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Environmental Factors in Cardiovascular Disease

Doctoral Thesis

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Environmental factors in cardiovascular disease
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"…Believe only what you yourself test and judge to be true."
S. Gautama

[Ergo: Bonum vinum laetificat cor hominis, ab imo pectore!]

Contents

Abstract

Cardiovascular disease is the main cause of death in Sweden and other developed countries. The purpose of this thesis is to assess the role of certain environmental factors in the etiology of cardiovascular disease, expressed as hypertension and myocardial infarction, focusing on aircraft noise, environmental tobacco smoke, drinking water hardness, and ambient air pollution.

The thesis is based on two epidemiological materials, i.e. an Environmental Health Survey (EH-survey) in Stockholm county during 1997 and the Stockholm Heart Epidemiology Program (SHEEP), which is a county-wide case-control study of myocardial infarction 1992-1994. Aircraft noise exposure was assessed for 266 residents in the vicinity of Arlanda airport and 2693 inhabitants in other parts or the county who answered the EH-survey. The SHEEP-study, comprising 2246 cases of myocardial infarction and 3206 population controls, was used to investigate the importance of exposure to environmental tobacco smoke, intake of drinking water magnesium and calcium, and exposure to source-specific residential air pollution.

Exposure to energy-averaged aircraft noise above 55 dBA was associated with an adjusted odds ratio for hypertension of 1.59 (95% CI 1.00-2.53), and maximum aircraft noise above 72 dBA was associated with an adjusted odds ratio of 1.76 (95% CI 1.12-2.77). A dose-response relation between aircraft noise and hypertension prevalence was suggested. Exposure to environmental tobacco smoke at home and work was associated with an increased risk of nonfatal myocardial infarction among never-smokers, both with regard to intensity, duration, time since last exposure, and cumulative dose. For example, spousal exposure of 20 cigarettes per day or more was associated with an adjusted odds ratio of 1.58 (95% CI 0.97-2.56), and cumulative combined exposure at home and work was associated with an adjusted odds ratio of 1.55 (95% CI 1.02-2.34) in the top decile of exposure. An inter-quartile range increase in the daily intake of drinking water magnesium was associated with an adjusted odds ratio for myocardial infarction of 1.01 (95% CI 0.87-1.17). There was no indication of dose-response for any of the drinking water parameters. An increased risk of fatal myocardial infarction was suggested in relation to long-term air pollution exposure, but not for incidence or nonfatal myocardial infarction. A difference in the 30-year average exposure to traffic-generated NO_2 of 30 µg/m³ was associated with an adjusted odds ratio for fatal myocardial infarction of 1.51 (95% CI 0.96-2.16) and 2.17 (95 CI 1.05-4.51) for out-of hospital death.

In conclusion, the results suggest that exposure to aircraft noise may be associated with an increased prevalence of hypertension, indicate that exposure to environmental tobacco smoke increases the risk of nonfatal myocardial infarction, do not support the hypothesis that drinking water hardness would protect against myocardial infarction, and point to long-term air pollution exposure as a risk factor for fatal myocardial infarction.

List of publications

This thesis is based on the following publications, which will be referred to in the text by their Roman numerals. Published papers were reproduced with permission from the BMJ Publishing Group and Lippincott Williams & Wilkins.

I. Rosenlund M, Berglind N, Pershagen G, Järup L, Bluhm G. Increased prevalence of hypertension in a population exposed to aircraft noise. Occup Environ Med 2001;58(12):769-73.

II. Rosenlund M, Berglind N, Gustavsson A, Reuterwall C, Hallqvist J, Nyberg F, Pershagen G. Environmental tobacco smoke and myocardial infarction among never-smokers in the Stockholm Heart Epidemiology Program (SHEEP). Epidemiology 2001;12(5):558-64.

III. Rosenlund M, Berglind N, Hallqvist J, Bellander T, Bluhm G. Daily intake of magnesium and calcium from drinking water in relation to myocardial infarction. Epidemiology 2005 (in press).

IV. Rosenlund M, Berglind N, Hallqvist J, Jonsson T, Pershagen G, Bellander T. Long-term exposure to urban air pollution and myocardial infarction. (Submitted)

Introduction

Cardiovascular disease is the main cause of death in Sweden and other developed countries.[1] It is also estimated to be the most important reason for loss of disability-adjusted life years worldwide.[2] The most common cardiovascular disorders are hypertension, coronary heart disease, and cerebrovascular disease.[3] After a century of increasing cardiovascular death rates in nearly all countries, mortality has decreased in many western countries, largely due to preventive measures, focusing on life-style changes, and better medical care.[4] However, coronary heart disease is still the leading cause of death and disability in the world.[5]

Well-known risk factors for coronary heart disease include age, sex, smoking, diet, physical inactivity, high blood pressure, diabetes, and high cholesterol levels.[6] Traditional risk factors have been claimed to explain only about half of the occurrence of coronary heart disease,[7-9] although others question that statement.[10] A recently conducted study in 52 countries worldwide suggested that nine modifiable risk factors account for most of the risk of myocardial infarction in the population.[11]

Beside the established risk factors, cardiovascular epidemiology has proposed more than 200 additional risk factors that might be associated with the disease.[12] The cardiovascular risk factors can be classified into those that are modifiable such as tobacco use, physical inactivity, and diet, and those that are not, for instance age, sex, or heredity.[1] The modifiable factors include life-style factors such as smoking, diet, and physical inactivity, social factors like social class and income, occupational factors comprising job stress and combustion products, and environmental factors that involve ambient air pollution and noise.

The major research focus in early years of epidemiologic studies since the past mid-century was on life-style factors and biological markers for cardiovascular disease,[9] followed by studies of genetic susceptibility, and social differences in incidence and mortality.[13] The geographical and regional variations in cardiovascular disease found in Sweden,[14-17] and many other countries have been suggested to partly be caused by environmental factors.[18-24] Compared to other risk factors, the association between environmental factors and cardiovascular disease has been studied less extensively, resulting in uncertainty as to which role the environment plays in the causation of cardiovascular disease.[25]

Environmental factors suggested to be of importance for cardiovascular disease include environmental tobacco smoke (ETS),[26,27] ambient air pollution,[28-30] noise exposure,[31-35] and the chemical composition of drinking water.[36] Furthermore, also other environmental exposures, such as lead and polyaromatic hydrocarbons,[25,37,38] and meteorological factors like temperature[39-43] and rainfall,[41] have been discussed in relation to cardiovascular disease. Yet, despite some research on the association

between environmental exposures and cardiovascular disease, many questions still remain regarding which environmental agents play a role and the nature of their pathophysiological mechanisms. The increasing interest for environmental factors in the etiology of coronary heart disease is manifested by a new emerging research field of *environmental cardiology*.[44]

The present thesis is focused on the epidemiology of environmental factors in cardiovascular disease that are preventable and important to public health since they affect many people. Behavioral factors are not within the primary scope of the thesis, and neither is medical treatment of the disease. The thesis addresses factors in the environment that may be important for policy making and public health prevention since they are not possible to easily modify by people themselves. Emphasis is on long-term exposures (years or decades) rather than the short-term exposure scale (hours, days or weeks). Even if these environmental exposures may be associated with low or modestly increased risks compared to many other established risk factors, they may have great public heath implications due to the high disease incidence and the large number of people that are exposed to these factors. The uncertainty of the role that the environment has on the risk of cardiovascular disease in combination with the high incidence rates and the large potential for preventive measures motivates more research on this topic and thus forms the basis of this thesis.

Background

Disease outcomes

The major cardiovascular diseases included in this thesis are hypertension and myocardial infarction. Hypertension is one of the most important risk factors for coronary heart disease, and together with myocardial infarction and stroke the most common of the cardiovascular diagnoses.[3] Myocardial infarction is the single most common cause of death today in Sweden and other western societies.[45]

Hypertension

Hypertension refers to a clinical diagnosis of persistently increased blood pressure that may be harmful to the cardiovascular system.[46] High blood pressure has deleterious effects on the coronary, renal, and cerebral arteries, and causes an increased work load on the heart.[3] Thus, hypertension is associated with increased risks for atherosclerosis, coronary heart disease and stroke. The definition of hypertension has been subject to much debate and scrutiny during the last decades, especially with regard to its arbitrary nature and when it should be treated.[47]

The blood pressure varies widely from individual to individual and within one individual at different times.[46] It changes with physical activity, stress, age, and many other circumstances of the individual.[3] Blood pressure is highest when the heart beats to push blood out into the arteries (i.e. systolic pressure), and lowest when the heart relaxes to fill with blood again (i.e. diastolic pressure). Blood pressure is measured in millimeters of mercury (mm Hg) and if a person's systolic pressure is 120 and diastolic pressure is 80, it is expressed as 120/80 mm Hg.

Hypertension can be defined in several ways in epidemiological studies, e.g. using different cut-points for systolic and diastolic blood pressure readings as described above, information on medication, or self-reports of diagnoses in a questionnaire.[47] Many people have hypertension without knowing it due to lack of symptoms.[3] A number of factors such as pain, stress or anxiety can cause a temporary increase in blood pressure. Thus, hypertension is not diagnosed from one high blood pressure reading, but is usually based on two or more readings after the first visit.[46] In epidemiological studies, it may be more efficient to use continuous blood pressure data than a dichotomy based on some arbitrary predefined clinical threshold that is used to defined whether a patient should receive medical treatment or not, given the continuous nature of the relationship between the level of blood pressure and the cardiovascular risk.[47]

The prevalence in a population will depend on the level of blood pressure used to define hypertension. The WHO defines hypertension as a blood pressure of 140/90 mm Hg or above in subjects who do not take antihypertensive medication.[47] Before

the WHO 1999 Guidelines for the management of hypertension, higher cut-points were usually applied to determine when treatment for hypertension was needed. In Sweden 160/95 mm Hg was often used, resulting in a lower prevalence.[48]

Worldwide, more than a quarter of the adult population had hypertension in 2000 using the WHO 1999 definition, which according to recent projections will increase to 29% by 2025.[49] The prevalence varies widely around the world, with rates as low as 3.4% in rural Indian men and as high as 72.5% in Polish women, but is generally between 20% and 50% in economically developed countries.[50] In Sweden, the prevalence of blood pressure above 140/90 among people over 20 years of age is 27%, corresponding to 1.8 million people.[46] In that group, 60% have "mildly increased blood pressure" (140-159/90-99 mm Hg), 30% have "moderately increased blood pressure" (160-179/100-109 mm Hg), and 10% have "seriously increased blood pressure" (>180/>110 mm Hg).

Prevalence estimates from questionnaire data will be more or less affected by bias, such as information bias due to the individual's memory (recall bias). Defining only those who report hypertension diagnosed by a physician may result in underestimation of true disease prevalence. However, some studies have shown substantial agreement between questionnaire responses and medical records or physician-reports of hypertension.[51-54] A US study reported prevalence estimates of hypertension based on questionnaire responses of 35.8% compared to diagnosis according to medical records of 37.7%.[51] Others have found that self-reports underestimate the prevalence of hypertension when compared to subsequent health examination.[55,56] A nationwide US study reported sensitivity of 71% and specificity of 90% for self-reported hypertension when interviewed compared to hypertension defined by blood pressure readings.[56] In a Swedish population-based study among people above 20 years in 1995, the prevalence of self-reported hypertension by questionnaire was 9%.[57]

Myocardial infarction

A myocardial infarction occurs when one or more of the coronary arteries that supply blood to the heart are completely blocked and blood to the heart muscle is cut off.[3] The blockage is usually caused by atherosclerosis, the build-up of plaques in the artery walls, and/or by a blood clot in a coronary artery. Myocardial infarctions are generally caused by blood clots that form on atherosclerotic plaques, blocking a coronary artery from supplying oxygen-rich blood to a part of the heart. The longer the artery remains blocked during a myocardial infarction, the more damage will be done to the heart, which could lead to sudden death.

Most cases experience symptoms before their myocardial infarction, often including chest pain that spreads to the shoulders, neck, or arms, and chest discomfort

accompanied by lightheadedness, fainting, sweating, nausea, or shortness of breath.[3] Diagnosis is usually based on information from the patient, heart rate and blood pressure readings, electrocardiogram, and blood samples to see any leak of enzymes or other biochemical markers from damaged cells in the heart muscle. A myocardial infarction may also be atypical or silent, i.e. without symptoms and therefore undetected until medical examination.

