TRAFFIC NOISE AND CARDIOVASCULAR DISEASE

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ABSTRACT

Traffic noise is an increasing problem in urban areas worldwide, but health effects in relation to traffic noise exposure are not well understood. Several studies show that noise may give rise to acute stress reactions, possibly leading to cardiovascular effects, but the evidence is limited on cardiovascular risks associated with traffic noise exposure. Cardiovascular effects have been indicated for other environmental stressors such as occupational noise exposure and job strain. However, interactions between these factors in relation to cardiovascular disease have not been investigated. Furthermore, studies regarding interactions between air pollution and noise from road traffic in relation to cardiovascular disease are lacking. The overall aim of this thesis was to investigate the association between traffic noise exposure and cardiovascular disease, including interactions with other factors.

The thesis is based on one case-control study and one cross-sectional study. The population based case-control study on risk factors in relation to first time myocardial infarction was conducted 1992-1994 in Stockholm County. The participants answered a questionnaire and underwent a physical examination. Exposure assessments were made of residential road traffic noise exposure, occupational noise exposure and air pollution between 1970 and 1992-94. Job strain was defined based on questionnaire data regarding the last employment. An increased risk of myocardial infarction was suggested in participants exposed to road traffic noise at the residence. The risk appeared particularly high among participants exposed to a combination of road traffic noise, occupational noise and job strain (OR 2.27, 95% CI 1.41–3.64). The association between road traffic noise and myocardial infarction did not seem to be affected by air pollution.

The cross-sectional study was carried out in six European countries. All participants were interviewed at home and blood pressure measurements were made by a field nurse. An association was found between night-time aircraft noise exposure and hypertension. In a subgroup of study participants cortisol was assessed through saliva samples as an indicator of stress. We observed an elevation in morning saliva cortisol level among women exposed to high levels of aircraft noise at the residence of 34%, corresponding to 6.07 nmol/L (95% CI 2.32-9.81). No clear association was seen in men.

It may be concluded that long-term traffic noise exposure at the residence seems to give rise to cardiovascular effects. Our results support the hypothesis that exposure to a combination of noise and job strain increases the risk of myocardial infarction substantially. In addition, our results suggest that exposure to aircraft noise increases the risk of hypertension, as well as morning saliva cortisol levels in women, which may be of relevance for noise-related cardiovascular effects.
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LIST OF ABBREVIATIONS

WHO  World Health Organization
MI  Myocardial infarction
BP  Blood pressure
HPA-axis  Hypothalamic-pituitary-adrenal axis
SHEEP  Stockholm Heart Epidemiology Program
HYENA  Hypertension and Exposure to Noise near Airports
JEM  Job Exposure Matrix
ICBEN  International Commission on Biological Effects of Noise
GIS  Geographical Information System
INM  Integrated Noise Model
1 INTRODUCTION

Traffic noise exposure is not a new phenomenon, records show that even in medieval times horse carriages and horse back riding were banned during night in some cities in Europe in order to prevent sleep-disturbance [1]. Today traffic noise is much more intense and an increasing problem in urban areas worldwide. The World Health Organization (WHO) estimates that about 40% of the population in Europe is exposed to road traffic noise levels exceeding the guideline value of 55 dB during daytime and more than 30% is exposed to levels exceeding this value during night time. In a recent review of epidemiological and experimental research conducted by the WHO, it was concluded that sufficient evidence exists of health effects related to noise exposure at the residence already at levels of 40 dB of night noise outdoor at the facade [2]. A substantial number of Europeans are exposed to this noise level or more, making traffic noise exposure an important environmental exposure to investigate. Noise pollution is not only a concern for the high income countries, there is also severe exposure of noise pollution in developing countries [1].

Causal associations between traffic noise exposure at the residence and various types of health effects have been established. These effects include interference with speech communication, disturbance of rest and sleep, psycho-physiological effects, mental-health and performance effects, effects on residential behavior and annoyance as well as interference with intended activities. [1] In addition, associations between traffic noise exposure and cardiovascular endpoints have been indicated [3, 4]. This thesis focuses on cardiovascular effects related to residential traffic noise exposure.

