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Cardiovascular Disease Among Professional Drivers and Subway Staff in Stockholm

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CONTENTS

ABSTRACT

Professional drivers are at an increased risk of myocardial infarction (MI), but the underlying causes are not clear. The aims of this thesis were to broaden our understanding of the causal factors involved in this elevated risk of MI in professional drivers, and to study time trends in the incidence of MI in professional drivers. The aim was also to study the risk of cardiovascular disease (CVD) in subway employees exposed to particulate matter. High levels of airborne particles have been detected in the subway system of Stockholm, as well as in several other large cities. This has raised concern about negative effects on health, in view of the well-known association between particulate air pollution in large cities and the risk of CVD.

The thesis is based on three source materials. The first is a population-based case-control study (Stockholm Heart Epidemiology Program - SHEEP) comprising cases of first MI and controls recruited 1992–1993 in Stockholm County. We used 1,067 cases and 1,482 controls to investigate possible causes of the increased risk of MI in professional drivers, and to study the risk in bus, taxi and truck drivers (Paper I). The second is a register-based case-control study of first MI cases recruited in Stockholm County during the period 1976–1996. To investigate time trends in the incidence of MI in bus, taxi and truck drivers, we included 20,364 incident first MI cases and 136,342 controls (Paper II). In the same source material we included 22,311 cases and 131,496 controls to study whether there is an increased incidence of MI in subway drivers exposed to subway-derived particles (Paper III). The third is a cross-sectional clinical study involving employees in the Stockholm subway with 79 participants recruited 2004–2005 for analysis of hematological risk markers of CVD (Paper IV).

Professional drivers were at an increased risk of MI with an odds ratio (OR) of 2.14 (95% CI 1.34–3.41) for bus drivers, 1.88 (1.19–2.98) for taxi drivers, and 1.66 (1.22–2.26) for truck drivers. Adjustment for confounders such as socioeconomic status, tobacco smoking, alcohol drinking, physical inactivity during leisure time, overweight, diabetes, and hypertension gave reduced ORs, although significantly increased risks remained for bus and taxi drivers. An exposure-response pattern (by duration of work) was found for bus and taxi drivers (Paper I). During the 20-year period 1977–1996, there was a greater decline in incidence of MI for professional drivers than for other manual workers. Despite this favorable trend, the relative risk (RR) of MI remained elevated for taxi and truck drivers during the entire period relative to other manual workers (Paper II). The RR of MI in subway drivers was not increased: the RR was 0.92 (95% CI 0.68–1.25) compared to other manual workers (Paper III). Subway employees working at the platforms, who were highly exposed to particles, had significantly higher plasma concentrations of plasminogen activator inhibitor-1 than employees with low exposure. Higher levels of high-sensitivity C-reactive protein, interleukin-6 and fibrinogen, although not significantly higher, were also found in the highly exposed group, which suggests that there may be a long-term inflammatory effect of particle exposure. These differences remained after adjusting for BMI (Paper IV).

In conclusion, the increased risk of MI in bus and taxi drivers could only be partially explained by unfavorable lifestyle factors, suggesting that the work environment may be a contributory cause, but for truck drivers, individual risk factors appeared to explain most of the elevated risk. During 1977–1996, the increased incidence of MI in professional drivers gradually approached the incidence for other manual workers, and bus drivers showed the most favorable trend. Stockholm subway drivers moderately exposed to airborne particles did not show an increased incidence of MI. There were indications of an inflammatory response in platform workers who were highly exposed to particles, which suggests that there may be an increased risk of future CVD in individuals who are highly exposed to airborne particles in subway systems.

Key words: myocardial infarction, occupation, particles, underground, hematological effects

SAMMANFATTNING

Yrkesförare har en ökad risk att drabbas av hjärtinfarkt men de bakomliggande orsakerna är oklara. Syftet med avhandlingen var att öka förståelsen av orsaker till hjärtinfarkt bland yrkesförare och att studera hur incidensen av hjärtinfarkt bland yrkesförare har ändrats över tid. Syftet var också att studera risken för hjärt-kärlsjukdom bland tunnelbanepersonal som exponeras för partiklar. Höga nivåer av luftburna partiklar har uppmätts i tunnelbanan i Stockholm liksom i flera andra storstäder. Detta har gett upphov till oro för negativa hälsoeffekter till följd av det välkända sambandet mellan luftföroreningar i storstäder och risk för hjärt-kärlsjukdom.

Avhandlingen baseras på tre källmaterial. Det första är en befolkningsbaserad fall-kontrollstudie (Stockholm Heart Epidemiology Program - SHEEP) som består av förstagångsfall av hjärtinfarkt och kontroller som rekryterades i Stockholms län 1992–1993. Vi använde 1,067 hjärtinfarktfall och 1,482 kontroller för att studera möjliga orsaker till den ökade hjärtinfarktrisken bland yrkesförare och för att studera risken bland buss-, taxi- och lastbilsförare (Delarbete I). Det andra är en registerbaserad fall-kontrollstudie där förstagångsfall av hjärtinfarkt rekryterades i Stockholms län under perioden 1976–1996. För att studera tidstrender i hjärtinfarktincidensen bland buss-, taxi- och lastbilsförare inkluderade vi 20,364 hjärtinfarktfall och 136,342 kontroller (Delarbete II). För att undersöka om tunneltågförare som exponeras för luftburna partiklar i tunnelbanan har en ökad hjärtinfarktincidens inkluderade vi 22,311 fall och 131,496 kontroller från samma källmaterial (Delarbete III). Det tredje är en klinisk tvärsnittsstudie bland tunnelbanepersonal i Stockholm där 79 studiepersoner rekryterades 2004–2005 för analyser av hematologiska riskmarkörer för hjärt-kärlsjukdom (Delarbete IV).

Yrkesförare hade en ökad risk att drabbas av hjärtinfarkt med en oddskvot (OR) på 2.14 (95% KI 1.34–3.41) för bussförare, 1.88 (1.19–2.98) för taxiförare och 1.66 (1.22–2.26) för lastbilsförare. Justering för confounders såsom socioekonomisk grupp, tobaksrökning, alkohol, fysisk inaktivitet på fritiden, övervikt, diabetes och hypertoni reducerade oddskvoterna men en signifikant ökad risk kvarstod för buss- och taxiförare. Det förelåg ett dos-responsförhållande (i form av antal år i yrket) bland buss- och taxiförare (Delarbete I). Under 20-årsperioden 1977–1996 var minskningen i hjärtinfarktincidens större bland yrkesförare än bland män i övriga arbetaryrken. Trots den positiva trenden kvarstod ändå en förhöjd relativ risk (RR) för hjärtinfarkt bland taxi- och lastbilsförare under hela perioden jämfört med män i övriga arbetaryrken (Delarbete II). Den relativa risken att drabbas av hjärtinfarkt var inte förhöjd bland tunneltågförare jämfört med män i övriga arbetaryrken (RR = 0.92 (95% KI 0.68–1.25)) (Delarbete III). Tunnelbanepersonal som arbetade på perronger med hög partikelexponering hade signifikant högre plasmakoncentration av plasminogen aktivator inhibitor-1 jämfört med personal med låg exponering. Nivåerna av högkänsligt CRP, interleukin-6 och fibrinogen var också högre även om skillnaden inte var signifikant, vilket sammantaget talar för en möjlig inflammatorisk långtidseffekt av partikelexponeringen. Skillnaderna kvarstod efter justering för BMI (Delarbete IV).

Sammanfattningsvis hade buss- och taxiförare en ökad risk för hjärtinfarkt som bara delvis kunde förklaras av ofördelaktiga livsstilsfaktorer och arbetsmiljön kan vara en bidragande orsak, medan risken för lastbilsförare nästan helt kunde förklaras av individuella riskfaktorer. Under perioden 1977–1996 närmade sig yrkesförarnas förhöjda hjärtinfarktincidens gradvis den bland män i övriga arbetaryrken, och bussförare hade den mest fördelaktiga trenden. Tunneltågförare som har en måttlig exponering för luftburna partiklar i Stockholms tunnelbana hade ingen ökad hjärtinfarktrisk. Det fanns tecken på aktiverade inflammationsmekanismer bland perrongarbetare med hög partikelexponering, vilket tyder på att det kan föreligga en ökad risk för framtida hjärt-kärlsjukdom bland personer med höggradig exponering för luftburna partiklar i tunnelbanan.

Nyckelord: hjärtinfarkt, yrke, partiklar, tunnelbana, hematologiska effekter

LIST OF ORIGINAL PAPERS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals (I–IV). Published papers are reproduced with permission from Lippincott Williams & Wilkins (Paper I) and the BMJ Publishing group (Paper II).

I. Bigert C, Gustavsson P, Hallqvist J, Hogstedt C, Lewné M, Plato N, Reuterwall C, Schéele P. Myocardial infarction among professional drivers. *Epidemiology* 2003;14:333-339

II. Bigert C, Klerdal K, Hammar N, Hallqvist J, Gustavsson P. Time trends in the incidence of myocardial infarction among professional drivers in Stockholm 1977-96. *Occup Environ Med* 2004;61:987-991

III. Bigert C, Klerdal K, Hammar N, Gustavsson P. Myocardial infarction in Swedish subway drivers. *Submitted*

IV. Bigert C, Alderling M, Svartengren M, Plato N, de Faire U, Gustavsson P. Blood markers of inflammation and coagulation and exposure to airborne particles in employees in the Stockholm underground. *Submitted*

LIST OF ABBREVIATIONS

BMI	Body mass index
CHD	Coronary heart disease
CI	Confidence interval
CO	Carbon monoxide
CVD	Cardiovascular disease
HDL	High-density lipoprotein
HRV	Heart rate variability
Hs-CRP	High-sensitivity C-reactive protein
IL	Interleukin
LDL	Low-density lipoprotein
MI	Myocardial infarction
OR	Odds ratio
PAHs	Polycyclic aromatic hydrocarbons
PAI-1	Plasminogen activator inhibitor-1
$PM_{2.5}$	Particulate matter less than 2.5 micrometers (μm) in aerodynamic diameter
PM_{10}	Particulate matter less than 10 micrometers (μm) in aerodynamic diameter
RR	Relative risk
SHEEP	Stockholm Heart Epidemiology Program
SMR	Standardised mortality ratio
tPA	Tissue plasminogen activator
vWF	von Willebrand factor

BACKGROUND

CARDIOVASCULAR DISEASE AND MYOCARDIAL INFARCTION

Cardiovascular disease (CVD) refers to the class of diseases involving the heart and/or blood vessels (arteries and veins). The most common CVDs are coronary (or ischemic) heart disease (CHD), cerebrovascular disease (stroke), and hypertension. CVD is the leading cause of death in Sweden and other developed countries, and the World Health Organization has estimated that by 2010, CVD will also be the leading cause of death in developing countries.[1]

Myocardial infarction (MI) is the main cause of death attributed to CVD. The term myocardial infarction refers to the changes that occur in the myocardium due to sudden deprivation of circulating blood. This is usually caused by arteriosclerosis, with fibrous plaques building up in the inner layer of the artery wall, and a subsequent stenosis (narrowing) of the coronary arteries. Inflammatory mechanisms and high levels of blood cholesterol play an important role in the development of atherosclerotic plaques.[2] If an atherosclerotic plaque ruptures, thrombocytes and plasma coagulation factors are activated and form a thrombus (blood clot), which may occlude the coronary artery completely or in part. The thrombosis may lead to death (necrosis) of myocardial tissue, resulting in permanent damage to the heart muscle.