Age-standardized incidence and mortality differs widely throughout the world and has declined in most countries during the last decades.[58,59] In western Europe, mortality from coronary heart disease increased in most countries until the 1980s and declined thereafter.[60] In the EU as a whole, age standardized mortality from coronary heart disease rose from 146.2/100,000 in the second half of 1960s to 158.9/100,000 in the end of 1970, but declined thereafter to reach 99.6/100,000 in 1995-97, corresponding to a decline of 37% since the late 1970s.[61] In the US, the age-standardized mortality from coronary heart disease declined from 448.0/100,000 in 1970 to 186.6/100,000 in 2000, i.e. a change of 58.3%.[62] Death rates from coronary heart disease is however increasing in other parts of the world, e.g. China, in recent decades.[58]

In Sweden, the incidence of myocardial infarction increased until 1980,[63,64] followed by and decreasing trend.[65-68] The decline was about 20% during the 10-year period 1987-1997.[69] The MONICA project has also registered a decline in the occurrence of traditional risk factors for myocardial infarction from 1985 to 1995.[70] The age-standardized incidence of myocardial infarction in Swedish men declined from 987 during 1987 to 881/100,000 in 1995, while mortality decreased from 443 to 381/100,000.[66] Corresponding figures for women was a decline in incidence from 444 to 400/100,000, and in mortality from 202 to 173/100,000. Between 1987 and 1995, the age-standardized incidence of myocardial infarction in Sweden thus declined by 11% for men and 10% for women, while mortality decreased by 14% for both genders. Incidence in myocardial infarction is about 15-20% lower in Stockholm county compared to nation-wide figures, with age-adjusted incidence rates of first-time myocardial infarction in men 30-89 years of 491/100,000 and in women of 297/100,000 during 1993-1995.[71]

In general, Swedish men have about 2,5 times higher death rate in cardiovascular disease than women.[69] Ischemic heart disease accounted for 61% of all cardiovascular deaths in men during 1998, while the corresponding figure for women was 49%. Myocardial infarction accounted for 40% of all deaths among men and 33% among women. A protective effect from oestrogen is assumed to be the reason for the sex difference, but environmental factors may also be important.[21]

Environmental exposures

There is great uncertainty regarding the environmental etiology of hypertension and myocardial infarction.[25] The present thesis is focused on the main factors related to hypertension and myocardial infarction discussed in the literature of relevance for public health prevention. These include community noise exposure, here represented by aircraft noise, environmental tobacco smoke, drinking water hardness, and ambient air pollution.

Environmental medicine focuses on exposures in the surrounding environment of the population, often represented by the community where people live.[72] The same exposures may be studied in occupational medicine, where the working place and its often higher exposure levels, is of interest.[73] Studies of associations between disease and the ambient environment may be hampered by lower levels and contrast in exposure, but are of great public health importance due to the large number of people that are unwillingly exposed to factors like air pollution and noise in their neighborhood. In addition, the general population may include people that are especially vulnerable to certain exposures, while the typical working force comprises more healthy subjects. These differences are reflected by higher occupational exposure limits than environmental standards and guideline values. Since occupational studies typically include smaller numbers of study subjects, small relative risks of low level exposures may be missed. Thus, even if good epidemiological data from occupational studies may suggest small or no association, the prevalence of exposure, the high disease incidence, the public health concern, and the large potential for prevention by society motivates research on environmental factors in cardiovascular disease. The application of geographic information systems (GIS) in environmental epidemiology has made geographical data more useful.[72]

Aircraft noise

Community noise, or environmental noise, such as road traffic or aircraft noise, causes annoyance in the population and have become a major environmental problem affecting a large proportion of today's urban population.[74] The relation between community noise exposure and subjective complaints, annoyance and sleep disturbance is well documented.[75] In recent years there has been a growing concern that persistent stress from long-term residence close to noisy roads or airports also may lead to adverse health effects, such hypertension and cardiovascular disease.[76] However, the proposed association between noise exposure and such outcomes has received limited scientific attention.[32]

Noise is defined as unwanted sound and is characterized according to it's frequency, temporal occurrence (day or night), and strength.[77] When assessing noise exposure, the level of the sound is usually expressed in dBA, which refers to the use of an A-filter to adjust the frequency of the sound according to the sensitivity of the human

ear.[78] The sound can be characterized according to time and frequency, and common measures include the maximum sound level (LAmax) and the average-energy equivalent level (LAeq).[74] Aircraft noise is generally modeled in contours on a map according to the geographical propagation and may be expressed in dBA as an energy-averaged level or the maximum level that occurs a certain number of times during a day.[79] In Sweden, the energy-averaged level is called FBN ("flygbullernivå"), and is calculated as the mean noise level of all overflights energy-weighted to one hour, during a typical 24-hour period in a year.[80] The maximum noise level (MNL) is calculated as the highest noise level from aircraft overflights that occurs at least three times during the average 24-hour period in a year.

WHO has set up guidelines for community noise arranged according to specific environments and critical health effects.[81] To protect most people from being seriously annoyed by noise at daytime it is recommended that the noise level (LAeq) should not exceed 55 dBA at balconies, terraces, and outdoor living areas. To avoid sleep disturbance, indoor guideline values for bedrooms are 30 dBA for continuous noise and 45 dBA for single sound events at night (LAmax). In Sweden, the national guideline for outdoor noise is 55 dBA (LAeq) at the façade of the dwelling, and 30 dBA indoors.[82] The national guideline for aircraft noise exposure is 55 dBA as averaged noise level (FBN), and 70 dBA as maximum noise level (MNL).

In the European Union about 40% of the population is exposed to traffic noise levels exceeding 55 dBA at daytime (LAeq) and 20% are exposed to levels exceeding 65 dBA.[74] More than 30% are exposed at night to noise levels exceeding 55 dBA (LAeq). A calculation in 1998 suggested that more than 2 million of the Swedish population were exposed to traffic noise above 55 dBA and 250,000 were exposed above 65 dBA outside their residence.[83] More than 100,000 were estimated to be exposed to aircraft noise above 55 dBA outside their residence, and 55,000 to levels above 70 dBA.

An association between aircraft noise and hypertension was first suggested by Knipschild in the late 1970s.[84] He investigated the association between living close to Schiphol airport outside Amsterdam in the Netherlands and different medical outcomes, such as medical drug use, cardiovascular hospital visits, and prevalence of hypertension.[84-87] In one of these studies comprising people between 34 to 64 years living in eight villages around the airport, the prevalence of hypertension was reported to be greater in the aircraft noise exposed areas.[84] However, that study suffered from a high non-response rate (58%), which might have resulted in selection bias. A recently published similar cross-sectional study of the population around the same airport (with a response-rate of 39%) suggested that the noise from the airport caused impaired health in the population and was related to the use of medicines for hypertension and cardiovascular disease as measured by self-reports in a questionnaire.[88] Some association has also been observed between aircraft noise

exposure and elevated blood pressure in cross-sectional studies of children, but the evidence is weak.[89] Recent reviews have concluded that studies to date have shown contradictory results, but that there is some epidemiological support linking traffic noise exposure to hypertension.[32,35]

Environmental tobacco smoke

Both active and passive smoking, i.e. exposure to environmental tobacco smoke, have been shown to constitute risk factors for coronary heart disease in epidemiological studies.[90,91] Following the increasing scientific evidence of second hand smoke as an important risk factor for lung cancer and heart disease, many countries have banned smoking in public places to protect the majority of the populations that are non-smokers.[92-94] However, passive smoking still poses a major preventable environmental risk factor for cardiovascular disease worldwide, and industry have put down much effort to discredit the evidence on passive smoking and disease by labeling it "junk science".[95] Sargent and coworkers reported a decrease in hospital admissions for myocardial infarctions of about 40% during the six months when a smoking ban in public and workplaces was in effect.[96]

The association between cardiovascular disease and exposure to environmental tobacco smoke has been assessed in several reviews,[97-100] cohort studies[101-107] and case-control studies.[108-113] Although some have failed to report any association,[109,110,114] the risk of cardiovascular disease from exposure to environmental tobacco smoke has been assessed both at home[101-111,113] and work.[101,108,112] Epidemiological studies have also estimated the risk of cardiovascular disease separately in men[102-104,106,108,110,111,113] and women.[101,103-108,110-113] Many studies have assessed the risk according to the average number of cigarettes daily smoked by the spouse,[102-104,106,108,111-113] and in relation to duration, mostly defined as never, former and current exposure.[103,106,107,111,112] Intensity and duration have been combined to assess the risk of cardiovascular disease from cumulative exposure to environmental tobacco smoke.[103,112]

Three meta-analyses have summarized the risk of cardiovascular disease from environmental tobacco smoke exposure.[26,90,115] Law and colleagues calculated the relative risk of ischemic heart disease associated with exposure to environmental tobacco smoke from 19 studies to be 1.30 (95% CI 1.22-1.38) for lifelong non-smokers who live with a smoker.[26] He *et al* estimated a relative risk of coronary heart disease from 18 studies of 1.25 (95% CI 1.17-1.32) for non-smokers exposed to environmental tobacco smoke compared to unexposed non-smokers.[90] Thun and coworkers assessed a relative risk of ischemic heart disease related to spousal environmental tobacco smoke exposure of 1.25 (95% CI 1.17-1.33) using data from 17 studies.[115]

A national Environmental Health Survey in 1999 recorded 11% of the adult Swedish population being daily exposed to environmental tobacco smoke.[116] In Stockholm county, 20% of the inhabitants in those ages reported that they were daily exposed to the smoke from other people during 1997,[117] which constituted a significant decrease compared to a similar survey in 1992 when 42% of those 18-65 years old reported daily exposure to environmental tobacco smoke.[77] The National Board for Health and Welfare has estimated that environmental tobacco smoke may be responsible for a few hundred annual deaths in cardiovascular disease in Sweden,[45] which corresponds to about one hundred cases each year in Stockholm county.[117]

Drinking water hardness

Since the end of the 1950s, numerous studies have reported an association between the hardness of the drinking water or its content of magnesium and calcium, and cardiovascular disease.[36,118] Such investigations have been performed in North America,[119-123] Europe,[19,124-143] Africa,[144] and Asia.[145-147] Many researchers have suggested that hard drinking water might be correlated with low mortality from cardiovascular disease,[19,124,130,131,135,136,138-142,146-148] while others have not found any association.[40,121,149-151] These studies have been summarized in reviews[148,152-155] and scientific theses.[17,36]

Initially, researchers hypothesized that there was a toxic effect of soft drinking water due to corrosion resulting in higher levels of certain metals such as lead and cadmium.[156] Since the water hardness is mainly determined by its content of calcium and magnesium, another theory emerged that the higher levels of magnesium and calcium in hard drinking water would protect against cardiovascular disease.[152] This initiated a large number of mainly ecologic (group-level) studies comparing the death rates in areas with different water hardness. Hard drinking water has therefore been considered to protect against myocardial infarction, and magnesium has been pointed out as the biologically most plausible protective factor of hard drinking water.[152]

In essence, there are only few studies which have used individual level data on exposure and disease. In 1983, Luoma and coworkers reported high relative risks of myocardial infarction in 50 male cases compared to population controls associated with low magnesium levels (<1.2 ppm) in the drinking water that was analyzed, but no association with calcium.[127] However, exposure was assessed after disease onset, only age and type of community was controlled for, and selection bias may have been present. In 1999, Rubenowitz and colleagues reported a protective effect on fatal myocardial infarction in the highest quartile of magnesium level in the tap water (>10 mg/l) in men[132] and subsequently also in women,[133] in whom also calcium appeared to protect against myocardial infarction death. However, age was the only potential confounder considered and the results have been criticized.[157] A subsequent study from this group did not show any association between the amount of these

water constituents and overall myocardial infarction incidence, but suggested a protective effect from magnesium but not calcium on the sub-group who died from their infarction.[134] Intake of magnesium from the water did not protect against myocardial infarction.

