mechanisms responsible is still incomplete. Nevertheless, it emphasizes the knowledge acquired: short-term exposure to a high level of particles is associated with increased risk of cardiovascular mortality, and an increased mean level of particles is associated with a marked increase of hospital admissions for several cardiovascular diseases. A very recent published study, based on 204 US urban counties,[90] confirmed a significant increase of 0.44 (0.02–0.86) in hospital admission rates for ischaemic heart diseases (patients aged $\geq$65) per 10 $\mu g/m^3$ increase of $PM_{2.5}$. In addition, it also pointed to higher risk for heart failure: 1.28 (0.78–1.78) and heart rhythm: 3.8 (3.3–4.2). The life expectancy of subjects with prolonged exposure to elevated PM levels could be reduced by some years.

Although a variety of technological advances have reduced the emissions of each individual vehicle, the development of the fleet of diesel vehicles in Europe, in particular, and of urban traffic account for the fact that fine PM and NO_x levels have remained stable for several years. Neither have the levels of O_3 decreased.[91]

Ischaemic heart disease is also associated with urban pollution in an occupational environment, where excess mortality was found in a cohort of Italian policemen[91] and in bus drivers.[92]

Even if the RR levels associated with urban atmospheric pollution are much lower than those of other known cardiovascular risk factors, this does not mean that their impact on health is only a minor one. The pollution levels measured are well below the WHO Air Quality Guidelines and the

limits of the 1999 EU Directive, and the number of subjects chronically exposed in these studies is considerable. Pope *et al.*[8] estimated that the all-cause mortality risk associated with pollution by $PM_{2.5}$ is comparable to the risk of cardiovascular mortality associated with moderate obesity (body mass index 30–31.9 kg/m^2).

The attributable risk related to urban pollution calculated for the London conurbation[36] in 1997 was estimated at 2% of myocardial infarction. This is lower than in the study carried out in Toulouse, France, in the population aged 35–64, where 4–5% of myocardial infarctions could be attributed to urban atmospheric pollution. This proportion reached 12% in adults aged 55–64.[22] These attributable risks are concordant with those calculated from average morbidity and mortality risk in short-term and long-term studies in the review.

In terms of public health, air pollution may be considered as a cardiovascular risk factor which requires urgent action. The French National Environmental Health plan,[93] which aims to reduce emission of diesel particles by 30% before 2010, stresses the importance of fitting new vehicles with particle filters. An intervention study in Dublin estimated that 243 deaths due to cardiovascular disease have been prevented each year since a government order reduced atmospheric concentrations of BS.[94]

This overview provides physicians, and cardiologists in particular, with arguments for the recognition of urban pollution as a new risk factor for coronary disease. This risk appears to exist in both the short term (time-series, case-crossover studies) and the long term (cohort studies).[16] It is present even for pollutant concentrations which are below regulation levels.

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