Almost 39,000 individuals suffered from first or recurrent MI in Sweden in 2002, and more than 30% died within 28 days of their MI.[3] The incidence of MI is about 15–20% lower in Stockholm County than the nation-wide figures.[4] In Stockholm County, a total of about 5,800 people had at least one MI in 2002, and of those 57% were men and 43% were women.[3] Both incidence and mortality of MI are strongly related to sex and age. The incidence for women in one age group is the same as for men five to ten years younger.[3]

Several risk factors for CVD and MI have been identified. Some of the major established risk factors are age, male gender, heredity, tobacco use, hypertension, dyslipidemia (especially high levels of low-density lipoprotein (LDL) cholesterol and low levels of high-density lipoprotein (HDL) cholesterol), diabetes, obesity, physical inactivity, unfavorable dietary habits, low socioeconomic status, and psychosocial strain.[5-8] Many of these risk factors – such as tobacco use, physical inactivity, and dietary habits – are modifiable, so many MIs can be prevented by maintaining a healthy lifestyle. Non-modifiable risk factors include age, gender, and family history of an early MI (before the age of 60), probably reflecting a genetic predisposition. Furthermore, there is evidence that elevated levels of inflammatory mediators, cell adhesion molecules, and acute-phase reactants correlate with increased cardiovascular risk.[9] Besides the established risk factors, more than 200 additional coronary risk factors have been proposed.[10] Possible occupational risk factors include job strain,[11] and exposure to combustion products,[12] and environmental risk factors that have been suggested to be of importance include environmental tobacco smoke,[13] ambient air pollution,[14] and traffic noise.[15]

TIME TRENDS IN INCIDENCE OF MYOCARDIAL INFARCTION

In Sweden and other western countries, there has been a decline in the incidence of CHD and mortality from CHD over the last 20 years.[16-18] The incidence of acute MI in the general population in Stockholm increased during the 1970s,[19] followed by a decline starting in the early 1980s,[20] and continuing during the period 1984–1996.[21] The time trend in incidence has shown a similar pattern in manual workers, although it started at a higher level and had a later peak.[22] Between 1987 and 1995, the age-standardised incidence of MI in Sweden declined by 11% for men and 10% for women, while mortality from MI decreased by 14% for both sexes.[16] Between 1987 and 2001 the decline in incidence was 20%, and the decrease in mortality even higher.[23] The decrease in MI-related mortality has been most pronounced in patients treated in hospital.[4]

The decrease in the incidence of MI may be attributed both to changes in risk factors in the population as a whole, especially smoking habits, and to improved medical intervention. The decline in mortality is related to coronary-event rates and changes in survival.[17] Since the majority of deaths from CHD occur outside hospital and in people who are unaware that they have CHD, primary prevention is still very important.[24] The WHO MONICA project registered a decline in the occurrence of traditional risk factors for MI from 1985 to 1995 in 38 populations in 21 countries, most of them in Europe.[25] In the city of Gothenburg in Sweden, smoking rates, mean blood pressures, and cholesterol concentrations decreased during the same period, while body mass index (BMI) and serum triglyceride levels increased.[26]

MYOCARDIAL INFARCTION IN PROFESSIONAL DRIVERS

Epidemiologic studies

An increased risk of MI in professional drivers was first reported over 50 years ago,[27] and has been reported repeatedly since then, especially for bus drivers.[28, 29] In Sweden, professional drivers is one of the occupational groups with the highest incidence of MI.[30] The standardised mortality ratio (SMR) for CHD was found to be significantly higher in professional drivers (SMR = 138) than in the reference group of Swedish men.[31] A comparison of male bus drivers in Sweden with other employed men over a 15-year period (1971–1986) showed an increased mortality from MI and CHD in bus drivers in the county of Stockholm and in Gothenburg and Bohus County, but not in the predominantly rural areas of Sweden.[32] The incidence of MI was increased in bus drivers in Stockholm County,[32, 33] and in taxi drivers both in Stockholm and in the surrounding rural counties.[33] A small increase in the incidence of MI was found for long-distance truck drivers, whereas the relative risk (RR) was close to unity in short-distance truck drivers.[33] Rosengren et al. (1991) found an increased risk of CHD in 103 middle-aged bus and tram drivers in Gothenburg (OR = 3.3, 95% CI 2.0–5.5), compared to men in other occupational groups, and the risk was independent of standard risk factor status.[34] In the same study, taxi drivers had an increased risk of CHD (OR = 3.1, 95% CI 1.6–6.2) that was not statistically significant in multivariate analysis, and truck drivers had no increased risk (OR = 1.2, 95% CI 0.6–2.1). Norwegian studies have shown increased mortality rates from CHD among bus and taxi drivers in Oslo, compared to other occupational groups, and the differences were only partly attributed to an unfavorable risk factor profile.[35, 36] Danish studies have shown an

increased risk of CHD in bus drivers compared to other employed men in Copenhagen,[37, 38] and a higher risk of hospital admission for CHD in bus and taxi drivers.[39] The standardised hospital admission ratios for diseases of the circulatory system were higher in Danish professional drivers than in the male working population, and were higher for drivers working in passenger transport than for drivers of goods vehicles.[40] Bus drivers in Denmark even had an increasing RR of CHD in the period from 1981 to 1993.[29] City bus drivers in Montreal were found to have a small, but not statistically significant, excess mortality from CHD and diseases of the circulatory system, compared to men in the general population.[41] New York City bus drivers were found to have a statistically significant excess mortality due to CHD.[42]

Possible underlying causes

The epidemiologic studies cited above show that professional drivers are at increased risk of developing MI compared to many other occupational groups, and that the risk varies for different types of drivers. Bus drivers in urban areas appear to be at a particularly high risk. The underlying causes for this increased risk are not fully understood and have been attributed both to chemical and psychosocial factors in the work environment, as well as to an overrepresentation of established coronary risk factors among drivers.[43, 44]

Rosengren and co-workers found no significant differences in smoking habits, serum cholesterol levels or blood pressure between bus and tram drivers and other men in Gothenburg.[34] The bus and tram drivers tended to be more physically active during leisure time, but had a significantly higher BMI than other men. In a study involving male professional drivers from the Swedish counties of Västerbotten and Norrbotten, significantly more drivers than referents were overweight, smokers, and shift workers; were sedentary in their leisure time; and had a work situation characterized by high demands, little room for decision-making, and low social support.[45] There were no significant differences in blood pressure or serum lipid levels. When bus and truck drivers were compared to industrial workers, the results showed higher mean values for serum cholesterol, serum triglycerides, blood pressure, and work-related stress in the driver group.[46] The groups were found to be equal regarding CHD-inheritance, physical activity during leisure time, and BMI. Bus and taxi drivers in Oslo were found to have a high prevalence of smoking, high serum triglycerides and cholesterol levels.[35] There was a particularly high risk score for bus and taxi drivers with low income and short education. These men were generally overweight and heavy cigarette smokers, and had high lipid levels.

While standard risk factors tend to be overrepresented in professional drivers, these factors have not been clearly shown to distinguish professional drivers from other groups of similar socioeconomic status, and the excess risk of CHD in professional drivers is not fully explained by standard risk factors.[47] There is a growing consensus that occupational factors must be given careful consideration.[28, 42] Factors of possible importance are psychosocial work conditions, sedentary job, and exposure to air pollutants generated by motor vehicles.

Many professional drivers have a sedentary working life. The work of truck drivers can involve much heavy lifting and dragging, although this is combined with periods of sedentary work. In a classic study from 1953, Morris et al. showed a higher incidence of CHD in bus drivers, compared to conductors.[27] The authors attributed this to less physical activity at work on the part of drivers. More recent studies have shown that walking or standing at work is associated with a reduced risk of MI, and that heavy lifting or carrying at work – where the occupational workload is perceived to be strenuous – is related to an increased risk of MI.[48]

Exposure to motor exhaust has been proposed to be a potential risk factor for MI in professional drivers, as a result of the presence of carbon monoxide (CO) and/or polycyclic aromatic hydrocarbons (PAHs) in the fumes.[12, 49] For more information on exposure to motor exhaust in relation to CVD, see the "Occupational exposure" section on page 9. However, professional drivers are only moderately exposed to motor exhaust. Personal measurements of motor exhaust exposure among bus, taxi, and truck drivers in Sweden showed that truck drivers had the highest exposure and taxi drivers had the least, irrespective of whether nitrogen dioxide (NO_2) or particles were used as the indicator of exposure.[50]

Several epidemiological studies have suggested a causal role for occupational stress.[34, 42, 44] Professional drivers report a higher overall exposure to stressful work factors than referents.[28, 45, 46] Catecholamine excretion was found to be elevated during driving, and ambulatory measurements have shown higher systolic and diastolic blood pressure in drivers before, during, and after driving shifts.[28] A combination of high demands and a low degree of control was common among Swedish bus drivers, and also in taxi drivers.[33] Long- and short-distance truck drivers were, however, found to be closer to other occupational groups in this respect. Surveys indicate that the most compelling problems for city bus drivers are threats, physical assault, traffic congestion, little or no influence on how the work is organized, time pressure, disorderly passengers, ergonomic/mechanical difficulties (regarding temperature, seat comfort, visibility), and interference of the work schedule with home life and leisure activities.[44] Thus, their job is characterized by a particular profile of job characteristics that has been shown to be strongly associated with CVD in several epidemiological studies.[51, 52]

AIR POLLUTION AND CARDIOVASCULAR DISEASE

Ambient particle exposure

The consequences of high levels of ambient air pollution in urban environments were obvious in the mid-twentieth century when cities in Europe and the United States experienced episodes of air pollution, such as the famous 1952 London smog episode, that resulted in many deaths and hospital admissions on the days following extremely high levels of air pollution.[53, 54] However, recent epidemiological studies have revealed negative effects on health from combustion-derived air pollution at levels even lower than those previously considered to be safe,[55] and it is unclear whether a threshold concentration exists below which no effects on health are likely.

Air pollution is a heterogeneous, complex mixture of gases, liquids, and particulate matter (PM), that may have a variety of effects on the health of individuals.[56]

Epidemiological studies have generally concentrated on the effects of airborne PM, and have demonstrated a consistently increased risk of cardiovascular morbidity and mortality in the general population associated with exposure to PM in urban air.[14, 55, 57, 58] These effects have been found in short-term studies,[14, 54, 57, 59-63] which have investigated day-to-day variations in air pollution in relation to health, and long-term studies,[64-69] which have followed exposed individuals over time.