Among the six most recent studies that have been published on this topic between 2000 and 2004, five were ecologic investigations,[124,138-140,145] and one was of experimental character suggesting that drinking water calcium was correlated with cardiovascular risk factors in the blood of about 200 subjects.[129] This issue remain unresolved, since the vast majority of the evidence stems from ecological data, and also recent large and detailed studies have not displayed any association.[128,145]

Ambient air pollution

Since the London Smog episode in December 1952 when a dramatic increase in mortality and morbidity followed the days after extremely high levels of air pollution,[158,159] the health effects of air pollution have been subject to intense research, especially in the last decade. A large body of scientific evidence has demonstrated that ambient air pollution is associated with short-term health effects,[28,160-166] and a handful studies have also addressed the health risk from long-term exposure.[167-172] Since these studies suggest that health effects might occur at lower levels than previously considered to be safe, many countries have reassessed their air pollution standards.[173-175]

Air pollution includes many different components, e.g. particles, ozone, and nitrogen dioxide that may contribute to a variety of health effects.[176] Generally, epidemiologic air pollution research has to a large extent been focused on mortality and morbidity especially related to airborne particles.[177] A large number of studies have shown associations between day-to-day variations in air pollution levels and increases in hospital admissions or mortality in lung- and heart disease.[28] Many studies, both experimental and epidemiological, have been conducted in order to elucidate possible mechanisms for the association reported in the epidemiological literature.[176-178]

In particular, two US cohort studies have received a lot of interest,[168,169] and together with another study[167] these long-term studies built up an early body of epidemiologic results suggesting that living in cities with high levels of air pollution may cause increased morbidity and mortality from respiratory and cardiovascular disease. These three American cohort studies provided the only data available for estimating the risk of increased mortality associated with long-term exposure to air pollution and thus the results from these studies have been used to estimate the number of deaths attributable air pollution in the US and in Europe.[29,30,179,180] Subsequently, two additional European cohort studies have confirmed the association between long-

term exposure to air pollution and cardiopulmonary mortality, and especially pointed towards pollution from traffic.[170,171] Because the US cohort studies have been subject to criticism of their estimated effect size, limited confounding control, group-level exposure assessment, and short follow-up times,[181] an independent reanalysis of the data used in these studies has been performed,[180] that largely confirmed the previously published results.[182]

Missing links

Despite various support for links between these environmental factors and cardiovascular disease, there are still gaps in the knowledge that make the scientific evidence uncertain and prone to criticism. Such "missing links" in the knowledge include issues related to study design, data analysis and reporting. Thus, several issues remain to be addressed. The perspective needs to be broadened and a number of methodological problems need to be solved.

With regard to a possible association between community exposure to aircraft noise and prevalence of hypertension, previous data have been very sparse, with essentially only one prior study published in the scientific literature.[84] Given the hypothesis generating character of that investigation and the biological plausibility of such an association between noise and hypertension often referred to by others,[32,35,78,89,183-187] more research should focus on the possible link between aircraft noise and hypertension.[188]

Previous studies on the association between exposure to environmental tobacco smoke and cardiovascular disease have not taken a potential risk reduction after exposure cessation into account and there are uncertainties regarding the importance of combined exposure in different environments, e.g. home and work. In addition, there has been a lack of Swedish studies on environmental tobacco smoke and cardiovascular disease, resulting in uncertainty in the risk assessment for the Swedish population. Critics have claimed that non-smokers who live with smokers tend to adapt to dietary habits of their spouse,[189] and previous studies on environmental tobacco smoke lacked control for confounding from diet. There is also limited data on possible effect-modification by other factors.

The association between drinking water hardness and cardiovascular disease has mainly been studied on a group (ecologic) level, and in essence only a few previous studies have had access to individual data.[127,132-134] The major criticism against the hypothesis has been the low relative daily intake of magnesium and calcium from the drinking water as compared to diet that accounts for about 90% of the daily intake.[157] However, it has been argued that magnesium in drinking water would be more easily absorbed by the body than dietary magnesium,[190] and that cooking in magnesium rich water would be an important added source of exposure.[191] Nevertheless, only

one previous study considered dietary magnesium and how much water the study subjects actually consumed,[134] thus the daily intake has been largely ignored. Beside age and sex, little is known regarding potential confounding from other factors.

Previous studies of long-term exposure to air pollution and cardiovascular disease have focused on cardiopulmonary mortality and only occasionally included cause-specific mortality such as myocardial infarction or coronary heart disease. In addition, since cohort studies have addressed mortality, little is known regarding possible associations between long-term air pollution exposure and incidence or nonfatal cardiovascular disease. The aggregated exposure data and the inter-individual differences in residential distance from the pollution monitors used to assess exposure, as well as limited longitudinal exposure information, makes misclassification of true individual exposure a major problem in previous studies. Since recent focus has turned towards traffic-generated air pollution,[170,171] particular attention to partial contributions from different sources is needed. Intensity of exposure, duration of exposure, cumulative dose, and different time windows for individual exposure, also need to be further explored. Susceptible individuals and population subgroups should be identified.[192] Potential confounding, including assessment of its magnitude, and possible modification of the effect by other factors like socioeconomic status,[193] need further exploration.

Aim of the thesis

The main purpose of this thesis is to investigate associations between the environment and cardiovascular disease in epidemiological studies, focusing on myocardial infarction and hypertension. The environmental factors studied include aircraft noise, environmental tobacco smoke, drinking water hardness, and ambient air pollution.

The following specific aims are addressed:

- To explore a possible association between community exposure to aircraft noise and the prevalence of hypertension, employing alternative exposure metrics.
- To investigate an association between exposure to environmental tobacco smoke and the risk of myocardial infarction, addressing specific issues of the exposure, i.e. time since last exposure, duration, intensity, and cumulative dose.
- To test the hypothesis that the hardness of the drinking water and the daily dose of drinking water magnesium and calcium is associated with a decreased risk of myocardial infarction.
- To examine if long-term exposure to residential ambient air pollution is associated with the risk of myocardial infarction mortality and morbidity, partitioned on major sources and their individual pollutants.

Material and methods

The papers that constitute this thesis are based on a large regional Environmental Health Survey on environmental exposures and prevalence of health symptoms in Stockholm County and the Stockholm Heart Epidemiology Program (SHEEP), which is a population-based epidemiological study on risk factors for myocardial infarction.

Environmental Health Survey

The details of the Environmental Health Survey used for study I have been described in a special report,[117] and some scientific papers.[194-198] In brief, a questionnaire was sent to 15,000 persons between 19 and 80 years old in Stockholm county in April 1997, with an overall response rate of 73%. The questionnaire covered a large set of issues related to the environment and public health, such as subjective symptoms related to the subject's indoor and outdoor environment, with a special focus on asthma and allergies, and traffic related ill-health. To secure a sufficient number of subjects in different parts of the region, a stratified sampling comprising 17 strata was performed by Statistics Sweden. Since one aim of the survey was to investigate symptoms related to noise from air traffic, a special sample was drawn among those who lived around Arlanda airport. Other strata included parts of Stockholm city and the rest of the county. Along with 87 questions, the subjects were also asked whether they had been diagnosed with hypertension by a physician during the last five years, which constituted the disease outcome of study I.

Stockholm Heart Epidemiology Program

The SHEEP-study used for papers II-IV, includes all cases of first-time myocardial infarction in the ages 45-70 during 1992-1994 in Stockholm county, and randomly selected control subjects stratified on age, sex and hospital catchment area. The study design has been described in detail elsewhere.[13,199] Altogether, 2246 cases and 3206 controls were included. The individual background information was collected by a questionnaire covering a large number of potential risk factors for myocardial infarction, including physical and psychosocial workplace conditions, social factors, and different life style factors. In addition to the questionnaire, a telephone interview was performed to fill-in on missing data and decrease non-response. A health examination was performed on surviving cases and controls in order to collect biological data related to cardiovascular disease. The study has generated a large number of scientific publications on the association between myocardial infarction and e.g. socioeconomic status,[200-203] occupational exposures,[204-211] biological and hereditary factors,[212-219] triggering factors,[220-223] alcohol habits,[224] tobacco exposure,[215,225,226] coffee consumption,[227] and physical inactivity.[228] Thus, studies II-IV of this thesis adds an environmental focus to the knowledge base generated by the

SHEEP-study, and make use of the information previously attained, e.g. in the assessment of confounding.

Study subjects

The study subjects were selected from Stockholm county. Study I included inhabitants living close to Arlanda airport and other parts of the county who participated in the Environmental Health Survey in 1997. Study II-IV included cases that suffered from their first myocardial infarction 1992-1994 and matched controls from the SHEEP-study. The criteria for selection of the subjects has been described in detail elsewhere.[13,199,229]

Study I included 2959 randomly selected adult subjects, 266 living close to the airport and 2693 resident in other parts of the county. Study II included 334 never-smoking myocardial infarction cases and 677 never-smoking controls. Only never-smokers were included since the study focused on passive smoking and would otherwise be prone to confounding from active smoking. In addition, only nonfatal subjects were included because of potential inaccuracy in historical exposure information from relatives of fatal cases, which may be of special importance regarding passive smoking long time ago and at work. Study III included 497 myocardial infarction cases and 677 controls in eight municipalities, selected on the basis of their drinking water quality. Study IV was based on 1397 cases of myocardial infarction and 1870 controls, who had sufficient historical residential address data.

Table 1 summarizes some general features of the subjects in the different studies. All were adult people in the ages 19-80 or 45-70 years. The mean age in the four studies was 46.9, 61.5, 60.4, and 60.9 years, respectively. There were slightly more men than women in all studies, corresponding to 54%, 59%, 63%, and 65%. Smoking was more common in the SHEEP-study than the EH-survey, probably due to an older age span and earlier recruitment. The prevalence of hypertension was 14% in study I, and 31-33% in the other studies, depending of the methodology used to define hypertension.

Exposure assessment

To determine noise exposure in study I, all residences in the study were given geographical coordinates by combining the National Population Register and a register on territorial properties (i.e. real estates). Contour lines from the Swedish Civil Aviation Administration, representing geographical boundaries with average and maximum aircraft noise levels during 1997, were superimposed on a digital map containing the resident's coordinates using geographical information system (GIS) techniques. These contours were generated by a computer model based on yearly

statistics of air traffic as input data, e.g. take off patterns, aircraft types, and speed. In principle, the model calculates the propagation of aircraft noise during the average 24-hour period for each year, i.e. on a typical day.[80]

In study II, all exposure data was collected by the SHEEP-questionnaire. The subjects reported exposure to second-hand smoke at home and at work throughout life. The following questions were asked (questions on exposure during childhood omitted due to lack of association): "Have you lived with a spouse or cohabit who smoked/smokes daily?"; "How much did your spouse/cohabit smoke daily at home?"; "Have you been exposed to other people's tobacco smoke at your workplace?"; "How long time did you spend in rooms where smoking occurred?" The subjects were asked to fill in age periods and type and number of tobacco items for the questions on intensity at home, and age period and number of hours per week and days per week for the questions on duration at work. Cumulative exposure was calculated as the number of "pack-years" (1 pack-year equals exposure to 365 packs of cigarettes or equivalent of 1 cigarette pack smoked by the cohabit per day for one year) or "hour-years" (1 hour-year is 365 hours of exposure to cigarette smoke or equivalent of 1 hour of exposure per day for one year).

The exposure assessment in study III was based on questionnaire data of the subject's home address during the last two years before inclusion in the study, which were linked to the waterwork each address was connected to by officials at the municipalities. Historical protocols of water analysis during 1990-1994 at each waterwork were collected and summarized to annual mean levels for each subject. Those who stated in the questionnaire that they used private well water were asked to take a sample of their drinking water from the well that was analyzed by a water laboratory. The mean level of drinking water parameters was multiplied by the questionnaire data on amount of domestic water consumed by each subject, to obtain an estimate of the daily dose of drinking water magnesium and calcium intake.

The assessment of air pollution exposure in study IV was done by translating each residential address to a geographical co-ordinate using a regional address database (Tätort 2000)[230] in combination with GIS, and then calculating the annual average source-specific pollution level at each address. The address data was collected in a questionnaire, where each subject, or their next-of-kin for fatal cases, was asked to report all their home address inhabited during at least two years since birth. Missing address data was replaced with information from registers at parish offices and tax authorities. The calculation of retrospective air pollution concentration at each address was done by SLB-analys at Stockholm Environment and Health Protection Administration by dispersion modeling that takes all known sources of pollution, landscape, meteorology, and other important factors into consideration.[231] The main input for the dispersion calculation is data on all identified emission sources for air pollution, which has been maintained in historical databases for each decade since

1960, i.e. 1960, 1970, 1980, 1990, and 2000. Linear interpolation of the pollutant level was performed for each address for the years between the emission databases. Thus, annual individual residential levels of air pollution from 1960 until study inclusion (1992-1994) were calculated for cases and controls. We allowed no more than five years of unknown residency during the 30-year period and years with missing air pollution data due to unknown residency was replaced by the mean among controls for that year. In total, 4% of all residential exposure years were missing and replaced by the mean among controls. Most subjects with missing in any year had one year absent and only 110 of the 3267 subjects had 4 of 30 years missing. To separate the two main sources of air pollution in the region, i.e. traffic and heating, nitrogen dioxide (NO_2), carbon monoxide (CO), and particulate matter with an aerodynamic diameter of less than 10 µm (PM_{10}) are used as markers for emissions from road traffic. Likewise, sulphur dioxide (SO_2) is used as an indicator of emissions from residential heating. A street canyon contribution to the traffic-generated pollution was added for addresses in segments of streets with intense traffic to account for the small scale (within-city) difference.