1.1 NOISE

Noise is defined as unwanted sound. It is often measured as sound pressure level, and expressed in a quantity that is proportional to the logarithm of the sound pressure. Environmental sounds contain energy in many frequencies. A frequency is measured in Hertz (Hz) and refers to the number of vibrations per second in the air in which the sound is propagating. Our hearing is not equally sensitive to all frequencies and to adjust for this, filters or weighting are used. The A-weighting filter is adapted after our hearing and weighs lower frequencies as less important than mid- and higher frequencies. A-weighted sound pressure level has the unit dBA. Noise could also be expressed using the C-weighting filter (dBC) where the dominance lies on the low frequency sounds, commonly found in ventilation noise [1].

The weakest sound that a human ear can hear is about 0 dBA and 125 dBA is the pain limit. Since the decibel scale is logarithmic, a doubling in traffic flow will only contribute to an increase of approximately 3dB. To be able to assess traffic noise at the residence a daily annual average is calculated. This average can be expressed in a 24-hour average $L_{Aeq,24h}$ or a 24 hour average with a penalty for evening (+5dB) and nighttime noise (+10dB) $L_{den}$. $L_{den}$ is a summary measure and can be divided into day, evening and night measures $L_{day}$, $L_{evening}$ and $L_{night}$. Traffic noise at the residence is usually calculated by the use of information regarding traffic flow, speed and distance.
1.2 CARDIOVASCULAR DISEASE

Cardiovascular diseases are the leading cause of death in the world and caused 32% of all deaths in women and 27% of all deaths in men in 2004. It is a major cause of death and disability in high-income countries, but also in middle- and low-income countries [5]. Among the cardiovascular diseases, ischemic heart disease is the leading cause of death, and 7.2 million people died of ischemic heart disease globally in 2004. Among these, 1.3 million died in high income countries, 3.4 million in middle-income countries and 2.5 million in low income countries. WHO foresees that ischemic heart disease will continue to be a dominating cause of death in the future [5].

Cardiovascular disease is a group of disorders of the heart and blood vessels that include ischemic heart disease, cerebrovascular disease, hypertension, peripheral artery disease, rheumatic heart disease, congenital heart disease and heart failure. Ischemic heart disease is characterized by reduced blood supply to the heart leading to oxygen deficiency in the heart muscle tissue. This reduced blood supply is usually caused by a disease of the blood vessels. The two dominating manifestations of ischemic heart disease are angina pectoris and myocardial infarction (MI) [6] MI is commonly known as a heart attack and involves necrosis (cell death) of parts of the heart muscle supplied by the blocked vessels. In figure 1 a blockage in the left coronary artery has resulted in a myocardial infarction, illustrated by a darkening of the area (2). The severity of the event is related to the placement of the blockage, the amount of time the blockage persists and the completeness of the blockage [7].

Figure 1. Illustration of myocardial infarction (2) of the tip of the anterior wall of the heart (an apical infarct) after occlusion (1) of a branch of the left coronary artery (LCA). Right coronary artery = RCA.
Important lifestyle related risk factors that have been associated with cardiovascular disease include an unhealthy diet, physical inactivity, smoking and stress. Environmental factors such as air pollution and noise have been suggested as risk factors. All these risk factors may affect the individuals through raised blood pressure, blood glucose and blood lipids, as well as through inflammation. These effects can be seen as intermediate risk factors indicating a step in the causal pathway to cardiovascular disease.