Studies on the health effects of airborne PM have traditionally focused on particles with an aerodynamic diameter of less than 10 μm (PM_{10}), which are small enough to reach the conductive airways and the lower respiratory system, or particles less than 2.5 μm in diameter ($PM_{2.5}$). The coarse particles (particles 2.5–10 μm) mainly originate from natural sources such as dust, soil and pollen, and from mechanically abrasive processes in industry and transportation. Fine particles ($PM_{2.5}$) are usually formed from gases, mainly as a result of fossil fuel combustion. The coarse fraction of PM_{10} has been studied only recently, and has shown an association with CVD, but the evidence is stronger for $PM_{2.5}$.[70]

Occupational exposure

Several toxicological and epidemiological studies have produced evidence that occupational exposure to PAHs is a risk factor for CHD. PAHs are formed during the burning of coal, oil, gas, wood, rubbish and other organic substances, and such exposure to exhaust means exposure to particles coated with PAHs. In a cohort of more than 12,000 male asphalt workers from Denmark, Finland, France, Germany, Israel, the Netherlands and Norway, exposure to benzo(a)pyrene, a PAH, was shown to be positively associated with mortality from CHD, with a consistent exposure-response relation.[71] A high risk of CVD has been reported for workers exposed to high levels of combustion products, e.g. chimney sweeps,[72, 73] waste incinerator workers,[74] and aluminum smelter workers.[75] In a Swedish study, the RR of MI was found to be elevated among those who were highly or intermediately exposed to combustion products, with a clear exposure-response pattern, while exposure to motor exhaust was not found to be consistently associated with MI.[76] Occupations included in the group that was highly exposed to combustion products were ship engine room crew, fire-fighters, chimney sweeps, blacksmiths, and engineers and technicians in energy production. In a cohort of Swedish construction workers particulate air pollution was associated with an increased risk of CHD, with an increased risk in workers exposed to inorganic dust (asbestos, man-made mineral fibers, dust from cement, concrete and quartz) and fumes (metal fumes, asphalt fumes and diesel exhaust), relative to unexposed workers.[77] An excessive number of cardiovascular deaths has also been reported in workers exposed to carbon disulfide, an organic solvent used in the manufacture of rayon.[12] An elevated risk of arteriosclerotic heart disease was observed in New York City tunnel officers exposed to CO, as compared with that of bridge officers, but the risk declined after cessation of exposure, with much of the risk dissipating within five years.[49] Thus, exposure to CO may increase the acute risk of CVD but probably has no lasting atherosclerotic effect.[12]

Particles in the subway system

In contrast to the well-documented negative effects of combustion-generated particles in urban air and certain occupational environments on the cardiovascular system, there have been no epidemiologic studies on the cardiovascular effects of exposure to particles from subway systems.

High levels of airborne particles have been detected on underground platforms in the subway systems of Stockholm,[78] London,[79, 80] New York,[81] and Rome.[82] The concentrations of particles and metals are significantly higher than in the general environment. The particles originate mainly from wear of wheels, rails and brakes, and contain a high proportion of iron (Fe). They are larger than particles generated by combustion engines and are mainly in the size range of 1–10 µm.[80, 83, 84] The mass concentration of underground particles is dominated by particles larger than 1µm in diameter, which is typical for particles generated by mechanical wear, and these particles are possibly more angular in shape than particles generated from exhaust.[85] Figure 1 shows electron microscopy images of cultured human lung cells exposed to particles in an experimental study by Karlsson et al. (2005).[86]

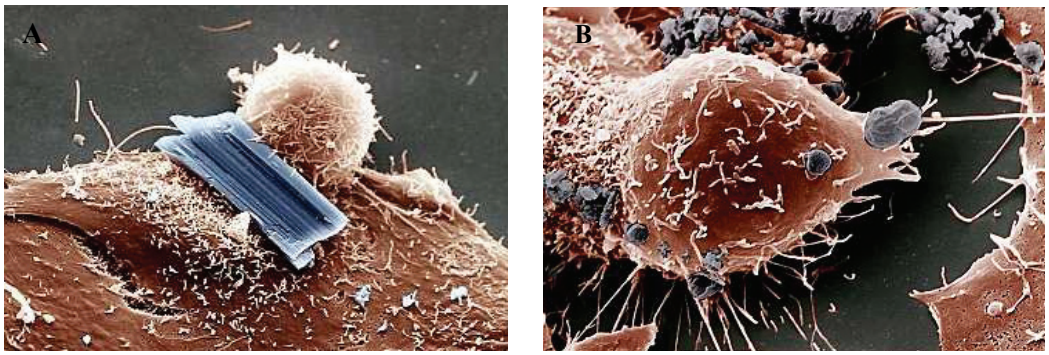

Figure 1. Electron microscopy images of cultured human lung cells exposed to subway particles (A) and particles from an urban street (B). The particles have an approximate width of 6 µm (major particle, A) and 1 µm (circular particle close to the middle section, B). Photo by Lennart Nilsson.

The concentration of PM_{10} on an underground platform in Stockholm was found to be 470 µg/m^3 (average level during weekdays between 7 a.m. and 7 p.m.), which is 4–5 times higher than the levels of PM_{10} found in one of the busiest streets in Stockholm.[78] Measurements in driver cabins on Stockholm's three subway lines have shown average PM_{10} levels of 62 µg/m^3, 108 µg/m^3, and 125 µg/m^3, respectively,[87] and the average PM_{10} at the underground platforms was found to vary between 52 and 418 µg/m^3 during daytime. Thus, the exposure to PM_{10} seems to be lower inside the driver cabins than on the platforms. Measurements in London showed that the average exposure to $PM_{2.5}$ was 3–8 times higher for people traveling by the underground than for those using surface transport modes (bicycle, bus, or car),[79] and about 8 times higher than for taxi drivers.[88]

There are no exposure limit values for the air quality in the underground. However, the levels registered at underground platforms are higher than limit values for ambient air quality. For PM_{10}, an annual average concentration in ambient air of greater than 40 µg/m^3 is not allowed in Sweden and other EU countries.[89] The daily average PM_{10} levels must not exceed 50 µg/m^3 more than 35 times during the course of one year.

Biological mechanisms

Potential mechanisms linking particle exposure to cardiovascular disease

Although associations have been found between airborne particles and CVD, little is known about the underlying mechanisms linking exposure to disease. Several plausible mechanistic pathways have been put forward, including pulmonary and/or systemic inflammatory responses with enhanced blood coagulability and accelerated atherosclerosis.[56, 90-93] Low-grade chronic inflammation in the artery wall may cause thrombosis and atherosclerosis.[9] Furthermore, deposition of particles in the airways seems to affect the autonomic nervous control of the heart in response to direct reflexes from receptors in the lungs and/or to local or systemic inflammatory stimuli.[94] Examples of other suggested mechanisms are cardiac malfunction due to ischemic responses within the myocardium and/or altered ion-channel functions in myocardial cells.[94] The available data are most consistent with the occurrence of a systemic response that involves inflammation, coagulation, and cardiac rhythm (Figure 2).

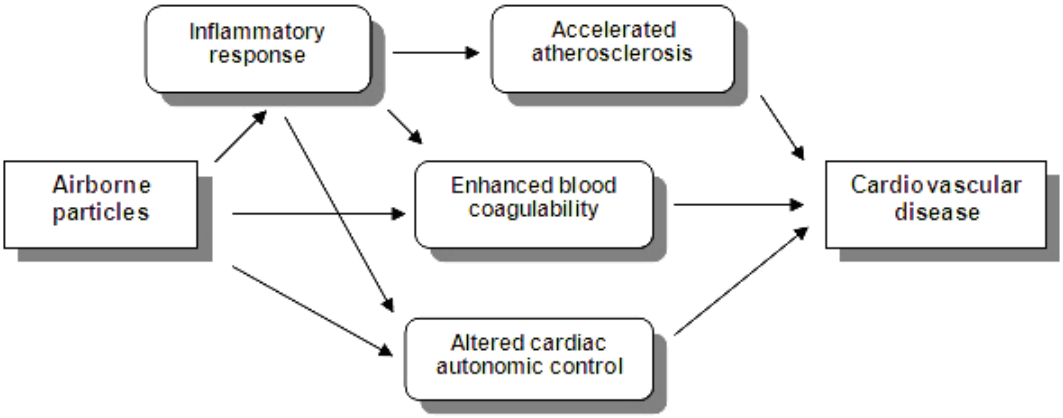

Figure 2. Possible mechanisms linking particle exposure to cardiovascular disease.

The inflammatory response

Inflammatory responses as a mechanistic pathway for particles deposited in the lung to cause CVD gain support from several empirical studies. Exposure to particles appears to result in systemic inflammation within hours of exposure. In a study involving healthy human volunteers, acute exposure to diesel exhaust was found to produce a systemic and pulmonary inflammatory response 6 hours after exposure.[95] One study found elevated levels of interleukin-1 (IL-1) and interleukin-6 (IL-6) in the plasma of young healthy individuals exposed to high levels of PM_{10} during an episode of acute air pollution.[96] Increased levels of plasma fibrinogen lead to increased plasma viscosity, and both fibrinogen and viscosity have been shown to be associated with PM exposure in epidemiological studies.[58, 97] In a study of office workers in London, an increase in the 24 hour mean NO_2 and CO during the previous day was found to be associated with increased concentrations of plasma fibrinogen in both seasons, with similar associations for PM_{10} in the warm season,[58] and $PM_{2.5}$ exposure inside patrol cars (with an average $PM_{2.5}$ of 24 $\mu g/m^3$) was associated with increased neutrophils, C-reactive protein (CRP) and von Willebrand factor (vWF) 14 hours after the work shift.[98] Fibrinogen and IL-6 were found to be increased after exposure of Norwegian tunnel construction workers to dust.[99]

Altered cardiac autonomic function

Studies supporting altered autonomic nervous control of the heart as a mechanistic pathway have related air pollution exposure to changes in heart rate or heart rate variability (HRV). A relationship has been shown both in the elderly and in patients with existing CVD,[100-107] and in healthy young adults.[98, 108-110] Reduced HRV has been linked to exposure to PM_{10} and $PM_{2.5}$, and recently also to $PM_{10-2.5}$ (coarse particles).[103] Changes in blood pressure have been noted as well.[111, 112] Furthermore, an association has been shown between exposure to the metal component of ambient $PM_{2.5}$ and alterations in cardiac autonomic function.[113] There is also a hypothesis that air pollution is associated with increased risk of cardiac arrhythmias, and in one study such an association was found in patients with implantable cardioverter defibrillators.[114] The changes in cardiac autonomic function may be partly due to the inflammatory response to particle exposure.[94, 109]

Relationship between blood markers and heart rate variability and disease

A number of markers of inflammation and coagulation, including plasminogen activator inhibitor-1 (PAI-1), CRP, IL-6, fibrinogen and factor VII, are known to be predictive of CVD.[91, 93, 115] Plasma concentrations of PAI-1, tissue plasminogen activator (tPA) antigen and tPA/PAI-1 complex have been shown to be predictive of MI in patients with manifest CHD,[116] and in a study by Hamsten et al. (1987) high plasma concentrations of PAI-1 were independently related to recurrent MI.[117] Fibrinogen was found to be an independent predictor of cardiovascular death or non-fatal MI in patients with stable angina pectoris.[118] In a study involving MI patients in Stockholm, fibrinogen, vWF, tPA antigen, PAI-1 and the tPA/PAI-1 complex were found to be risk markers of recurrent MI.[119] Progression of coronary artery disease in male post-infarction patients was linked to high PAI-1 activity.[120] In a large meta-analysis, moderately strong associations were found between plasma fibrinogen level and the risk of CHD in healthy middle-aged adults.[121] Altogether, it seems that these markers play an important role in the pathogenesis of the adverse effects on cardiovascular health associated with air pollution. There is also a well-established association between reduced HRV and adverse prognosis in patients after MI,[122] and several studies have shown that low HRV is a predictor of cardiac events and mortality from all causes in the general population.[123]