Figure 1 illustrates the procedure for assessing exposure in each study.

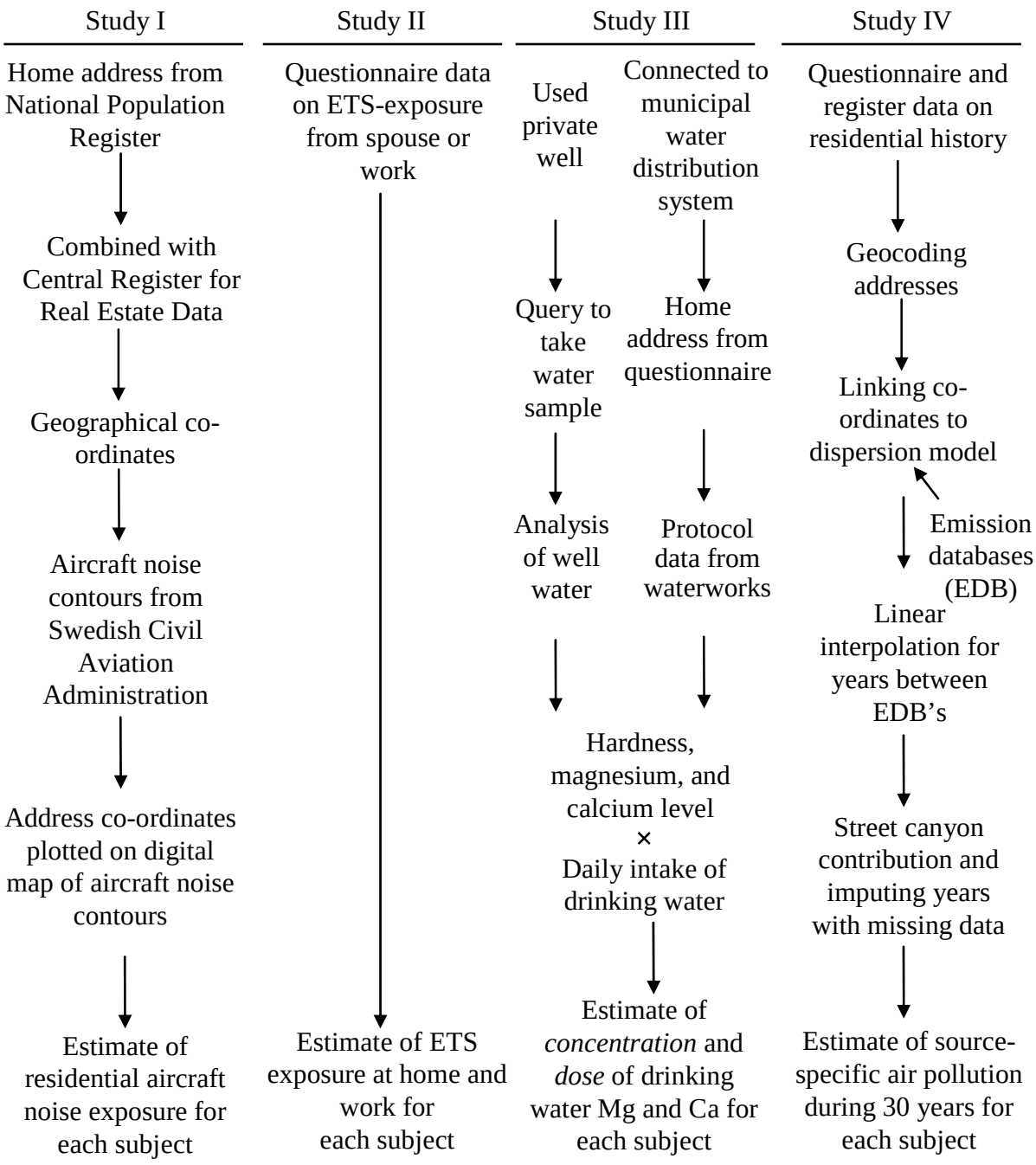

Figure 1. Schematic picture describing the exposure assessment process in each study.

Thus, chemical analysis, computer modeling or direct calculation of exposure from questionnaire data was used as methods to produce the relevant exposure estimates that were used in the epidemiological analysis. Table 1 summarizes some important characteristics of the exposure assessment in each study, along with data on the disease outcome.

Table 1. General description of exposure and disease outcome in studies I-IV, and selected characteristics of the study subjects in the thesis (percent of all responding subjects in parenthesis unless otherwise stated).

	Study I	Study II	Study III	Study IV
Exposure data				
Main exposure	Noise	ETS	Water	Air pollution
Exposure data point	Address	Questionnaire	Address	Address
Exposure data source	Register	Questionnaire	Questionnaire +Register	Questionnaire +Register
Assessment method	Modeling	Questionnaire	Analysis	Modeling
Important parameters/ metrics*	FBN, MNL	Pack years, hour years	Mg, Ca, hardness	NO_2, NO_x, CO, PM_{10}, $PM_{2,5}$, SO_2
Main exposure unit	dB(A)	g/day	mg/l, mg/day	µg/m^3
Follow-up time	1 year	Lifetime	2 years	30 years
Outcome data				
Data source	EH-survey	SHEEP	SHEEP	SHEEP
Inclusion period	1997	1992-1994	1992-1994	1992-1994
No. of subjects	2959 (100)	1011 (100)	1174 (100)	3267 (100)
No. of cases	422 (14)	334 (33)	497 (42)	1397 (43)
Sex				
Men	1604 (54)	600 (59)	745 (63)	2137 (65)
Women	1355 (46)	411 (41)	429 (37)	1130 (35)
Mean age (±SD)	46.9 (15.6)	61.5 (6.9)	60.4 (7.2)	60.9 (6.8)
Smoking				
Never	1445 (49)	1011 (100)	393 (33)	1142 (35)
Former	897 (30)	0 (0)	303 (26)	912 (28)
Current	617 (21)	0 (0)	478 (41)	1213 (37)
Hypertension†	422 (14)	337 (33)	365 (31)	1015 (31)
Diabetes‡	–	116 (11)	159 (14)	431 (13)
Overweight§	–	267 (26)	336 (29)	858 (26)

* FBN=energy-averaged aircraft noise ("flygbullernivå"); MNL=maximum noise level occurring 3 times on the average 24-hour period of a year. 1 "pack-year"=365 packs or equivalent of 1 cigarette pack per day for one year; 1 "hour-years"=365 hours of exposure or equivalent of 1 hour of exposure per day for one year.

† Defined as self-reported hypertension by a physician during the last 5 years in study I, and as medical treatment (at inclusion or during the last 5 years) according to the questionnaire or a blood pressure above 170/95 at the clinical examination in study II-IV. Missing values were reported for one subject in study II, 15 subjects in study III, and 52 subjects in study IV.

‡ Defined as treatment according to the questionnaire or a glucose level >6.7 mmol/l on clinical examination. Missing reported for one subject of study III and 4 subjects of study IV.

§ Defined as a body mass index above 28 kg/m^2 at the clinical examination. Missing values were reported for 13 subject in study III, and 45 subjects in study IV.

Statistical analysis

Associations between the environment and disease were estimated by odds ratios and their 95% confidence limits. The logistic regression models were adjusted for matching variables where applicable using the statistical software Stata (versions 6-8). Adjustment for important covariates was done by including either continuous variables or categorical (indicator) variables in the model. The environmental exposures of interest were used as continuous variables or categorical variables with cut-offs at percentiles according to the distribution among controls or exposed, or at pre-defined values based on environmental regulation standards.

Correlation between variables was tested using the Spearman's rank correlation coefficient when ordered categorical variables were used, or the Pearson correlation coefficient when applying continuous numerical variables. Linear trends over categories were analyzed by treating the indicator variable as continuous in the logistic regression model.

Effect-modification was explored by stratified analysis, including an interaction term between the exposure of interest and other variables, or by calculating the proportion of cases among those with joint exposure that might be attributable to their interaction using a SAS-program that allows for control of confounding.[232]

Attributable proportion of disease due to exposure was estimated by the aflogit command in Stata,[233] which uses the data to calculate the distribution of exposure among cases and the odds ratio of disease, and applies these to the formula AF=Pr(exposed|disease)(1-(1/RR)), with adjustment for confounding.

Results

Below is a summary of the main results from each study. Additional information and more comprehensive descriptions and illustrations of the study results are given in the papers of study I-IV. Any new results that are not included in those papers are referred to below as “reanalysis”.

Aircraft noise and hypertension

Aircraft noise exposure was associated with self-reported prevalence of hypertension. Exposure to energy-averaged aircraft noise above 55 dBA yielded an odds ratio of 1.59 (95% CI 1.00-2.53) when adjusted for age, sex, smoking, and education, compared to those exposed below that level. Similarly, maximum aircraft noise above 72 dBA was associated with an adjusted odds ratio of 1.76 (95% CI 1.12-2.77). A dose-response relation between aircraft noise and hypertension prevalence was suggested (figure 2).

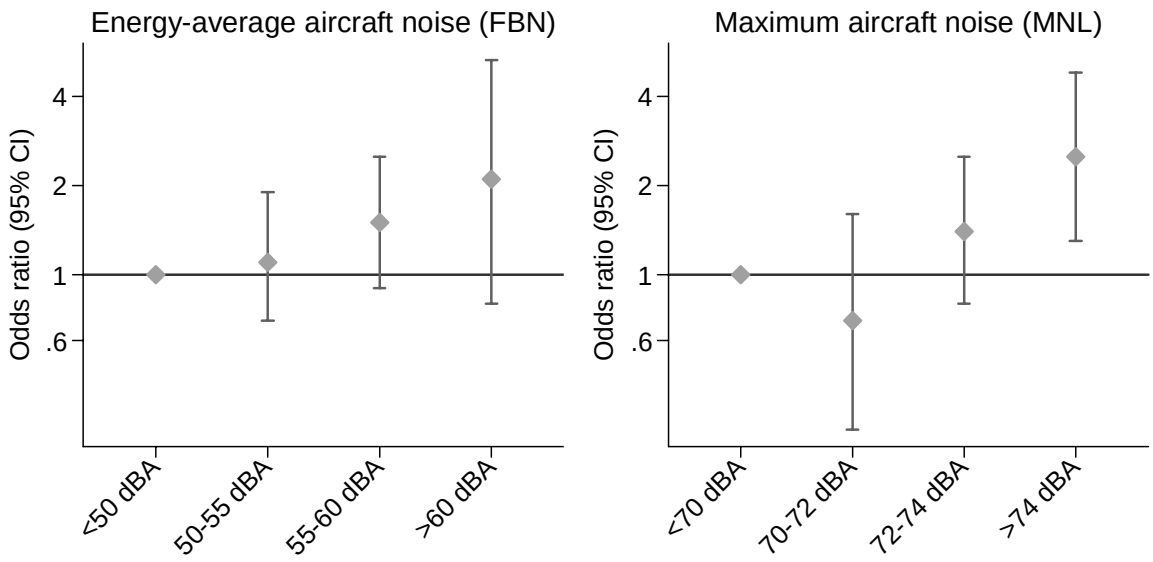

Figure 2. Odds ratios and 95% confidence intervals for hypertension associated with exposure to aircraft noise according to different categories of equal-energy (FBN) and maximum noise (MNL). Estimates were adjusted for age, sex, smoking, and education.

Analysis of trend over exposure categories resulted in an adjusted odds ratio for hypertension prevalence per 5 dBA increase in equal-energy aircraft noise of 1.30 (95% CI 0.78-2.16). There was some indication of effect-modification by age and hearing loss, suggesting higher estimates among the elderly and those without hearing loss. Analyses where the subjects were grouped according to either energy-averaged or maximum levels suggested higher estimates among those exclusively exposed to high maximum noise levels.

Environmental tobacco smoke and myocardial infarction

Exposure to environmental tobacco smoke at home or work was associated with an increased risk of nonfatal myocardial infarction among never-smokers. Figure 3 displays the prevalence of exposure to environmental tobacco smoke among never-smoking men and women over time separately for the two major exposure sources, i.e. home and work. In general, women were more exposed to spousal environmental tobacco smoke than men during the 60s and 70s, while that difference became smaller during the 80s and changed to the opposite during the 90s. This reflects that more men than women smoked in early years, while today more women than men smoke. For occupational exposure to environmental tobacco smoke, men were more exposed than women in all time periods.

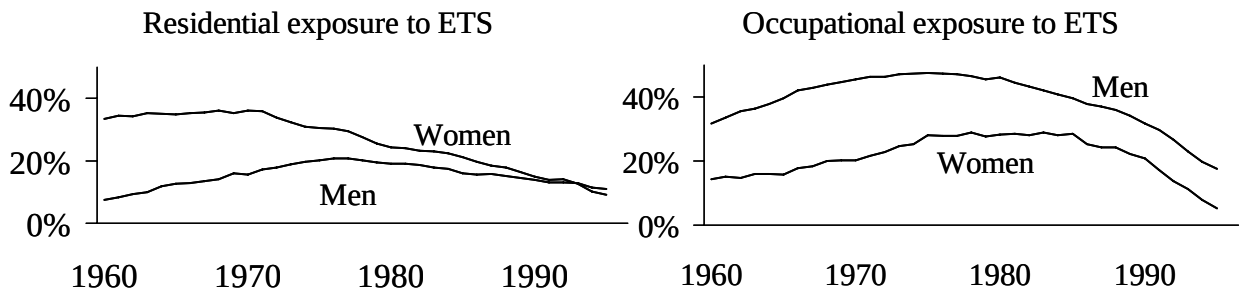

Figure 3. Prevalence of exposure to environmental tobacco smoke (ETS) among never-smokers from spouse and work in Stockholm county during 1960-1994 (data from the SHEEP-study).

Ever living with a smoking partner was associated with an odds ratio for nonfatal myocardial infarction adjusted for age, sex, hospital catchment area, body mass index, socioeconomic status, job strain, hypertension, diet and diabetes of 1.14 (95% CI 0.85-1.54). For women the adjusted odds ratio was 1.53 (95% CI 0.95-2.44), while no association was suggested among men (0.96, 95% CI 0.64-1.44). For exposure at work, a slightly increased risk was suggested among men but not women, although the results for current occupational exposure were similar for both genders, with a combined odds ratio of 1.31 (95% CI 0.89-1.95). There was no clear association between childhood exposure to environmental tobacco smoke and nonfatal myocardial infarction for men or women, with a combined odds ratio of 0.87 (95% CI 0.65-1.15).

Increasing intensity of residential exposure was associated with higher risk estimates, with an adjusted odds ratio of 1.58 (95% CI 0.97-2.56) among those exposed to 20 cigarettes per day or more from the spouse. Longer duration of exposure appeared to convey higher risks of both spousal and workplace exposure, with an adjusted odds ratio of 1.25 (95% CI 0.77-2.02) for more than 33 years of exposure to the partner's

smoking and 1.30 (95% CI 0.86-1.98) for more than 32 years of exposure at work. The cumulative exposure measures “pack-years” at home and “hour-years” at work were associated with adjusted odds ratios of 1.33 (95% CI 0.81-2.20) and 1.48 (95% CI 0.99-2.22) above the 75th percentile of exposure, respectively. Combined exposure at home and work suggested dose-response patterns for intensity, duration and cumulative exposure.

The risk appeared to decrease with time since last exposure at home or work, with an adjusted odds ratio of 1.39 (95% CI 0.91-2.10) among the currently exposed and 0.92 (95% CI 0.58-1.44) for those exposed during more than 16 years ago (figure 4). Combined cumulative exposure at home and work suggested a dose-response, with an adjusted odds ratio of 1.55 (95% CI 1.02-2.34) in the most extreme category above 90 hour-years of exposure (figure 4). There was some indication of higher risk estimates among diabetics and those with a family history of coronary heart disease.

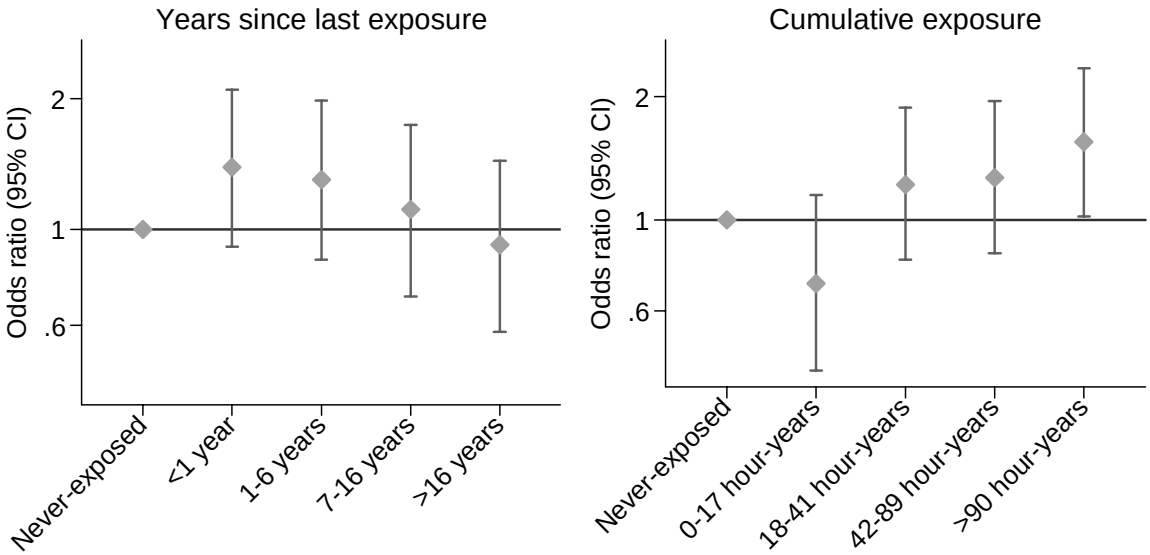

Figure 4. Odds ratios and 95% confidence intervals for nonfatal myocardial infarction associated with exposure to environmental tobacco smoke among never-smokers at home and work, expressed as years since last exposure and combined cumulative exposure. Estimates were adjusted for age, sex, hospital catchment area, body mass index, socioeconomic status, job strain, hypertension, diet and diabetes.

Drinking water hardness and myocardial infarction

There was no apparent protective effect from the drinking water hardness, magnesium or calcium level, or for the estimated daily intake of these drinking water constituents. The odds ratios for myocardial infarction associated with drinking water hardness, magnesium and calcium were above one in most analyses. Considering the daily dose by incorporating questionnaire data on consumption of drinking water suggested small and non-significant protective effects associated with magnesium in some exposure categories (figure 5).

None of the dose variables suggested any dose-response. Reanalysis using an inter-quartile range increase in magnesium content of the water yielded an odds ratio adjusted for age, sex, hospital catchment area, smoking, socioeconomic status, hypertension, job strain, diabetes, body mass index, and physical inactivity of 1.00 (95% CI 0.99-1.02), and a corresponding odds ratio for calcium concentration of 1.00 (95% CI 0.97-1.03). The adjusted odds ratio for an inter-quartile range increase in the daily dose of magnesium from the water was 1.01 (95% CI 0.87-1.17) and 0.97 (95% CI 0.86-1.10) for calcium. Analysis of fatal cases gave similar results.

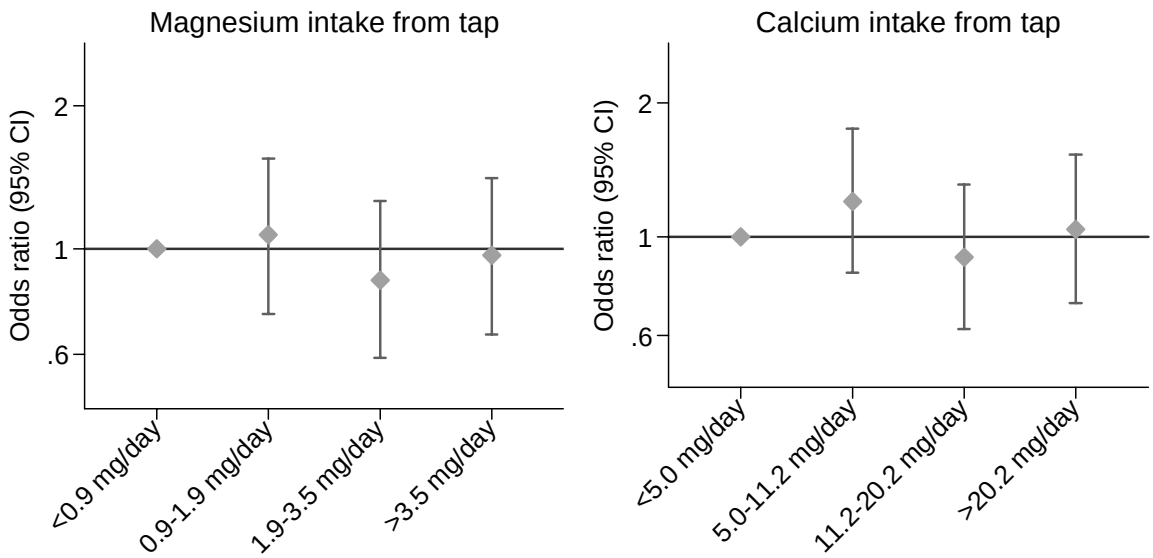

Figure 5. Odds ratios and 95% confidence intervals for myocardial infarction associated with magnesium and calcium intake from tap water during two years before diagnosis. Estimates were adjusted for age, sex, hospital catchment area, smoking, socioeconomic status, hypertension, job strain, diabetes, body mass index, and physical inactivity.

Air pollution and myocardial infarction

The results suggested an association between the 30-year average exposure to air pollution and myocardial infarction mortality, but not for incidence or nonfatal myocardial infarction. The association appeared to be strongest among those who died outside hospital. After adjustment for age, sex, hospital catchment area, smoking, diabetes, physical inactivity, and socioeconomic status, the odds ratio for fatal myocardial infarction associated with a difference in the 30-year average traffic-generated NO_2 exposure of 30 µg/m^3 was 1.51 (95% CI 0.96-2.37). A 300 µg/m^3 difference in average long-term traffic-generated CO exposure was associated with an adjusted odds ratio for fatal myocardial infarction of 1.22 (95% CI 0.98-1.52). The corresponding PM_{10}-estimate for a difference of 5 µg/m^3 was 1.39 (95% CI 0.94-2.07). A concentration difference in average exposure to SO_2 as an indicator of

heating during three decades of 40 µg/m^3 was associated with an adjusted odds ratio for fatal myocardial infarction of 1.24 (95% CI 0.77-2.02). Analyses of categorical exposure variables to explore dose-response displayed similar patterns for the traffic-generated pollutants NO_2, CO, and PM_{10}, suggesting increased estimates for fatal myocardial infarction especially in the top category of exposure (figure 6).