Information on some markers of inflammation and coagulation

Thus, a large number of mediators are involved in the inflammatory response induced by exposure to airborne particles. Some of them are discussed below. The acute inflammatory process in the airways results in an influx of inflammatory cells such as neutrophils, alveolar macrophages and lymphocytes. Macrophages have an important role in the clearance of inhaled particles. The inflammation leads to the release of IL-6 from macrophages and subsequent stimulation of hepatic secretion of acute-phase proteins such as fibrinogen and CRP.[96, 124] IL-6 also stimulates the production of platelets.[96] Inflammatory cytokines including IL-1, tumor necrosis factor (TNF), and CRP induce the expression of cellular adhesion molecules, which mediate adhesion of leucocytes to the vascular endothelium.[124] CRP can also induce monocytes to express tissue factor (TF), which plays an important role in coagulation.[125] The main function of vWF is binding to other proteins, particularly factor VIII, and it is important in platelet adhesion. PAI-1 acts as an acute-phase reactant in plasma, and the plasma concentration follows a typical diurnal pattern, with peak levels in the early morning and lower levels during the day and evening.[126] PAI-1 is the principal inhibitor of tPA

and urokinase plasminogen activator (uPA), and is thus an inhibitor of fibrinolysis. It is mainly produced by the endothelium, but is also secreted by other tissue types such as adipose tissue. High levels of several inflammation-related markers such as IL-6, IL-8, TNF-α, and PAI-1 are associated with obesity and the metabolic syndrome.[126, 127] Cigarette smoking is known to alter cytokine regulation,[128] although the effect of PM exposure seems to be independent of the effect of cigarette smoking.[96]

Particles in the subway

Subway-derived particles differ from particles in urban air with respect to size range, mass concentration, chemical composition, and shape. The source of these particles is mainly mechanical wear, instead of a result of combustion, and the metal content (mostly iron (Fe)) is higher in subway-derived particles. Chemical analysis of PM_{10} from a subway station in Stockholm and from a traffic-intensive street showed that iron was the predominant element in subway particles together with some silica, calcium, barium, and copper, while the street PM_{10} had more mixed content resulting in peaks of silica, sodium, sulfur, chloride, calcium, and barium.[129] High iron content in subway particles has also been reported from London,[80] New York,[81] and Rome.[82] The iron in subway particles is mainly in the form of iron oxide.[80, 86] Metals are probably causative agents in induction of oxidative stress (a disturbance in the balance between oxidants, e.g. free radicals, and antioxidants) and they have also been shown to be important for inflammatory effects in cellular studies.[130-132] Thus, some of the inflammatory effects of exposure to subway particles, as indicated by the experimental studies discussed below, may possibly be caused by the metal content.

Experimental data show that PM_{10} from the Stockholm subway induce oxidative stress in cultures of human lung cells, and that the effect of subway particles is stronger than that of street-level particles when compared on a weight basis.[86, 133] Subway particles can also induce an inflammatory response from human macrophages,[129, 133] and in bronchial epithelial cells.[129] Particles from the London underground were shown to have inflammatory properties when samples of dust were tested toxicologically.[80]

MISSING LINKS

Despite the epidemiological support for associations between working as a professional driver and MI, there are still gaps in our knowledge concerning the underlying causes of the increased risk. A central question is to what extent the increased incidence of MI in some driver groups can be explained by increased smoking habits, overweight, or other risk factors in MI that might confound the associations under study. In several epidemiological studies, individual data on risk factors for MI were not available, and sometimes indirect comparisons were used. Characteristics of the psychosocial work environment appear to be of special importance, but more information on both lifestyle factors and exhaust exposure would also be of use for a better understanding of the causes of MI in professional drivers. There is also a need for further investigation of the risk of MI in different groups of professional drivers, and to study the extent to which the incidence of MI in drivers has changed in recent years.

Although associations have been found between airborne PM in the environment and CVD in the general population, and between occupational exposure to particles from certain sources and CVD, little is known about the possible cardiovascular effects of

high exposure to particles prevailing in the subway system. There have been very few previous studies, and essentially only experimental studies have been published in the scientific literature. High exposure to PM has led to concern about negative effects on the health of both commuters and subway staff. Given the high degree of exposure to subway particles on underground platforms, the experimental data indicating that the particles have inflammatory properties, and the lack of human studies, it is of importance to investigate whether there is an effect of exposure to subway particles on the risk of CVD. It is also of importance to clarify more in detail which kinds of airborne particles and what fraction(s) might pose the greatest risk to health, and to explain the mechanisms behind the induction of CVD in greater depth.

AIMS OF THE THESIS

The main goal of this thesis was to broaden our understanding of the relationship between professional driving and risk of MI, and to investigate the risk of CVD in employees exposed to particles in the subway system.

The specific aims were:

- To investigate possible causes of the increased risk of MI seen in professional drivers, and to study the risk in bus, taxi and truck drivers separately.
- To investigate time trends in the incidence of MI in bus, taxi, and truck drivers.
- To investigate whether there is an increased incidence of MI in subway drivers.
- To determine whether there is an effect of exposure to subway particles on risk markers for CVD in subway employees.

MATERIALS AND METHODS

The papers that constitute this thesis are based on three source materials. The first is the Stockholm Heart Epidemiology Program (SHEEP), a population-based epidemiological study on risk factors of MI (Paper I). The second is a register-based case-control study of the incidence of MI in Stockholm County (Paper II and III). The third is a cross-sectional study involving employees in the Stockholm subway (Paper IV).

STOCKHOLM HEART EPIDEMIOLOGY PROGRAM (PAPER I)

Study design

The SHEEP study is a population-based case-control study of causes of MI in men and women in Stockholm County. The study included cases of first-time MI and controls in the ages 45–70 recruited 1992–1994 in Stockholm County and randomly selected control subjects stratified on age, sex and hospital catchment area. We identified cases from three sources: the medical care units at the 10 emergency hospitals within the Stockholm County, other hospital units (obtained from a computerized hospital discharge register), or death certificates from the Causes of Death Register at Statistics Sweden. The cases were diagnosed according to specified criteria using information on symptoms, ECG, enzymes and autopsy findings.[134] The study design has been described in detail elsewhere.[135] Altogether, 2,246 cases and 3,206 controls were identified. Paper I in this thesis focuses on MI in professional drivers.

The individual background information was collected by a questionnaire covering a large number of possible risk factors for MI, including physical and psychosocial workplace conditions, social factors and life style factors as well as a lifetime occupational history including occupation, work tasks, and company name and address, for all jobs held for at least one year. For fatal cases, the questionnaires were completed by next-of-kin. In addition to the questionnaire, a telephone interview was performed to fill in on missing data and increase response rate. Non-fatal cases and a similar proportion of controls were invited to a health examination at three months after either the onset of disease (cases) or inclusion (controls). The examination included blood samples and recording of blood pressure, height and weight.

Study subjects

We restricted study I to men, as there were very few MIs among the female drivers. The cases comprised all men who had their first MI in 1992 or 1993, whether fatal (death within 28 days) or non-fatal. We selected controls randomly from the study base through a computerized population register, stratified for sex, 5-year age group, hospital catchment area and year of enrolment in the study (1992 or 1993). The number of identified and responding cases and controls was 1,202 (response rate 81%) and 1,538 (74%), respectively. The cases were mainly identified from the medical care units at the emergency hospitals (87%), but also from other hospital units (1%), and death certificates (12%).

Exposure assessment

Data from the questionnaire, interview and health examination were combined, if applicable, when classifying subjects into exposure categories. We classified possible confounding factors: socioeconomic status, smoking habits, alcohol consumption, physical inactivity at leisure time, overweight, diabetes, hypertension and job strain (see Table 1). Blood laboratory data were available only for the non-fatal cases, and due to a high proportion of missing data we did not include blood lipids in the standard set of confounding variables. We coded occupations according to the Nordic version of the international classification of occupations.[136] An occupational code was assigned to every job held for at least a year. There were 1,067 cases (72% of all identified cases) and 1,482 controls (71% of all identified controls) with sufficient information for coding of occupational history and confounders. Among the cases, 86% were non-fatal. There were 147 cases and 129 controls who had worked as a driver (for at least one year). These included 77 bus drivers, 78 taxi drivers and 179 truck drivers; 53 persons had worked in two of these categories, and 5 had worked in all three. Characteristics of the professional drivers and of all men in the study are shown in Table 1.

Table 1. Characteristics of professional drivers and of all men in study I

	Bus drivers		**Taxi drivers**		**Truck drivers**		**All included**	
Exposure factor	Cases	Contr.	Cases	Contr.	Cases	Contr.	Cases	Contr.
No. of subjects	46	31	44	34	95	84	1,067	1,482
Age group (years) (%)								
45-50	9	16	14	12	16	13	16	15
51-55	13	7	25	9	19	6	17	16
56-60	33	26	21	27	30	36	22	21
61-65	35	29	32	35	23	33	24	25
66-70	11	23	9	18	13	12	21	23
Smoking pattern (%)								
Never smoked	9	26	9	18	7	23	21	36
Ex-smokers	22	42	23	35	22	29	29	34
Current smokers	70	32	68	47	71	49	50	30
Alcohol consumption (grams/day)*	18	14	19	19	24	18	19	17
Physical inactivity at leisure time† (%)	74	42	57	62	56	46	45	34
Overweight‡ (%)	39	52	41	32	54	36	42	29
Diabetes mellitus§ (%)	17	3	14	---	15	7	13	6
Hypertension‖ (%)	26	23	21	18	25	24	30	23
Socioeconomic status¶ (%)								
High-level employees and agricultural workers	7	10	5	6	4	5	23	32
Low- and middle-level employees and self empl.	33	45	41	47	42	45	45	45
Manual workers	61	45	55	47	54	50	32	24
Job strain# (%)	11	10	14	6	15	7	7	4

***** Grams of alcohol/day; mean value during the exposure period; † No regular exercise other than occasional walks during the last 5–10 years; ‡ BMI > 27; § History of drug- or diet-treated diabetes; ‖ Use of antihypertensive drugs, or a systolic blood pressure exceeding 180 mmHg or a diastolic pressure exceeding 100 mmHg at the health examination; ¶ Coded according to occupation ten years before inclusion; # Average exposure during the last five years before recruitment or retirement. Exposed to both high demands (over 75th percentile) and low decision latitude (below 25th percentile). 14 subjects had missing data.

Statistical analysis

We estimated the odds ratio (OR) of developing MI, and 95% confidence intervals (CIs), by unconditional logistic regression. We used SPSS statistical software for all analyses. The OR in each category of driver (bus, taxi and truck drivers) was calculated using all men who never worked as a driver at all as "unexposed". We adjusted all analyses for the stratification factors used in the selection of controls. The confounders were introduced in the regression model in steps, in order to evaluate confounding from different types of exposures separately. We also calculated the OR of MI in drivers subdivided by duration of employment (1–10 years, or >10 years) and number of years since end of employment (current, 2–20 years, or >20 years).

REGISTER-BASED CASE-CONTROL STUDY (PAPER II AND III)

Study design

The study population comprised all men 40–69 years of age residing in Stockholm County during the period 1977–1996 in study II, and 1976–1996 in study III. We identified incident cases of acute MI in the study population by using registers of hospital discharges and deaths in accordance with a previously developed and validated method.[21, 137, 138] For the period 1976–1984, data used in this study were compiled in the late 1980´s .[30, 33] For the years 1985–1996, data were compiled more recently and in a similar fashion but with a more extensive sample of controls. In study II we identified 22,972 incident first MI cases in total and in study III 24,315. We selected controls randomly from the general population using registers of the total population of Stockholm County on December 31st each year 1976–1996. For the period 1976–1984, sampling of controls was frequency-matched for gender, age (5-year age groups) and calendar year, and we selected two controls for each case. For the period 1985–1996, we selected 1,500 controls per age (5-year age groups) and calendar year stratum. In study II controls sampled December 31st 1984 were included also for the period 1985–1996, to be able to calculate incidence rates. Controls with a previous history of MI were excluded. Due to the small number of cases of MI in female drivers, study II and III were restricted to men.