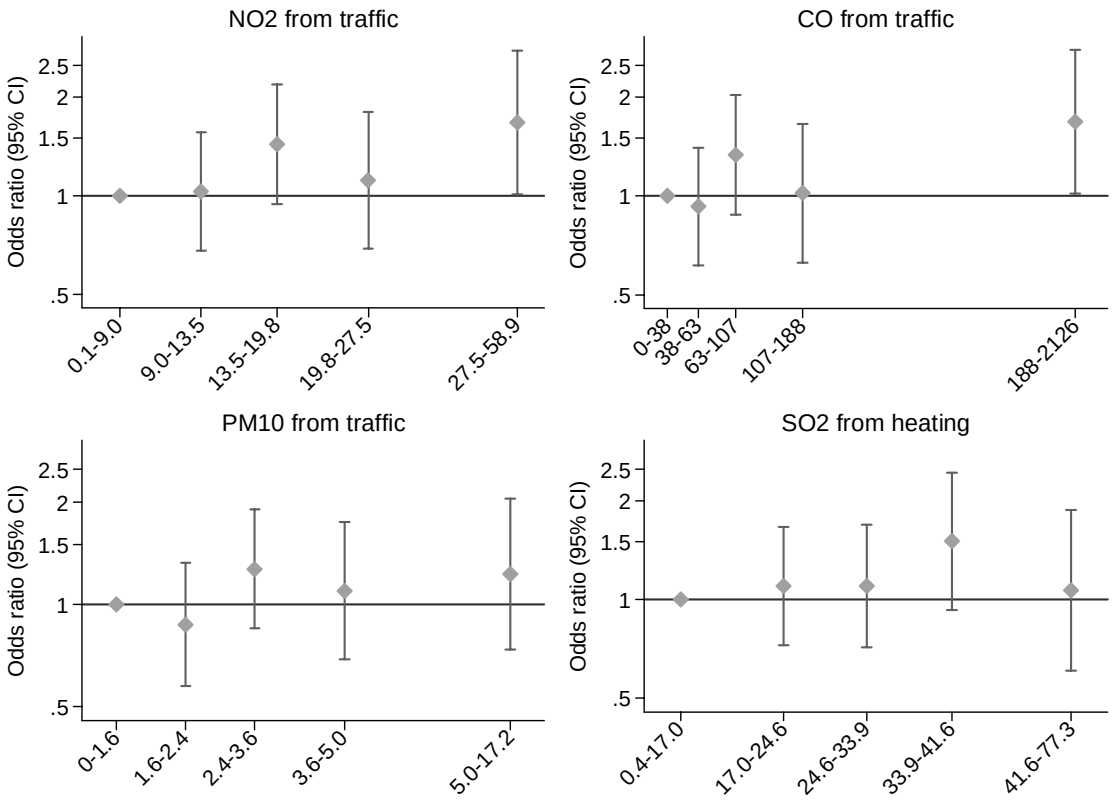

Figure 6. Odds ratios and 95% confidence intervals for fatal myocardial infarction associated with 30-year average exposure to traffic-generated NO_2, CO, and PM_{10}, and SO_2 from heating in µg/m³. Cut-points correspond to 25th, 50th, 75th, and 90th percentiles and the first quartile is used as reference. Estimates were adjusted for age, sex, hospital catchment area, smoking, physical inactivity, diabetes, and socioeconomic status.

A 30 µg/m³ difference in the traffic-generated NO_2-exposure during 30 years was associated with an adjusted odds ratio of 2.17 (95% CI 1.05-4.51) for out-of-hospital death. Corresponding estimates for out-of-hospital death was 1.36 (95% CI 1.01-1.84) for a 300 µg/m³ difference in CO and 1.84 (95% CI 1.00-3.40) for a 5 µg/m³ difference in PM_{10} from traffic. A 40 µg/m³ difference in the SO_2 from heating yielded an adjusted odds ratio for out-of-hospital death of 1.54 (95% CI 0.64-3.46).

Stratified analysis suggested higher estimates for women, never-smokers, those with higher educational level, and non-diabetics. Other covariates showed small or no difference in risk in different strata. Multi-pollutant models suggested increased odds ratios for the traffic-generated pollutants NO_2, CO, and PM_{10}, but shifted the estimates for SO_2 towards the null. In addition, binary analysis of ever living close to streets with high traffic resulted in an adjusted odds ratio of 1.23 (95% CI 0.85–1.78) for myocardial infarction and 1.40 (95% CI 0.78–2.52) for fatal myocardial infarction. The estimate for fatal myocardial infarction increased to 1.58 (95% CI 0.86–2.90) when adjusted for heating.

Summary and impact assessment

The most important results of these studies can be summarized in the following statements:

- Energy-averaged aircraft noise exposure above 55 dBA was associated with an adjusted odds ratio for hypertension of 1.59 (95% CI 1.00-2.53).
- Combined exposure to environmental tobacco smoke at home and work in the top decile of the cumulative exposure (hour-years) was associated with an adjusted odds ratio for nonfatal myocardial infarction among never-smokers of 1.55 (95% CI 1.02-2.34).
- An inter-quartile range increase in the daily intake of magnesium from the domestic drinking water was associated with an adjusted odds ratio for myocardial infarction of 1.01 (95% CI 0.87-1.17).
- A 30 µg/m³ difference in the 30-year average exposure to traffic-generated NO_2 was associated with an adjusted odds ratio for fatal myocardial infarction of 1.51 (95% CI 0.96-2.37).

Based on the results of these studies, the proportion of disease that might be attributable to these environmental exposures can be estimated. The calculation can be done using different definitions of the exposure variables, depending on which strategy for prevention that may be feasible. If a complete removal of exposure is possible, e.g. passive smoking, a continuous or never/ever exposure variable may be suitable, but if the focus is to implement an environmental guideline or regulation standard at a certain cut-point of ambient concentrations, e.g. for a specific air pollutant, the exposure prevalence above that cut-off would be suitable to use. In the calculations below, different approaches have been applied and the results are displayed as a range derived from many different calculations given the uncertainties and assumptions of causality (in this case from only one study) inherent in the estimation.

Since a stratified sampling was used to ensure enough exposed subjects around the airport in the Environmental Health Survey, calculating the exposure prevalence throughout the county from that data would result in an overestimation. Thus, it was

not possible to calculate the attributable proportion directly from the data using the multivariate approach (see statistical analysis). However, national data suggest that 100,000 people in the whole country are exposed above FBN 55 dBA, i.e. less than 1%,[116] which suggests that the proportion of hypertension attributable to aircraft noise would be about 0.6%. For exposure to environmental tobacco smoke, the proportion of nonfatal myocardial infarction due to passive smoking among never-smokers would be 7-13%, depending on the definition of the exposure variable. Using never/ever exposure at home and work yields a proportion of 11% and current workplace exposure of 7%. Because of the lack of any clear association, the attributable proportion of myocardial infarction due to exposure to drinking water hardness was not estimated. The calculation of attributable proportions from air pollution was primarily done on continuous exposure variables, i.e. assuming a concentration difference from the 5th to the 95th percentile of the control subjects, resulting in a proportion of fatal myocardial infarction due to ambient air pollution of 7-15%. Cut-offs at the median of all subjects, i.e. assuming an exposure prevalence of 50%, yielded similar attributable proportions, close to 10% for all traffic-generated pollutants.

Applying age and sex standardized incidence rates of myocardial infarction in the ages 45-70 years derived from the regional myocardial infarction register during 1993-1995,[71] suggests that the rate of nonfatal myocardial infarction that might be due passive smoking among never-smokers in Stockholm county would be about 20-30 per 100,000 person-years. The rate of fatal myocardial infarction that might be due to long-term ambient air pollution exposure would be about 10 per 100,000 person-years. A similar calculation of the proportion of hypertension from aircraft noise exposure in the population is difficult since the true incidence of hypertension is unknown. However, assuming that hypertension is a chronic condition and applying the overall prevalence from study I (i.e. approximately 14%), suggests that the rate of hypertension due to aircraft noise exposure in the ages 19-80 years in Stockholm county during 1997 would be about 1 per 100,000 inhabitants. Nevertheless, the calculation of the attributable proportion of hypertension prevalence due to aircraft noise exposure might be questionable due to the cross-sectional design and hypothesis generating character of that study.

Discussion

Self-reported prevalence of hypertension appeared to be associated with the geographical propagation of aircraft noise around Arlanda airport. There was also an indication of a dose-response between both the maximum and energy-averaged noise levels and the prevalence of hypertension. There is very limited evidence on hypertension prevalence in relation to aircraft noise exposure,[84] but our results accords with some studies of occupational noise exposure and hypertension,[187,234] and reports suggesting that traffic noise exposure might affect blood pressure,[235,236] although previous data is unconvincing and contradictory.[31,237,238]

Passive smoking at home and work was associated with an increased risk of nonfatal myocardial infarction among never-smokers, both as intensity, duration and cumulative exposure. In particular, combined exposure from both these sources and time since the exposure ceased was of importance. Thus, our results are in accordance with previous publications and adds some key aspects to the growing body of evidence showing that exposure to secondhand smoke is an important risk factor for myocardial infarction. Meta-analyses have estimated the risk of cardiovascular disease to be 25-30% higher for non-smokers who live or work in environments where smoking regularly occurs.[26,90,115]

Our data suggest risk estimates relatively close to that among light active smokers or recent ex-smokers.[239,240] Smoking cessation reduces the risk of myocardial infarction close to that of never-smokers after about two-three years or more.[241-243] The risks of smoking obtained in the SHEEP-study appear somewhat higher than estimates previously reported for the corresponding ages, as discussed by Reuterwall *et al*.[199] However, previously reported effect estimates for active smoking on the risk of myocardial infarction were not based on a reference group free of passive smokers. Analyzing the effect of smoking regardless of exposure to environmental tobacco smoke in the whole SHEEP population resulted in odds ratios of 1.17 among those formally smoking less than 15 cigarettes per day, and 1.43 among former heavy smokers (table 2). Among light and heavy current smokers the odds ratio was 2.37 and 3.43, respectively. Analysis using never-smokers who had never been exposed to environmental tobacco smoke as reference category yielded an odds ratio of 1.52 among those with high cumulative exposure to environmental tobacco smoke (69 hour-years or more from spouse and work), and higher odds ratios in all categories of active smoking than the regular analyses with passive smokers in the reference group. Although it is unclear whether bias contributed to the high effect measures, dilution from passive smoking when studying acting smoking might be a part of the explanation to the somewhat high estimates in some analysis.

Table 2. Subjects classified according to their history of active or passive smoking, data from the SHEEP-study.[199]

	ETS ignored (never-smokers as reference category)		ETS included (never-smokers never exposed to ETS as ref.)	
Active or passive smoking	OR*	95% CI*	OR*	95% CI*
Never-smokers never exposed to ETS			1	–
Never-smokers exposed to low ETS†	1	–	0.99	0.71–1.38
Never-smokers exposed to high ETS†			1.52	1.02–2.27
Former smokers < 15 cig/day‡	1.17	0.91–1.49	1.27	0.90–1.79
Former smokers ≥ 15 cig/day‡	1.43	1.12–1.83	1.56	1.11–2.19
Current smokers < 15 cig/day	2.37	1.88–2.99	2.57	1.85–3.58
Current smokers ≥ 15 cig/day	3.43	2.76–4.26	3.72	2.71–5.12

*Adjusted for age, gender, hospital/catchment area, BMI, socioeconomic status, job strain, hypertension, and diabetes.
†Cut-points are set at the 75th percentile of hour-years for all environmental tobacco smoke (ETS) exposed never-smoking controls.
‡Former smokers are those who have stopped smoking at two years before inclusion in the study.

There was no suggestion that the hardness of the drinking water would convey a lower risk of myocardial infarction, neither as its contents of magnesium and calcium or the calculated daily intake of these chemicals from the water. Thus, our results are discordant with the majority of the epidemiological literature showing lower death rates in cardiovascular disease in regions with hard drinking water.[36,119,122,124,125,130,132-136,144,244] However, the evidence is still conflicting since other studies have reported no association[129,137] and that few have used individual data or considered the amount of magnesium and calcium that people drink. In addition, a very large and carefully conducted geographical investigation, that also adjusted for socioeconomic status and other ecological variables, have failed to report any association between cardiovascular disease and drinking water hardness.[128]

The average levels of ambient air pollution exposure during 30 year appeared to be associated with an increased risk of fatal myocardial infarction, also reported in large cohort studies.[167-171] However, there was no association between air pollution exposure and incidence or nonfatal myocardial infarction. A previous case-control study have suggested an association between myocardial infarction incidence, although based on crude aggregated exposure information at one address from 12 monitors during at most four years before disease onset.[245] Our data also suggest a particularly strong association between long-term air pollution exposure and out-of hospital death, which has not been previously reported. Although the study was not designed to disentangle biological mechanisms, this finding may support the

hypothesis of arrhythmia as an important pathway for the association between long-term air pollution exposure and myocardial infarction. Our results are in accordance with recent studies that especially point toward traffic-generated pollutants.[170,171] Since recent data indicate an increased risk of myocardial infarction also from exposure road traffic noise,[33] it is important for future studies to assess the role of traffic noise on the association between air pollution and cardiovascular disease.