Study subjects

In study II we included subjects with employment in any of the two national censuses preceding the year of inclusion in the study. We used 20,364 first MI cases and 136,342 controls in total (Table 2).

In study III we included subjects with employment in any census preceding the year of inclusion in the study. We used 22,311 first MI cases and 131,496 controls in total (Table 2).

Exposure assessment

We obtained information on occupation, branch of industry, and socioeconomic group for cases and controls using the national censuses of 1970, 1975, 1980, 1985, and 1990. We classified socioeconomic group for cases and controls primarily from the preceding census. If the subject was not employed at that census we used information from the next previous census back in time. The subjects were subdivided into manual workers, non-manual employees and self-employed.

In paper II we identified bus drivers, taxi drivers and truck drivers by combining the occupational code for "motor vehicle driver" with the appropriate branch of industry code. [139] A subject was classified as a professional driver if he had reported working as such in any of the two censuses preceding the year of inclusion. Altogether, 241 cases and 1,339 controls had worked as bus drivers, 315 cases and 1,436 controls as taxi drivers, and 662 cases and 3,481 controls as truck drivers (Table 2). Drivers who had recently been driving two different types of vehicles were included in both driver categories.

In paper III we identified subway drivers by combining the occupational code for "locomotive driver" with the branch of industry code for "bus and tram traffic".[139] A subject was classified as a subway driver if he had reported working as such in any census preceding the year of inclusion in the study. Altogether, 54 cases of MI and 250 controls had worked as subway drivers (Table 2).

Table 2. Number of cases and controls included in study II and III

	1977–1996 (Study II)	
	Cases	**Controls**
Bus drivers	241	1,339
Taxi drivers	315	1,436
Truck drivers	661	3,481
Other gainfully employed	19,181	130,270
other manual workers*	6,943	39,593
Total (all drivers and other gainfully employed)	20,364	136,342
	1976–1996 (Study III)	
	Cases	**Controls**
Subway drivers	54	250
Other gainfully employed	22,257	131,246
other manual workers*	8,694	43,432
Total (all drivers and other gainfully employed)	22,311	131,496

***** Subcategory of other gainfully employed. Includes manual workers who never worked as bus, taxi or truck drivers (Study II) or manual workers who never worked as subway drivers (Study III).

Statistical analysis

In study II we calculated age-standardised (5-year age groups) incidence rates by two year calendar periods for different categories of professional drivers, for manual workers other than professional drivers, and for all gainfully employed other than professional drivers. The population total was derived by multiplying the prevalence of the different categories among the controls with the number of persons in Stockholm County in each stratum. The person-time at risk used in the incidence estimates was calculated as the average of the population total at 31 December on the previous and the current year. The age distribution for men aged 40–69 in Stockholm County in 1990 was used in the age standardisation. The variance of the incidence was calculated using the Gauss approximation formula. We estimated the average annual change in incidence of first acute MI during the study period in relative terms by Poisson regression, adjusting for secular changes in the age distribution, and in absolute terms by calculating the average yearly change in incidence per 10,000 person years by linear regression. The association between work as a professional driver and first acute MI

was evaluated by computing ORs from stratified analysis in accordance with the Mantel-Haenszel method, adjusting for age group (5-year) and calendar year (4-year). In these analyses, we used manual workers other than bus, taxi or truck drivers, or gainfully employed subjects other than bus, taxi or truck drivers, respectively, as comparison group. In addition we performed analyses restricted to persons holding the same type of job in two censuses (job duration ≥ 5 years) preceding inclusion in the study as case or control.

In study III, the association between work as a subway driver and first acute MI was evaluated by computing ORs by stratified analysis using the Mantel-Haenszel method, adjusting for age (5-year age groups) and calendar year (3-year calendar groups). In these analyses, we used manual workers other than subway drivers, or all gainfully employed other than subway drivers, as unexposed comparison group. We also performed analyses restricted to people holding the same type of job in two censuses (job duration ≥ 5 years) preceding inclusion in the study as a case or a control, analyses restricted to individuals first holding an occupation ten years or more before inclusion, and analyses restricted to individuals who were still in the occupation, or had stopped no more than five years before inclusion.

In view of the study design for study II and III, the ORs may be interpreted as RRs. Random variation was accounted for by computing 95% CIs. We used SAS statistical software for all analyses.

CROSS-SECTIONAL STUDY IN SUBWAY STAFF (PAPER IV)

Study design

Study IV is a cross-sectional study involving subway employees in Stockholm, focusing on hematological effects of particle exposure. The participants were investigated between November 2004 and March 2005. They were interviewed about the state of their health and also whether they were on medication. Height, weight and blood pressure were recorded. The first blood sample was taken before the start of a work shift, after at least two days of vacation. The second sample was taken 48 hours later, after two days of work. Both blood samples were taken after one night of fasting and at the same time of the day, with a maximum two hours time difference. The blood samples were collected for analysis of the coagulation parameters vWF, factor VII and fibrinogen and the inflammatory markers PAI-1, high-sensitivity CRP (hs-CRP) and IL-6. The first blood sample also included cholesterol (total and HDL) and triglycerides.

Study subjects

The 79 participants were non-smokers of both sexes, aged 25–50. No requirements regarding freedom from disease were used, although subjects on medication that could influence the hemostatic balance (such as anti-coagulation medication) were not included. Three exposure groups were formed according to the level of exposure to subway particles (see below). There were 29 highly exposed platform workers (cleaners and ticket collectors with the main working site on the platforms), 29 moderately exposed subway drivers and 21 ticket sellers with low exposure (control group).

Exposure assessment

We calculated BMI from information on weight and height (BMI = weight in kg/(height in m)^2). We coded individuals with a history of drug- or diet-treated diabetes as being diabetic. We assessed the presence of hypertension from information on the use of antihypertensive drugs, or a systolic blood pressure exceeding 160 or a diastolic pressure exceeding 90 at the examination. Persons who had smoked on a regular basis any time before inclusion were coded as ex-smokers. Background characteristics of the exposure groups are shown in Table 3.

Table 3. Background characteristics of the exposure groups in study IV

	Ticket sellers (n = 21)	**Subway drivers** (n = 29)	**Platform workers** (n = 29)
No. of men (%)	13 (62)	18 (62)	23 (79)
No. of women (%)	8 (38)	11 (38)	6 (21)
Age in years, mean and range	38 (25–50)	38 (25–50)	40 (25–50)
BMI, mean and range	25.4 (18.8–35.0)	25.7 (19.0–34.9)	28.1 (20.2–38.5)
No. of ex-smokers (%)	6 (29)	18 (62)	6 (21)
No. with hypertension (%)	0	1 (3)	5 (17)
No. with diabetes (%)	0	0	2 (7)
No. with asthma (%)	3 (14)	4 (14)	1 (3)
Triglycerides, mmol/L, mean and range	1.2 (0.4–4.7)	1.4 (0.3–3.8)	1.4 (0.4–4.1)
Cholesterol, mmol/L, mean and range	4.9 (3.4–7.7)	5.1 (3.3–7.6)	5.1 (3.1–9.6)
HDL cholesterol, mmol/L, mean and range	1.2 (0.7–1.7)	1.3 (0.7–2.1)	1.1 (0.7–1.7)
LDL cholesterol, mmol/L, mean and range	3.2* (1.9–5.3)	3.1 (0.5–5.8)	3.3 (1.7–7.7)

***** Data were missing for one subject.

For 44 of the participants, the exposure to particles (measured as $PM_{2.5}$ and by DataRAM) was investigated by personal sampling during three work shifts.[140] The levels of $PM_{2.5}$ for the platform workers were about 6 times higher than for the control group (ticket sellers), and in subway drivers they were about twice as high, with an average $PM_{2.5}$ of 65 μg/m^3 for platform workers, 19 μg/m^3 for subway drivers and 10 μg/m^3 for the control group. The corresponding DataRAM (nefelometric $PM_{0.1\text{-}10}$) levels were 182 μg/m^3, 33 μg/m^3 and 13 μg/m^3, respectively.

Statistical analysis

To investigate short-term effects of the particle exposure, we analysed the average of the individual percentage change in serum concentration from the first to the second sample, and used paired t-tests to analyse whether there was a significant percentage change. To investigate long-term effects, we compared the arithmetic average of the values between exposure groups using independent sample t-tests. In this analysis we used the second blood sample in order to include both acute and long-term effects. We calculated the standard deviation (SD) of the absolute values and of the percentage changes. There was a correlation between the blood parameters PAI-1, hs-CRP, IL-6 and fibrinogen and BMI and therefore we adjusted the values of these parameters for BMI in the comparison between groups.

ETHICAL APPROVALS

The studies in paper I and II were approved by the Ethics Committee of Karolinska Institutet (Dnr 91:259 and 99:106). The studies in paper III and IV were approved by the Regional Ethics Committee in Stockholm (Dnr 04-071/1).

RESULTS AND COMMENTS

Below is a summary of the main results from each study. Additional information and more comprehensive descriptions of the study results are given in paper I–IV.

CAUSES OF MYOCARDIAL INFARCTION IN DRIVERS (PAPER I)

The crude OR of MI was elevated in professional drivers, compared to men who never worked as a driver (Table 4). In bus drivers the OR was 2.14 (95% CI = 1.34–3.41), in taxi drivers 1.88 (1.19–2.98), and in truck drivers 1.66 (1.22–2.26). The ORs decreased somewhat after adjustment for socioeconomic group but were still clearly elevated in all driver groups ("adjusted A" in Table 4). Additional adjustment for smoking, alcohol, physical inactivity at leisure time, overweight, diabetes, and hypertension further lowered the ORs: 1.49 (0.90–2.45), 1.34 (0.82–2.19), and 1.10 (0.79–1.53), respectively ("adjusted B"). For bus drivers and taxi drivers there was still a tendency to an increased risk, but for truck drivers the OR was close to unity after this adjustment. Including job strain in the regression model generally lowered the risks only slightly ("adjusted C").

Table 4. Risk of myocardial infarction in professional drivers, with and without adjustment for possible confounding factors. ORs are given with 95% confidence intervals (CIs)

Driver group	Cases	Controls	**Crude**[*] OR (95% CI)	**Adj. A**[†] OR (95% CI)	**Adj. B**[‡] OR (95% CI)	**Adj. C**[§] OR (95% CI)
Bus drivers	45	31	2.14 (1.34–3.41)	1.83 (1.14–2.94)	1.49 (0.90–2.45)	1.46 (0.89–2.41)
Taxi drivers	43	34	1.88 (1.19–2.98)	1.62 (1.02–2.58)	1.34 (0.82–2.19)	1.32 (0.81–2.16)
Truck drivers	94	84	1.66 (1.22–2.26)	1.44 (1.05–1.98)	1.10 (0.79–1.53)	1.07 (0.77–1.50)

* Adjusted for design variables only (age group, year of selection, and hospital catchment area).
† Adjusted for design variables and socioeconomic status.
‡ Adjusted for design variables, socioeconomic status, smoking, alcohol, physical inactivity at leisure time, overweight, diabetes and hypertension.
§ Adjusted for design variables, socioeconomic status, smoking, alcohol, physical inactivity at leisure time, overweight, diabetes, hypertension and job strain.

Additional analyses restricted to non-fatal cases showed that the adjusted ORs for MI in the various driver groups were slightly lower for bus and taxi drivers, but slightly higher for truck drivers.