However, it is important to recognize methodological aspects that may affect validity and precision in these studies. Such potential bias is discussed below, followed by a description of some biological mechanisms that may explain the associations between these environmental exposure and the health outcomes.

Study size and precision

The numbers of subjects affect precision and thus the potential for random errors, which is reflected by the confidence intervals. In particular, few subjects with certain common characteristics hamper the possibility to draw firm conclusions from stratified data and sub-group analyses. This may also affect precision in analysis of effect-modification. In addition, contrast in exposure and the distribution of subjects according to key characteristics may also affect precision and the possibility to detect any true associations. Limited range and poor contrast in exposure was a particular problem in study III, which may have reduced the possibility to find a potential inverse relation between domestic drinking water and myocardial infarction reported by others.

Study I had a large non-exposed group including more than 2000 individuals, but the number of hypertensive subjects in each exposure category was limited (17, 20, and 7, using the FBN-metric) which would affect precision in the dose-response analysis. All analyses based on never/ever exposure variables in study II included at least 100 exposed cases, although some results from multi-categories of source-specific (home or work) intensity and duration of exposure included down to about 30 exposed cases. However, the main results from cumulative combined data analysis included enough subjects to allow for dose-response exploration.

The main results from study III were based on exposure variables in quartiles comprising between 60-182 exposed cases of myocardial infarction, but some conclusions were drawn from analyses of down to 18 exposed cases. Reanalysis suggest similar results based on continuous exposure variables. However, precision in that study might have been affected by limited exposure contrast, as mentioned above. Collecting exposure data for all subjects in the SHEEP-study would not improve exposure contrast. During the study period, approximately 95% (n=1,625,400) of the population in the study area were connected to a waterwork through the municipal water distribution system. About 1,5 million people were

dependent on surface water from the major lake in the area (Mälaren), providing water to the three largest waterworks in the region (Norsborg, Görväln, Lovön). Beside these three major waterworks, some of the municipalities distributed water to their inhabitants from smaller waterworks, using either surface or ground water (especially the smaller ones). Because the magnesium levels in the three major waterworks ranged between 4 to 6 mg/l and the levels in the smaller ones ranged between 3 to above 10 mg/l (highest levels in those using ground water), it was more important that the smaller waterworks were included than the three largest ones, and especially areas were private wells were used where the highest levels are expected to occur.

In study IV, some conclusions were drawn from results of sub-group analyses using 89 cases that died outside of hospital. However, the main results were based on analyses including more than 1000 nonfatal or 289 fatal cases using continuous exposure variables.

Selection bias and disease classification

Response rates were high, above 70% in all studies, which together with the random sampling of subjects in study I and control subjects in the SHEEP-study reduces the risk of selection bias. Subjects in studies II-IV were also included independently of exposure histories. Non-participation in the SHEEP-study was not systematically different across age groups and geographical areas,[13,199] which should further reduce any potential effects of possible selection bias in studies II-IV. Since participation rates were high, any systematic differences in exposure will probably have to be extreme in order to seriously affect the validity.

Misclassification of disease is of special importance with regard to the self-reported hypertension used in study I. The overall prevalence of self-reported hypertension in that study was 14%, which is much lower than the prevalence estimate of 27% reported in a recent national evaluation.[46] Although misclassification of true disease prevalence due to underreporting is likely to occur, most of that difference probably depends on the introduction of the new WHO guideline for hypertension management of 140/90 in 1999.[47] The level for treating hypertension in Sweden during the 1990s was 160/95,[48] i.e. when the subjects were asked about their diagnosis. However, any misclassification of disease would probably be independent of the aircraft noise exposure and would thus dilute any association. In particular, potential non-systematic misclassification of disease can not explain the results of the exposure-response analysis.

Misclassification of disease in the other studies is less likely. In the SHEEP-study, the cases were diagnosed according to standard criteria using many partly overlapping information sources on symptoms, ECG, and enzymes.[199] They were

recruited from the internal medicine departments at all hospitals across the county, the regional computerized discharge register, and the death certificates from the Cause-of-death register. These procedures minimized the number of undetected cases. In addition, over 70% of the cases who died were autopsied, which further reduces the risk of disease misclassification. Furthermore, cross-checks with different registers suggest that the number of unidentified myocardial infarction cases was small (less than 3%) in the SHEEP-study.[13]

Misclassification of exposure

Assigning exposure to each individual is a crucial part of any study in environmental epidemiology, whether described by measurements in the environment, as results of some sophisticated data modeling, or as self-reports from the study subjects or their next-of-kin.[72] Misclassification of exposure is almost always present in large population-based studies, making it important to reduce and properly describe the potential effects of such bias. If misclassification of exposure does not depend on disease status it will tend to bias the association towards the null (non-differential), but if the exposure classification depends on whether a subject has the disease or not (differential), the association could be over- or underestimated. Differential misclassification of exposure is unlikely to have seriously affected the results, but non-differential misclassification of exposure is likely occur in all studies and may have been particularly important in studies III and IV.

Assessment of individual long-term environmental exposures during years or decades is often made from measurements and modeling, since personal sampling which may be suitable in occupational studies is rarely feasible on such large populations and long time-scales. Since environmental exposures show geographic variation, a geographic approach to exposure assessment is often suitable and along with the rapid development of computer software, there has thus been a growing use of GIS in environmental epidemiology.[72] The home address therefore presents a suitable point for exposure assessment. The exposure in the studies of this thesis was assessed using different approaches, all with a focus of the subject's residence (study II also included assessment at work). The ways that the individual exposure to the environmental factors was assessed include questionnaires (passive smoking, home address), registers (home address, water protocols), measurements (water samples), and modeling (aircraft noise, air pollution). In general, the objective exposure was assessed without knowledge of disease status, thus minimizing the potential for disease-related misclassification of exposure.

Another reason for misclassification of true individual exposure that may have affected all studies is lack of potentially important information on exposure in other locations, such as the workplace or during transportation. Such data gaps may introduce more imprecision in the exposure assessment and thus blur the picture and

further attenuate any associations. Since studies I, III and IV were based on address information, exposure at other places was ignored which may thus have contributed to imprecise exposure estimates.

Aircraft noise exposure was assessed as the most common residential noise situation during one year, using register address data and calculated noise propagation from the aviation authority. Thus, lack of information on exposure to noise at other places (e.g. work) would lead to misclassification of true individual exposure. In addition, the design of the study was essentially cross-sectional and therefore longitudinal exposure was not considered. Even if the exact date of diagnosis was not known (during the last 5 years), and that the information on duration of residence was limited to the categories 1-10 years or more than 10 years (those less than 1 year were excluded), only 21 subjects with hypertension in the vicinity of the airport may have been diagnosed prior to exposure classification because they had lived at address during 1-10 years, corresponding to 5% of all hypertensive subjects in the study population. Thus, only a small proportion of the hypertensive subjects may have been diagnosed before they were classified according to the 1997 aircraft noise contours. There was no evidence that bias with regard to reported health status for those living near the airport was present. In addition, the geographical propagation of aircraft noise around the airport is, beside meteorology and topography, mostly determined by the location of the runways and the flight pathways for landing and take off, which has largely been unchanged throughout the years, until the introduction of a third runway six years after this study was performed. Some studies have used annoyance from noise as a measure of exposure due to lack of objective exposure data.[32] Using self-reported data on aircraft noise annoyance as stated in the questionnaire instead of the modeled exposure may give some indication of the quality of the objective exposure assessment, since there is a well-documented association between exposure to aircraft noise and annoyance.[89,246,247] Annoyance due to aircraft noise was more common among those with higher exposure also in our study. Among those exposed above FBN 55 dBA, 70% reported that they were frequently annoyed by the noise from aircrafts. The proportion of subjects who reported frequent annoyance from aircraft noise also increased with increasing exposure level, from 12% among the least exposed (<50 dBA), to 61% among those exposed to 50-55 dBA, 64% in the group 55-60 dBA, and 93% among those exposed above 60 dBA. This provides some support that the objective exposure measure appear to adequately assess exposure to those who are really exposed.

Underreporting of smoking may be an issue to consider in studies of passive smoking. Although the information on smoking status in study II was not validated, previous Swedish data indicate that possible bias from misclassification of never-smoking status is unimportant even in studies of environmental tobacco smoke and lung cancer, where the much higher risk from smoking makes this a greater problem.[248] Biological markers on smoking, e.g. cotinine in serum, urine or saliva,

could provide some information on misclassification rates of current smokers. However, such data reported by others have indicated little effects on the results from underreporting of smoking among never-smokers. For instance, data from a random sample of US adults indicates that only 1.3% of self-reported nonsmokers had levels of serum cotinine high enough to suggest they were in fact current smokers.[249] Similar cotinine data from a case-control study showed lower misclassification rates among cases (0.6%) than controls (2.3%).[250] By asking the relatives of those who reported their never-smoking status also previous data can be obtained, i.e. information on misclassification rates of former smokers. A Swedish study evaluating smoker misclassification in two large population-survey cohorts, reported misclassification of ever-smokers as never-smokers in 4.9% and 5.0% among men, and 4.5% and 7.3% among women.[251] The study also confirmed previous findings that most misclassified ever-smokers had quit smoking earlier and had smoked less than the average smoker. The risk of lung cancer among misclassified smokers was lower than that among former smokers, and close to that in never-smokers. Validation data from a multicentre case-control study showed that only 1.2% of the subjects classified as never-smokers were reported by next-of-kin to be former regular smokers.[248] Thus, misclassification in carefully conducted case-control studies may be less important than previously suggested by survey-type studies.

In study III, exposure was assessed using data from the waterworks during two years before infarction, thus ignoring earlier exposure and longer time-series of exposure. Collection of exposure data was limited to the two years prior to study inclusion because of practical reasons, data availability, and others claiming that primarily recent exposure would be of importance and that even less than two years of exposure would be sufficient to adapt to magnesium of the local water supply.[134] It was practically difficult to go further back in time since we found limited historical drinking water data readily available. Instead, for the purposes of the present study, this information was collected manually from protocols kept in paper files at each waterwork. This was then put into a computer file, which finally included data on 21 waterworks/blended zones × 3 water parameters (Mg, Ca, hardness) × 5 years (yearly means calculated from data for each waterwork). Data availability was also limited since some waterworks did not store their protocols for longer periods. Nevertheless, the hardness of the water distributed by the waterworks in Stockholm county have been largely unchanged during at least 10 years before the study period. According to the Swedish Water and Wastewater Association (SWWA) and an inventory of exposure data access performed before the investigation was started, the annual mean levels of hardness at the most important waterwork in the region (Norsborg) ranged between 4.0-4.6 mg/l during the years 1980, 1985, and 1989. Figure 7 shows the time trend of that data along with the corresponding levels from study III.

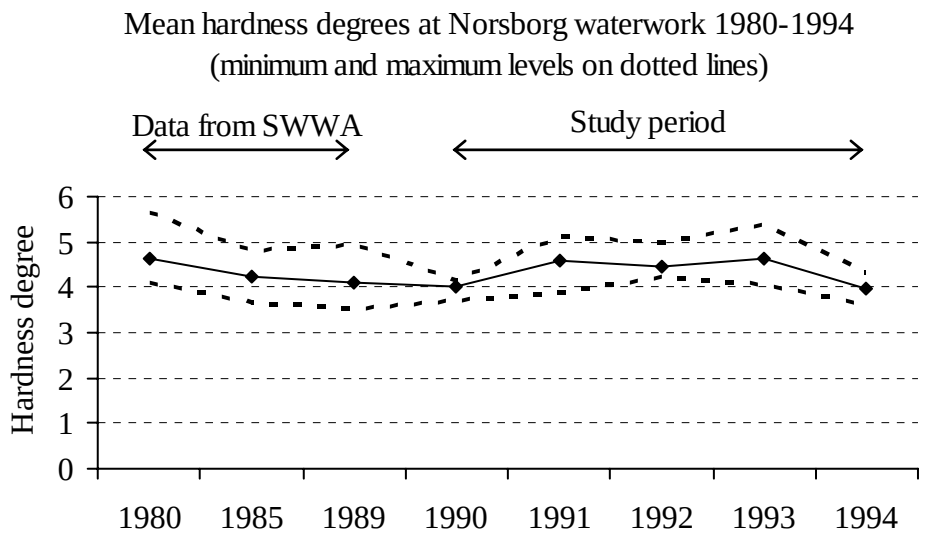

Figure 7. Annual mean hardness degrees at Norsborg waterwork between 1980-1994.

In study IV, possible reasons for misclassification of exposure may include false address information by study subjects or their relatives, errors when translating the addresses to geographical coordinates, or inexact and crude dispersion calculations. Nevertheless, the address information was collected from several overlapping sources and a more crude geographical position than the exact location was used for only about 9% of all 10,662 addresses. These somewhat more uncertain locations, corresponding to the right parish, village, or similar small area, were nearly almost in the outskirts of the study area where the largest grids of 500 meters were used to assess air pollution. In addition, the allowance of up to five years of missing address data which was replaced by the mean pollution level among controls may result in wrong exposure estimates during certain periods for that subject and decrease exposure contrast. However, this applies to less than 4% of all residential exposure years and most had only one year missing far back in time. Only 110 of the 3267 subjects had the maximum of 4 missing years allowed of all 30 years, mostly due to unknown residency in early years. The potential for misclassification of exposure was probably equal among cases and controls and would thus affect the results towards unity.

Confounding

Potential confounding was judged on evaluation of several regression models including a large set of covariates. Decision on the final model was primarily based on univariate assessment of the impact of each covariate on the exposure-disease effect estimate. Some variables were however entered in the final model for other reasons, such as diet in the study of environmental tobacco smoke due to previous

criticism of previous studies not accounting for different dietary habits in families where smoking is present.[95,189] Age, sex, smoking, and socioeconomic status were controlled for in all studies, while also hospital catchment area was adjusted for in studies II-IV on the basis of matching criteria. The degree of assessment and control for confounding thus depends on the information available, the number of subjects in the study, the number of subjects with missing data on the covariate, and the influence of other factors on the effect estimates. Reasons for not including a covariate in the final model include that the variable did not affect the effect estimate, too many subjects had missing on that variable which would thus compromise precision, or that information was simply not available. Some variables may also be considered as part of the mechanistic chain between exposure and disease. Therefore, it may be questionable to adjust for hypertension in the studies of passive smoking and drinking water hardness, but that variable was nevertheless included due the strong influence on the results. Likewise, other covariates might be proxies of the same cause and thus highly correlated, making it doubtful to adjust for too many similar variables (e.g. BMI, diet and diabetes).

In general, there appeared to be little influence of confounding in study I, as indicated by relatively small differences between crude and adjusted estimates. In study II, several covariates exerted confounding and were included in the multivariate analyses. In study III, important cardiovascular risk factors were included in the model, and the influence from many other factors possibly related to the intake of magnesium and calcium, e.g. other fluids and diet were evaluated. In study IV, several variables exerted positive confounding, e.g. smoking and physical inactivity, and the risk estimates were reduced following adjustment. In addition, several other model were evaluated.

Table 3 summarizes the information used for confounding control. Age was entered as a continuous variable in study I and II, and in 5-year age groups in study III and IV. Smoking was controlled for by restriction in study II and adjusted for by a three level categorical variable (never/former/current) in studies I and III, and in five levels with further categorization of current smokers into 1-10 cig/day, 11-20 cig/day, and more than 20 cig/day in study IV. Socioeconomic status was controlled for by educational level as a proxy in study I and a three level variable of blue collar workers, lower white collar workers, and intermediate to upper white collar workers using the latest job title of their occupational history before study inclusion in studies II-IV. The definition of the other covariates is described in detail in each paper.

Table 3. Assessment of potential confounding and decision on the final multivariate regression model of each study (BMI=body mass index, SES=socioeconomic status, CVD=cardiovascular disease, ETS=environmental tobacco smoke).

Study	Final model	Other models tested
I.	Sex, age, smoking, education	Physical activity, diet, residential type, duration of residence, income, outdoor activities
II.	Sex, age, hospital, BMI, SES, job strain, hypertension, diet, diabetes	Family history of CVD
III.	Sex, age, hospital, smoking, SES, hypertension, job strain, diabetes, BMI, physical inactivity	ETS, diet, family history of CVD, alcohol, coffee, drinking water
IV.	Sex, age, hospital, smoking, physical inactivity, diabetes, SES	Hypertension, ETS, BMI, diet, alcohol, coffee, occupational exposure, job strain

In air pollution studies, confounding could occur if individuals who lived in areas with higher levels of air pollution also tend to have jobs with exposure to hazardous agents in the workplace. This concern is reinforced by the epidemiologic evidence that certain occupational exposures can lead to increased mortality from cardiovascular disease. The inclusion of three occupational exposure indices adopted from Gustavsson *et al*[207] in the air pollution study had almost no impact on the association between ambient air pollution exposure and myocardial infarction. In an attempt to assess possible confounding by short-term effects, adjustment for time-series data of air pollution during the days or week directly preceding infarction was performed. These analyses did not change the estimates for long-term exposure and myocardial infarction, suggesting that short-term exposure would not confound the effects from long-term exposure.

Biological mechanisms

Since cardiovascular disease may be caused by several factors and the process until manifestation may include many pathways, a number of biological mechanisms have been proposed for the association between the environment and cardiovascular disease reported in epidemiological studies. Although different main biological hypothesis have been described in relation to each environmental factor, some of the proposed pathways are also shared between the environmental agents. One recently suggested such mechanistic pathway is low-grade chronic inflammation mediating atherosclerosis and thrombosis,[252] which has led to research of associations between environmental exposures, especially air pollution and environmental tobacco smoke, and inflammatory markers such as C-reactive protein and fibrinogen.[253-256] For some exposures, the biological hypothesis have preceded epidemiological research (noise), while for other factors the biological mechanisms have been put forward to support epidemiological data (air pollution). Some of the main hypotheses for the

environmental exposures studied include stress (noise), arrhythmia (water magnesium, environmental tobacco smoke, air pollution), increased atherosclerosis (environmental tobacco smoke, air pollution), and inflammation (environmental tobacco smoke, air pollution).

The hypothesis of an association between community noise exposure, such as aircraft noise, and hypertension is mainly that the noise induces stress by causing disturbed sleep, interfered relaxation, impaired concentration, irritation, headache, and many other cognitive effects that activates the sympathetic nervous system and the endocrine system.[32,74,89,185,186] Physiological effects such as short-term changes in blood pressure, heart rate, and stress hormonal levels (adrenaline, noradrenaline, and cortisol) have been related to noise exposure in experimental settings.[32,74,76] The hypothesis has therefore emerged that persistent environmental noise exposure would result in permanent changes in these cardiovascular factors and thus increase the risk of hypertension and ischemic heart disease. There are epidemiological studies suggesting that residential traffic noise exposure is association with an increased risk of hypertension and ischemic heart disease.[33,34,88,184,235] These studies have has been summarized in reviews and meta-analysis,[35,89,185,186] although the evidence is still limited and inconclusive.[257,258]

Many explanations have been suggested regarding possible mechanisms by which environmental tobacco smoke might cause cardiovascular disease, including changes in blood gases, effects on platelet function and induced or accelerated development of atherosclerosis.[97,98,259,260] Recent data suggest that markers of inflammation, such as C-reactive protein and fibrinogen, are more present among nonsmokers exposed to environmental tobacco smoke than unexposed nonsmokers.[253] Environmental tobacco smoke has also been suggested to be associated with endothelial dysfunction among nonsmokers,[261-264] and affect endothelial cell count and platelet aggregation.[265] Reduced cardiac autonomic function has been suggested as a mechanism by which environmental tobacco smoke might increase cardiac vulnerability, as indicated by a reduced heart rate variability.[266]

It is still unclear which is the best measure of environmental tobacco smoke to represent a relevant biologic exposure. Cotinine as a biological marker of present exposure have been increasingly used in studies on environmental tobacco smoke, and Whincup *et al* suggest that environmental tobacco smoke may be more strongly related to coronary heart disease when assessed using serum cotinine concentrations.[267] Present exposure and cumulative dose may both be relevant measures with regard to these biological hypotheses, but they might represent different aspects of the association. Pack-years have been used as dose metric in studies of both active and passive smoking. Another dose metric recently developed is hour-years. In our study, both pack-years and hour-years appeared to be associated with an increased risk of myocardial infarction. It is still unclear which is the

optimum or most relevant exposure metric with regard to the biological mechanisms for an effect by passive smoking on myocardial infarction. If the mechanism of action involves blood gases, measures of long-term exposure might be less suitable than measures of recent exposure. More long-term measures might be important if environmental tobacco smoke e.g. induces or accelerates the development of atherosclerosis. Because both intensity and duration of exposure may influence the risk, cumulative dose metrics such as pack-years and hour-years would constitute relevant long-term exposure measures. In most studies, current exposure results in higher risk estimates than past exposure. This was also true in our study. In addition, cumulative dose measures showed a strong association between environmental tobacco smoke and myocardial infarction, particularly when combining the exposure from the two major sources, i.e. spouse and work. Adding parental exposure during childhood did not increase these estimates. Both effects on blood gases (recent time period) and increased platelet aggregation or development of atherosclerosis (medium/long-term intensity) are possible biological mechanisms of action. Thus, cumulative dose during a relevant part of life (i.e. adulthood), including the two major sources of exposure (spouse and work), may represent a suitable exposure metric for studying the risk of myocardial infarction.

The biological mechanisms for an association between the hardness of the drinking water and coronary heart disease refers either to the early theory of increased hypertension or atherosclerosis due to toxic metals in soft water,[118,126,152] or to potentially beneficial effects from magnesium in hard water.[120,132,134,144,148,152] The main theory today is however that the higher levels of magnesium in hard drinking water would protect against arrhythmias and sudden death.[153,268]

Air pollution epidemiology has proposed several plausible mechanistic pathways that may be of importance for the observed relation between exposure and cardiovascular disease. These include for example enhanced coagulation and thrombosis, increased susceptibility of arrhythmia, systemic inflammation, and promotion of atherosclerosis.[176,269] Especially pulmonary and systemic inflammation, accelerated atherosclerosis,[270,271] and altered cardiac autonomic function have been proposed as plausible mechanistic pathways for the risk of cardiovascular disease from fine particles.[177] The inflammation/accelerated atherosclerosis pathways is supported by studies demonstrating increased levels of inflammatory markers in humans exposed to air pollution, e.g. C-reactive protein,[178,255,272,273] fibrinogen,[178,254,273-277] and platelet count.[275] Altered cardiac autonomic control as a mechanistic pathway is supported by studies relating air pollution exposure to changes in heart rate,[278-280] heart rate variability,[278-289] and blood pressure.[284,290,291] In addition, air pollution has also been associated with the risk of cardiac arrhythmia as indicated by increased activation of autonomic defibrillators carried by certain patients to prevent life threatening cardiac arrhythmias,[292] although others have not found such associations.[293,294] The well established associations between active and passive smoking with cardiovascular

disease has been suggested to further support the plausibility of an adverse effect of ambient air pollution on the cardiovascular system.[176]

Conclusions

Environmental factors of potential importance for cardiovascular disease, such as air pollution and noise, are often geographically distributed and may thus be represented by the home address of the study subjects in epidemiological investigations. Our data indicate that long-term individual exposure may be assessed using such information in combination with geographical information system (GIS) techniques.

An association between exposure to aircraft noise and the prevalence of hypertension was suggested. Others have recently reported an increased risk of myocardial infarction related to road traffic noise. The growing body of evidence on adverse cardiovascular effects from exposure to community noise is of great public health concern and further studies in this field have a high priority.

The results indicate that passive smoking at home and work increases the risk of nonfatal myocardial infarction among never-smokers, which is influenced by time since last exposure, intensity, duration and combined cumulative exposure. Exposure to environmental tobacco smoke is an important preventable public health problem, and the overall evidence is sufficient to motivate actions to minimize exposure.

The results do not support the hypothesis that drinking water hardness protects against myocardial infarction. However, our study was hampered by limited contrast in exposure affecting the possibility to detect any potential effects. Further studies on this topic should use individual data on exposure and other relevant information, as opposed to applying an ecological design.

Our results point to long-term ambient air pollution exposure as a risk factor for fatal myocardial infarction, but not for incidence or nonfatal myocardial infarction. The results support recent findings suggesting that traffic-generated pollutants may be of particular concern. Further studies are needed to investigate a possible difference in effects of long-term exposure to air pollution on mortality and the development of cardiovascular disease, and the role of traffic noise as a potential confounder.

Respondeat superior!

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Cur gallina per viam transire maluit? –Ut in altera parte viae ambularet!