An exposure-response pattern (by duration of employment) was evident for bus drivers, with an almost two-fold adjusted OR in those who had been working more than 10 years as a bus driver, but an only slightly increased OR in those who had been working 1 to 10 years (Table 5). A similar but less pronounced trend was present for taxi drivers. In truck drivers there was no evidence of an increased risk with longer exposure.

Table 5. Risk of myocardial infarction in professional drivers, subdivided by duration of employment (years) as a driver, with and without adjustment for possible confounding factors. ORs are given with 95% confidence intervals (CIs)

Driver group	Cases	Controls	**Crude*** OR (95% CI)	**Adj. A†** OR (95% CI)	**Adj. B‡** OR (95% CI)
Bus drivers					
1–10 years	24	20	1.73 (0.95–3.17)	1.56 (0.85–2.86)	1.30 (0.69–2.47)
>10 years	22	11	2.95 (1.42–6.13)	2.41 (1.15–5.06)	1.92 (0.88–4.15)
Taxi drivers					
1–10 years	24	19	1.83 (0.99–3.36)	1.63 (0.89–3.01)	1.27 (0.66–2.43)
>10 years	20	15	2.00 (1.02–3.94)	1.67 (0.84–3.31)	1.51 (0.74–3.06)
Truck drivers					
1–10 years	49	40	1.78 (1.16–2.73)	1.57 (1.02–2.43)	1.30 (0.82–2.04)
>10 years	46	44	1.55 (1.01–2.36)	1.32 (0.86–2.03)	0.92 (0.58–1.46)

* Adjusted for design variables only (age group, year of selection, and hospital catchment area).
† Adjusted for design variables and socioeconomic status.
‡ Adjusted for design variables, socioeconomic status, smoking, alcohol, physical inactivity at leisure time, overweight, diabetes and hypertension.

We also estimated the OR in drivers subdivided by number of years since the end of employment. In bus drivers, the risk was highest in the intermediate class (stopped driving 2–20 years ago). There was no apparent excess risk in bus drivers who currently were driving, or in those who had stopped more than 20 years ago. Current taxi drivers had an increased risk of developing MI, but no increased risk was noted for taxi drivers who had stopped working more than 2 years ago. The risk was slightly increased in truck drivers who had stopped driving 2–20 years ago, but no excess risk was noted in those who currently were truck drivers.

Because some of the drivers had been driving more than one vehicle type, we also investigated the risk in those who had been bus, taxi or truck drivers only. This gave slightly reduced risks in all driver groups. However, an exposure-response pattern was still evident for bus drivers and to a lesser extent for taxi drivers.

TRENDS IN MYOCARDIAL INFARCTION INCIDENCE IN DRIVERS (PAPER II)

The average annual incidence of MI in professional drivers paralleled the trend in the general male population throughout the whole study period, although at a higher level (Figure 3). During 1977–1996 the average yearly change in incidence was -1.7 per 10,000 person years for bus drivers, -0.9 for taxi drivers and -1.1 for truck drivers. Thus, in absolute terms, the decrease in incidence was most pronounced for bus drivers. In relative terms the pattern was similar, with the highest average yearly change in incidence for bus drivers (-3.2%). Analyses of the change in incidence starting from 1981 (the general peak in MI incidence) instead of 1977 resulted in a more marked average yearly change in incidence in particular for taxi drivers: (-2.1% starting from 1977 and -4.1% starting from 1981. Analyses restricted to persons holding the same

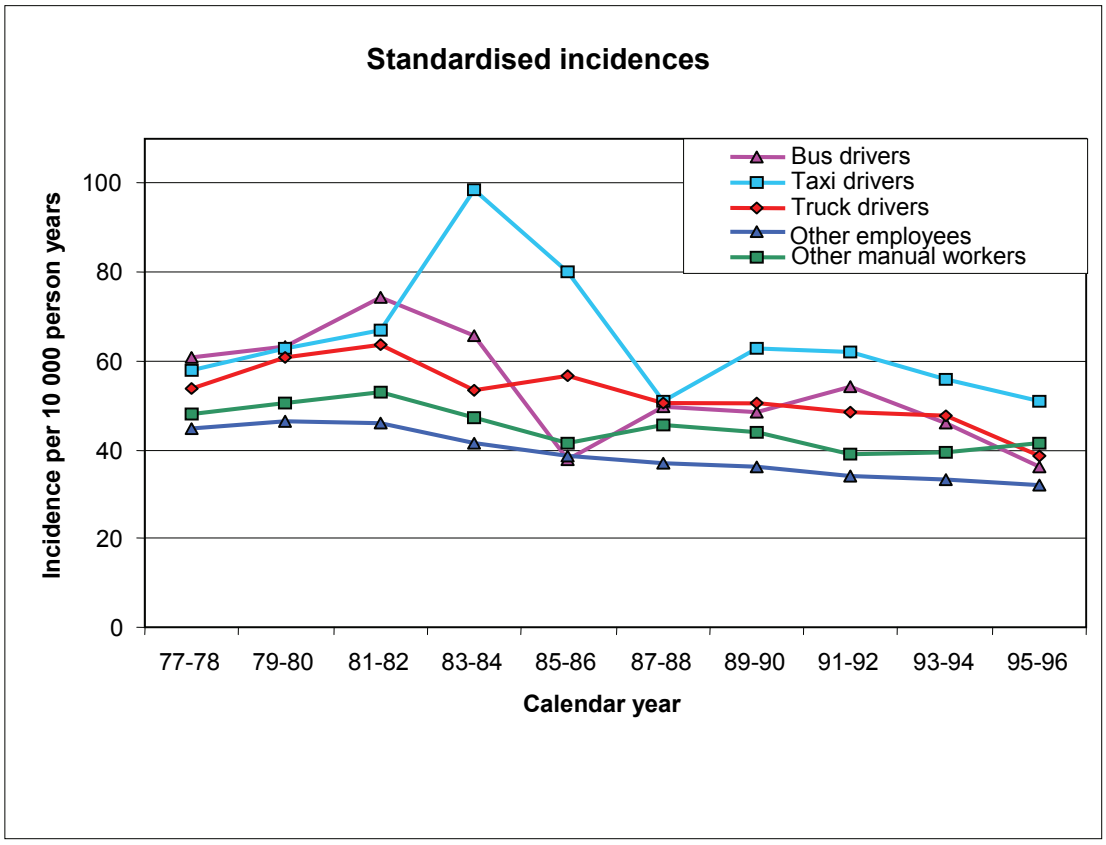

Figure 3. Time trends in the incidence of acute myocardial infarction in male professional drivers in Stockholm 1977–1996 (standardised for the age distribution).

type of job in two censuses showed similar results as those reported for all included, although the downward trend was more pronounced for taxi drivers.

The incidence of MI was increased in all three drivers groups compared to other manual workers during 1977–1984: bus drivers RR = 1.30 (95% CI = 1.03–1.64), taxi drivers RR = 1.38 (95% CI 1.12–1.71), truck drivers RR = 1.14 (95% CI 1.00–1.30) (Table 6). For taxi and truck drivers the RR remained elevated during 1985–1996, but for bus drivers no increased incidence was seen in 1985–1996 (RR = 1.03, 95% CI = 0.86–1.25). Taxi drivers had the highest RR of MI during the study period. When other gainfully employed were used as comparison group, the risk excess was more pronounced. Since the percentage of drivers with foreign ethnic background increased during the study period (8% of drivers included 1977–1984 were foreign born and 18% 1985–1996) we also analysed the RR of MI in drivers standardised for birth country. However, this did not have much influence on the risk estimates.

Table 6. Relative risk (RR) of myocardial infarction (drivers compared to other manual workers or other gainfully employed subjects). RR values given (with 95% CI) have been adjusted for age group and calendar year

	Compared to other manual workers			Compared to other gainfully employed
	1977–1984 RR (95% CI)	**1985–1996** RR (95% CI)	**1977–1996** RR (95% CI)	**1977–1996** RR (95% CI)
All drivers	1.20 (1.08–1.33)	1.17 (1.07–1.28)	1.19 (1.10–1.27)	1.40 (1.31–1.50)
Bus drivers	1.30 (1.03–1.64)	1.03 (0.86–1.25)	1.13 (0.98–1.31)	1.34 (1.16–1.55)
Taxi drivers	1.38 (1.12–1.71)	1.35 (1.14–1.59)	1.36 (1.19–1.55)	1.62 (1.43–1.84)
Truck drivers	1.14 (1.00–1.30)	1.14 (1.01–1.29)	1.14 (1.04–1.25)	1.35 (1.23–1.47)

SUBWAY DRIVERS AND MYOCARDIAL INFARCTION (PAPER III)

The incidence of MI was not elevated in subway drivers, either compared to other manual workers (RR = 0.92 (95% CI = 0.68–1.25)) or compared to gainfully employed other than subway drivers (RR = 1.06 (95% CI 0.78–1.43)) (Table 7). In all, there were 23 cases of MI in subway drivers with a duration of employment of five years or more. No increased risk was observed in this subgroup and the RRs were close to those reported for all subway drivers included. Analyses of latency time did not show any elevated risk for subway drivers with a long latency time (10 years or more since the start of employment) or for current/recent drivers (5 years or less since the end of employment).

Table 7. Relative risk (RR) of myocardial infarction in subway drivers in any census, and in subway drivers according to timing/duration of employment: job duration ≥ 5 years, start of employment ≥10 years previously, and end of employment ≤ 5 years previously. RR values given (with 95% CI) have been adjusted for age group and calendar year

	Subway drivers in any census before inclusion	**Job duration ≥ 5 years before inclusion**	**Start of employment ≥ 10 years before inclusion**	**End of employment ≤ 5 years before inclusion**
Comparison group	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Other manual workers	0.92 (0.68–1.25)	0.84 (0.53–1.33)	0.73 (0.48–1.13)	0.99 (0.59–1.65)
Other gainfully employed	1.06 (0.78–1.43)	0.96 (0.61–1.52)	0.86 (0.56–1.32)	1.10 (0.66–1.84)

Additional analyses not included in paper III showed no increased RR of MI in subway drivers when the risk was calculated for the time periods 1976–1984 and 1985–1996 separately (Table 8).

Table 8. Relative risk (RR) of myocardial infarction in subway drivers subdivided by time periods. RR values given (with 95% CI) have been adjusted for age group and calendar year

	1976–1984	**1985–1996**
Comparison group	RR (95% CI)	RR (95% CI)
Other manual workers	1.04 (0.70–1.54)	0.93 (0.54–1.59)
Other gainfully employed	1.15 (0.78–1.70)	1.10 (0.64–1.89)

SUBWAY PARTICLES AND HEMATOLOGICAL EFFECTS (PAPER IV)

Table 9 shows plasma concentrations of PAI-1, hs-CRP, IL-6, fibrinogen, vWF and factor VII for sample 1 and sample 2 in the various exposure groups, and the arithmetic mean of percentage difference between sample 2 and sample 1.

Table 9. Findings of markers of inflammation and coagulation per exposure group. Arithmetic mean and SD before (sample 1) and after (sample 2) two days of exposure. Means of percentage change with SD are also shown

	Ticket sellers (n = 21)			**Subway drivers** (n = 29)			**Platform workers** (n = 29)		
Risk marker	Sample 1 Mean (SD)	Sample 2 Mean (SD)	Change % (SD)	Sample 1 Mean (SD)	Sample 2 Mean (SD)	Change % (SD)	Sample 1 Mean (SD)	Sample 2 Mean (SD)	Change % (SD)
PAI-1 kIE/L	11.9 (12.1)	15.8 (16.6)	+ 43.4* (72.2)	17.4 (16.4)	17.8 (17.0)	+ 34.8 (114.6)	26.0 (20.9)	33.6 (30.4)	+ 40.2* (104.2)
Hs-CRP mg/L	1.70 (2.12)	1.30 (1.08)	+ 9.5 (60.0)	1.98 (3.18)	1.51 (2.33)	+ 21.1 (130.5)	3.53 (5.13)	2.21 (2.71)	- 14.1* (41.3)
IL-6 ng/L	1.944 (1.227)	1.652 (0.789)	- 4.4 (41.6)	1.880 (1.944)	2.014 (1.610)	+ 51.9 (176.6)	2.482 (1.340)	2.290 (1.542)	- 1.2 (47.8)
Fibrinogen g/L	3.12 (0.58)	3.05 (0.55)	- 1.4 (12.8)	2.93 (0.81)	3.07 (0.61)	+ 6.9* (12.5)	3.27 (0.60)	3.25 (0.65)	- 0.8 (7.4)
vWF kIE/L	1.23 (0.50)	1.19 (0.46)	- 1.8 (6.6)	1.14 (0.31)	1.11 (0.26)	- 0.2 (11.5)	1.23 (0.34)	1.21 (0.37)	- 2.1 (12.0)
FVII kIE/L	1.12 (0.26)	1.19 (0.33)	+ 5.2* (12.6)	1.22 (0.31)	1.23 (0.27)	+ 2.5 (11.0)	1.16 (0.27)	1.19 (0.25)	+ 3.5 (11.5)

* Significant percentage change (t-test, $p < 0.05$).

For PAI-1, there was an increase in the plasma concentration after two working days in all exposure groups ($p = 0.01$ for the percentage change in ticket sellers, 0.06 for subway drivers, and 0.02 for platform workers). Hs-CRP was significantly reduced in platform workers ($p = 0.04$) but not in the lower exposure groups. IL-6, fibrinogen and vWF were marginally reduced both for platform workers and the control group, and fibrinogen was increased in subway drivers. There was an increase in factor VII in all exposure groups and the increase was most marked in the control group, which had a p-value of 0.04 for the percentage change. Thus, we found no acute changes that could be attributed to the particle exposure. However, the comparison of mean

plasma levels in the three groups showed higher levels of the inflammatory markers PAI-1, hs-CRP, IL-6 and fibrinogen for the highly exposed platform workers than for subway drivers and ticket sellers, both in sample 1 and sample 2 (Table 9). Since there was a correlation between these markers and BMI, the analyses were adjusted for this parameter. After adjustment, the difference remained in both samples. The difference was most marked for PAI-1 in sample 2 in the comparison between platform workers and the control group with ticket sellers ($p = 0.04$) and in the comparison between platform workers and subway drivers ($p = 0.05$) (Table 10).

Table 10. Average plasma concentrations in sample 2, adjusted for BMI. Arithmetic mean and SD are shown

	Ticket sellers (n = 21)	**Subway drivers** (n = 29)	**Platform workers** (n = 29)
Risk marker	Sample 2 Mean (SD)	Sample 2 Mean (SD)	Sample 2 Mean (SD)
PAI-1 kIE/L	18.5 (16.0)	19.7 (13.8)	29.7* (29.0)
Hs-CRP mg/L	1.49 (1.10)	1.64 (2.11)	1.94 (2.67)
IL-6 ng/L	1.733 (0.740)	2.071 (1.604)	2.174 (1.506)
Fibrinogen g/L	3.11 (0.54)	3.11 (0.58)	3.16 (0.58)

*Significantly ($p < 0.05$) different from ticket sellers.

Additional analyses of sample 2 were restricted to individuals without diabetes or high blood pressure, and adjusted for BMI. The findings were similar to those for all individuals included, but the difference was slightly smaller for PAI-1, and slightly higher for hs-CRP and fibrinogen, in the comparison between platform workers and ticket sellers.

DISCUSSION

MAIN RESULTS

Causes of myocardial infarction in drivers

Study I showed a high risk of MI in male professional drivers in Stockholm County 1992–1993, relative to men who never worked as a driver. The risk remained high for bus and taxi drivers, but not for truck drivers, when adjusting for socioeconomic, lifestyle, and metabolic risk factors. We conclude that the increased risk of MI in urban bus and taxi drivers could only be partially explained by an overrepresentation of individuals with these risk factors. It seems possible that the work environment may be a contributory cause for the increased risk of MI in bus and taxi drivers, but for truck drivers, individual risk factors appeared to explain most of the elevated risk. Occupational exposure to motor exhaust is a possible risk factor of MI in drivers, although they are only moderately exposed to motor exhaust.[50] In addition, truck drivers are more exposed than bus and taxi drivers,[50] which does not fit with the pattern of disease risk in the present study. Psychosocial factors related to the work situation are possibly a more plausible explanation. In study I, perceived job strain was more common in bus, taxi and truck drivers than in other men, although the proportion of exposed persons was small. However, job strain in terms of demand/control explained only a small part of the risk in bus and taxi drivers after adjustment for the other risk factors. It is possible that this way of measuring stress does not adequately reflect the aspects of job stress that are relevant for the drivers, such as e.g. stress related to transportation of passengers. Since job strain was assessed according to the average exposure during the last five years before recruitment or retirement it is also evident that several drivers included in the study held another occupation at that time.

The results also indicate an increased risk of developing MI for bus drivers who stayed more than 10 years in the profession of driving. A similar but less pronounced tendency was present for taxi drivers. This exposure-response pattern would not emerge if the risk excess was caused by a selection of individuals with unfavorable lifestyle into the driving occupation. In taxi drivers, there was a pronounced excess in risk only in current drivers and drivers who had stopped working less than 2 years ago, pointing towards an effect of a very short duration. The reason why bus drivers who stopped driving 2–20 years ago had a higher risk than the group including current drivers is unclear. These apparently contradictory patterns may be caused by random variation since numbers are small, but may possibly be explained by differences in the type of employment contract for bus and taxi drivers. Bus drivers are employees of large companies in contrast to taxi drivers who often are self-employed. The bus drivers working hours are fixed and they have small opportunities to adjust the job to the health situation. MI is often preceded, sometimes for many years, by symptoms of coronary insufficiency, angina pectoris. Bus drivers may more often have to leave their job in case of symptoms of preliminary stages of CHD. Taxi drivers, on the other hand, might instead in case of disease only reduce their working-hours and stay in service.

Our findings are in accordance with results from other studies showing an increased MI and CHD incidence or mortality in professional drivers,[29-42] with a particular focus on

urban bus drivers,[29, 32-35, 37-42] and taxi drivers.[33-35, 39, 40] The increased risk has only partly been attributed to an unfavorable risk factor profile.[34, 35] Added stressors in the form of demands and job stress from passengers have been proposed as an explanation for the higher CHD risk for drivers working in passenger transport than for drivers of goods vehicles.[40] Our findings point in the same direction.

Time trends in myocardial infarction incidence in drivers

The clearly increased incidence of MI for professional drivers noted in 1977 gradually approached the incidence for other manual workers. Bus drivers showed the most favorable trend in the incidence of MI during the study period. The analysis of incidence per 2-year period indicated that the incidence of MI still tended to be higher for bus drivers than for other manual workers and close to the incidence for truck drivers. The risk excess was most evident for taxi drivers.

The underlying causes for the decrease in incidence of MI for professional drivers are unclear, although it is likely that the decline in risk to some extent may be attributed to changes in major known risk factors. A possible explanation for the pronounced decrease in incidence of MI for bus drivers compared to other manual workers could be that smoking has declined more rapidly among bus drivers than among other manual workers. In the beginning of the 1970s, male bus and taxi drivers in Oslo had a high smoking prevalence (55% and 65% respectively),[35] and in study I in this thesis, current smoking was more common among taxi (47%) and truck drivers (49%), than in bus drivers (32%) and in the general population (30%) in Stockholm 1992–1993.[141] The decreasing trend in the incidence of MI for drivers can hardly be explained by changes in ethnic background since the risk estimates were not much affected when we standardised for country of birth. Changes in the work environment, such as psychosocial work conditions, may also be of importance for the reduced incidence of MI. In Stockholm, an intervention study was carried out to investigate possible effects of improving working conditions for bus drivers.[142] The intervention was designed to decrease traffic congestion, lessen passenger demands, and ease bus operation in general. The study showed fewer on-the-job hassles while driving, decreased systolic blood pressure and heart rate at work and less perceived distress after work for drivers in the intervention group. However, possible changes in these work conditions in recent years may not yet have resulted in changes in the incidence of MI.

Our findings concerning time trends in the incidence of MI in the general population are consistent with those from previous studies using a similar methodology.[19-21] We are not aware of any previous studies of long-term time trends in the incidence of first MI in professional drivers. However, bus drivers in Denmark had an increasing RR of CHD in the period from 1981 to 1993.[29] The RRs from study II are basically consistent with those from study I of MI in bus, taxi and truck drivers in Stockholm 1992–1993,[141] although bus drivers showed the most pronounced excess risk of MI in that study. Additional analyses of study II applying the same criteria as in study I showed about the same crude RR estimates for the driver groups as those presented in paper I.

Subway drivers and myocardial infarction

Subway drivers exposed to airborne particles in the Stockholm underground did not show an increased incidence of MI relative to other manual workers. Several factors

should be taken into account in the interpretation of these findings. Even though very high levels of particles in the 1–10 μm range have been found on the underground platforms, the drivers spend only part of their working time at the platforms, and negative health effects on individuals who stay at platforms for longer periods cannot be excluded. Analyses restricted to individuals who started working at least ten years or more before inclusion in the study showed similar results to those for everyone included, indicating that the negative finding was not caused by short follow-up. Furthermore, a very short duration of the effect cannot explain the negative findings, since analyses restricted to individuals who recently worked showed no increased risk. Analysis of individuals with a job duration of ≥ 5 years did not differ from the main results. We are not aware of any previous studies on the risk of MI in subway drivers.

Subway particles and hematological effects

The highly exposed platform workers showed elevated levels of several inflammatory markers relative to employees with low exposure, both before and after two working days in the underground. Although the difference was significant only for PAI-1, the same tendency was seen for hs-CRP, IL-6 and fibrinogen. These findings indicate a possible long-term inflammatory effect of exposure to airborne particles. However, the study was mainly designed to investigate short-term effects, and the observed difference in plasma levels between the groups cannot be linked to the particle exposure with certainty. Several of the inflammatory markers, especially PAI-1, are associated with parameters related to metabolic syndrome.[126, 127] Although the findings were adjusted for BMI, it cannot be excluded that some of the differences in plasma levels of inflammatory markers between the groups may have been caused by differences in such parameters, other than BMI. We investigated this possibility by restricting the analysis to individuals without diabetes or high blood pressure, and simultaneously adjusting for BMI, which did not change the results to any marked degree. The elevated markers of inflammation in highly exposed workers may thus actually reflect an activation of a low-grade inflammation in the blood vessels. Such an activation of the inflammatory response would theoretically increase the risk of CVD,[91-93, 143, 144] especially MI, and exposure to subway particles is a possible explanation for this activation. The hypothesis of an inflammatory response to particle exposure has support from several empirical studies,[58, 98, 99] and there are experimental data to suggest that airborne subway particles do have an inflammatory effect.[80, 86, 129, 133]

There were no acute changes in blood markers of inflammation and coagulation that could be attributed to the particle exposure. It is possible that subway particles have no short-term effect on the risk markers that we studied. It is also possible that the work-free period of two days before the first blood sample was insufficient to reach baseline or that two days of exposure is insufficient to cause an effect. The reason for the increase in PAI-1 after two working days in all exposure groups is unclear. It might have to do with some parameter that differs between the situation at work and leisure time. Although physical activity may cause a short-term inflammatory response, it does not seem likely that this can explain the findings since ticket sellers have a sedentary work situation.

METHODOLOGICAL CONSIDERATIONS

The size of the study affects the precision of the point estimates and thus the potential for random errors, which is reflected by confidence intervals. Of importance for study I–III are the large study bases including the entire population of Stockholm County during two years in study I, and during 20 years in study II and III. In the study bases we were able to identify all first MI cases. Even though we had such large study bases, the number of cases in some occupational groups in study I–III was small, especially in the sub-group analyses, which would affect precision in the analyses. Study II takes advantage of a unique possibility to use information from heart and population registers that enables studies of long-term time trends in first MI in specific occupational groups, and an obvious strength is the possibility to compare incidence rates in both absolute and relative terms. Study IV was mainly designed to study short-term effects of particle exposure, where each individual would serve as his or her own control. However, the main results were found comparing the exposure groups, witch made it more difficult to interpret the findings. It is still possible that short-term effects may exist but that they could only be detected in an even larger group of exposed subjects.

Selection bias

Selection bias arises if the association between exposure and disease differs for those who participate and those who do not participate in a study, e.g. by self-selection. Selection bias can also arise from choices made more directly by the investigator. One example is the so called healthy worker effect, which can be avoided by comparing the workers in a specific job with workers in other jobs that differ in occupational exposure or hazards. In the SHEEP study (Study I), the overall participation rate was high and the non-response was probably unrelated to the exposure, but a healthy worker effect may be present since the various driver groups were compared to all men in the population who never worked as a driver, thus including people in the general population who cannot work because of ill health. Therefore, the risk estimates in study I may have been diluted in relation to the actual effect. In the register-based studies II and III there is no problem with non-participation, and since the driver groups were compared with workers in other jobs there would be no healthy worker effect. In study IV the participants were included in the various groups based on the exposure level. All who volunteered fulfilled the study and all were currently employed. The mechanism for non-participation would probably not differ between the exposure groups, implying that the differences in hematological effects between the groups would probably not be affected.

Classification of outcome

In study I–III the case ascertainment was high and misclassification of disease is probably a minor problem. The cases in study I were diagnosed according to specified criteria using overlapping information sources on symptoms, ECG, enzymes, and autopsy findings.[134] They were recruited from all the emergency hospitals across the county, the regional computerized discharge register, and the death certificates from the Causes of Death Register. These procedures minimized the number of undetected cases. Crosschecks based on various registers in combination with SHEEP data have shown that at least 97% of the cases who met the inclusion criteria were identified in the SHEEP study.[145] In study II and III the cases were identified through the combined

use of hospital discharge registers and deaths records. The method of identifying cases has been evaluated and found to give a very high agreement with established diagnostic criteria for MI.[21, 137, 138] In study IV markers of inflammation and coagulation were used as outcomes. All links in the handling of blood samples were carefully performed. The samples were centrifuged immediately, and were then frozen to -70°C without delay. The blood samples were analysed at the same laboratory, and any misclassification due to errors in the analyses of these factors is not likely to be associated with the exposure, and would, if present, result in a dilution of the estimated associations.

Information on occupation or occupational exposure

In study I information on occupation was collected by questionnaires. An advantage was that the occupational information covered the whole lifetime up to the time of inclusion in the study. The occupational history included occupation, work tasks, and company name and address, for all jobs held for at least one year, and an occupational code was assigned to every job held for at least a year. The hygienist was "blinded" in the coding process. Any misclassification of occupation would probably be unrelated to the diagnosis of MI, thus leading to a non-differential misclassification of exposure, which means that the RR estimates may have been biased towards one. Since the study included both non-fatal and fatal cases and the exposure information for fatal cases was provided by close relatives, it is possible that the information on occupation was not as precise for fatal cases. The classification of occupation in study II and III was based on census information with self-reported data available every fifth year, and the occupation may have been miscoded for some men. However, any misclassification of occupation would probably be unrelated to the diagnosis of MI. The risk of misclassification of occupation was lower in the analyses of individuals with a job duration of ≥ 5 years. Since misclassification of occupation would be present throughout the whole time period in study II, the trend in MI incidence is not likely to be substantially affected. In study IV our classification into exposure groups was confirmed by personal exposure measurements for about half of the participants. Thus, the risk of misclassification of exposure was low, and would be unrelated to the outcome. The contrast between highly exposed and mildly exposed workers was high; in terms of $PM_{2.5}$ the exposure levels were about 6 times higher for platform workers than for the control group, and for DataRAM the levels were about 14 times higher.[140]

Residual confounding

In study I we had individual background information on a large number of possible confounders for MI. Adjustment for socioeconomic status partially reduced the risks in professional drivers. Uncontrolled and residual effects of socioeconomic status seem unlikely because socioeconomic status did not differ much among the driver groups, and therefore cannot explain the higher risk of MI for bus and taxi drivers than for truck drivers, and additional analyses with the original six groups of socioeconomic status instead of three groups did not change the results. The drivers smoked more than the general population, but the excess risk of MI that was observed in bus and taxi drivers was only partially explained by their tobacco smoking habits. An extended model using a larger set of variables to adjust for smoking (including continuous variables for time since stopping smoking among ex-smokers and the average consumption of tobacco per day among current smokers) showed no indication of residual confounding by smoking habits. Furthermore, there was no change in the risk estimates when duration

of smoking was added to the regression model. To further investigate the effect of job strain, we included the job strain ratio (the ratio of the sum score of demand to the sum score of control) as a continuous variable in the regression analysis. However, this variable had no additional effect on the risk estimates for the drivers. Because an occupational factor such as stress may exert its effect through mechanisms such as hypertension or metabolic changes, the adjustment for hypertension, diabetes and BMI may introduce an "over-adjustment" if the purpose is to evaluate the influence of occupational factors alone. Thus, both the crude risk and the various adjusted risks should be considered when evaluating the effect of occupational factors.

In study II–III we had information on important demographic factors such as gender, age distribution and socioeconomic conditions as well as how the occupation had changed over time. However, we did not have access to data on smoking or other important individual risk factors for MI. Since study II is a descriptive study, with the main objective to investigate time trends in the incidence of MI, the lack of information on risk factors should not be regarded as a major limitation. In the analyses of RRs in study II and III the restriction of the comparison group to manual workers gave an indirect adjustment for lifestyle factors. Even so, the lack of individual risk factors is a limitation, especially in study III.

In study IV we had information on some important risk factors for CVD. Analyses restricted to persons without diabetes or high blood pressure, and adjusted for BMI, did not change the results substantially. However, it is possible that other factors of importance for the plasma concentration of the markers that we studied may be imbalanced between the exposure groups and thus result in residual confounding.

GENERAL DISCUSSION AND FUTURE RESEARCH

Despite the favorable trend in the incidence of MI in professional drivers our findings suggest that preventive measures to reduce the risk of MI in particular in taxi and truck drivers, but also in bus drivers, continues to be of importance. Even though bus drivers had the most favorable trend during the 20-year period 1977–1996, the incidence of MI still tended to be higher for bus drivers than for other manual workers and close to the incidence for truck drivers. It would be interesting to investigate how the MI incidence in professional drivers has changed in the years after 1996 but at the time of study II this was not possible. In addition to changes in individual risk factors for all driver groups, bus and taxi drivers would probably also benefit from changes in psychosocial work conditions, especially if the transportation of passengers is more stressful than the transportation of goods. Psychosocial work factors may also influence traditional risk factors such as hypertension, hyperlipidemia, obesity, smoking, and alcohol consumption in a harmful way.[146] Further investigations of the psychological demands in various driver groups are warranted. It is not yet fully clarified whether occupational exposure to motor exhaust is an important risk factor for MI. In an ongoing project (Exposure to particles and motor exhaust and the risk of myocardial infarction and lung cancer - PAHL) we intend to further investigate dose-response relationships for exhaust fumes and MI by extension of the SHEEP study with measurement-based data on exposure to motor exhaust.

We found no increased incidence of MI in subway drivers in Stockholm. The negative findings do not appear to be explained by chance fluctuations, uncontrolled negative confounding from lifestyle factors, or an insufficient follow-up time. Rather, the

findings suggest that exposure to airborne particles in the Stockholm subway did not cause an elevated risk of MI, either because average exposure to particles was too low or because there is no such effect. Although this study did not directly address the risk for commuters, it does not seem likely that commuters would be at a substantially increased risk of MI from exposure to subway particles. Their exposure would generally be less than that of the subway drivers, although an effect in sensitive groups such as children or those predisposed to CVD cannot be excluded. Our findings of a possible activation of an inflammatory response in employees highly exposed to subway particles suggest that there may be an increased risk of future CVD in individuals who are highly exposed to such particles. Even though the results are not conclusive, it is important to continue efforts to reduce the levels of airborne particles in the subway system for the benefit of employees, and to reduce the possible risk to health of commuters.

At the time of study IV we also measured HRV in the subway drivers. We intend to analyse whether their HRV was affected by the rapid changes in particle exposure levels while driving in and out of underground tunnels. There is also an ongoing study in the Stockholm subway studying possible short-term health effects in healthy subjects exposed to airborne subway particles. Among other things, measurements of pulmonary and systemic inflammatory responses and changes in HRV are performed. This latter study is performed by another research group at our Department. The main aim is to investigate whether exposure to subway particles have the same effects as previously shown from exposure to traffic related air pollution.[147] A possible future study would be to investigate the risk of MI in a cohort of platform workers highly exposed to particles in the Stockholm subway, relative to workers with low exposure.

The contribution of the different particle origin or size fraction to cardiovascular effects is not clarified, nor is the mechanism behind the effect. Therefore, it is important to further clarify which type of particles and which fraction(s) that might cause health risks, and if the particles per se or the substances they are carrying are responsible for the effects.

CONCLUSIONS

- Bus, taxi and truck drivers in Stockholm County were at an increased risk of MI in 1992–1993 relative to other men. The increased risk in bus and taxi drivers could only partially be explained by unfavorable lifestyle factors, suggesting that the work environment has probably contributed to their increased risk. In truck drivers, individual risk factors appeared to explain most of the elevated risk.

- During the 20-year period 1977–1996, there was a greater decline in incidence of MI for bus, taxi, and truck drivers than for other manual workers in Stockholm County. Bus drivers showed the most favorable trend. The incidence of MI was increased in all three driver groups during 1977–1984, relative to other manual workers. Despite the favorable trend, the relative risk in taxi and truck drivers remained elevated also during 1985–1996. The risk excess was most evident for taxi drivers.

- Subway drivers exposed to airborne particles in the Stockholm subway did not show an increased incidence of MI during 1976–1996, relative to other manual workers. Our findings suggest that exposure to airborne particles in the Stockholm subway did not cause an elevated risk of MI, either because average exposure to particles was too low or because there is no such effect.

- Subway employees working on the platforms, who were highly exposed to airborne particles, had elevated plasma concentrations of several inflammatory markers, relative to employees with low exposure. Our findings indicate a possible association between high exposure to subway particles and activation of an inflammatory response, which may lead to an increased risk of future CVD in individuals who are highly exposed to such particles.

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