Hypertension, commonly known as high blood pressure, is classified as a disease of the circulatory system. However, it is also one of the most important risk factors for other cardiovascular diseases. In addition, it can be regarded as an intermediate risk factor, since it is associated with many of the exposures that are related to cardiovascular disease. Hypertension is common and approximately 25% of the adult population is affected [7]. Blood pressure (BP) is a measurement of the force applied to artery walls. During each heartbeat, BP varies between a maximum (systolic) and a minimum (diastolic) pressure in mmHg. An individual’s blood pressure is usually expressed as the systolic pressure in combination with the diastolic pressure for instance 125/85. A blood pressure consistently at 140/90 mmHg or higher is regarded as hypertension [7]. Hypertension can be divided into three categories, mild elevation of blood pressure 140-159/90-99 mmHg, moderate elevation of blood pressure 160-179/100-109 mmHg and severe elevation of blood pressure > 180/> 110 mmHg. Furthermore, treatment can be applied to individuals with lower levels of blood pressure than 140/90 if other medical conditions exist, for instance diabetes mellitus.

Stress can increase the risk for MI. Stress is a wide concept that can include many different types of exposures. One of these exposures can be defined as “occupational stress” and can be assessed by estimation of “job strain”. Job strain is a sum score including both psychological demand and decision latitude [8, 9]. People that report high demand and low control (low decision latitude) at work may be regarded as exposed to job strain. Numerous studies suggest an association between job strain and cardiovascular disease [9-12].

A stressful event may affect the HPA-axis (Hypothalamic–Pituitary–Adrenal axis), that constitutes a significant part of the neuroendocrine system controlling reactions to stress. The HPA-axis involves interactions between the hypothalamus, the pituitary gland and the adrenal glands. In the event of acute stress, the pituitary gland releases the hormone ACTH into the blood. ACTH reaches the adrenal gland and the hormone cortisol is released. About 90% of the cortisol that is released into the blood stream is bound to the protein globulin, only 10% is free and active. Long-term stress may contribute to a dysfunction of the HPA-axis that may result in persistently increased levels of cortisol [13] and may eventually lead to metabolic changes and cardiovascular disease [14-20].

Cortisol is sometimes referred to as the “stress hormone” and it is a biomarker of a stress response in the body. It is produced by the adrenal gland and involved in glucose metabolism, distribution of fat and immune function. Under normal circumstances the cortisol level peaks approximately 30 minutes after awakening. It decreases throughout the day and reach the lowest levels at night [21]. A chronic increase in cortisol, that occurs in for instance Cushing’s syndrome, can lead to increased risks for a number of severe complications such as cardiovascular disease and diabetes mellitus[13].
1.3 NOISE AND CARDIOVASCULAR DISEASE

Many studies show that short-term exposure to noise is a stressor that activates the sympathetic and endocrine system, which may lead to acute changes in blood pressure and heart rate, as well as elevated levels of stress hormones [22-26]. It has therefore been hypothesized that exposure to traffic noise may cause permanent vascular effects, with hypertension and ischemic heart disease as potential outcomes. Previous epidemiological studies have suggested an increased risk of hypertension and MI among subjects exposed to traffic noise [3, 4, 27].

A review by van Kempen et al in 2002, described the scientific evidence for a relation between noise exposure and ischemic heart disease as inconclusive and concluded that only a small blood pressure effect was evident [27]. Since then more studies have investigated the relationship between long-term air- and road traffic noise exposure at the residence and hypertension [28-32], but almost all of these studies have relied on self reported hypertension and not on actual measurements. One exception is a recent study on incidence of hypertension and aircraft noise in Stockholm, which indicated a significant association with aircraft noise exposure [28]. Only two studies have investigated the association between ischemic heart disease and long-term road traffic noise exposure [33, 34]. In these studies an association was indicated, but the study by Beelen was performed on very few cases and the study by Babisch included only high noise exposure (>60dB). Several large epidemiological studies have indicated an association between air pollution and MI [34, 35], but only the Beelen study investigated the association between air pollution and road traffic noise exposure in association with MI [34], and no previous study investigated possible interactions. In addition, no study has investigated the association between MI and traffic noise exposure in relation to other environmental stressors such as job strain and occupational noise exposure, even though they may have a similar pathway to cardiovascular disease and earlier studies have indicated an association with MI [11, 12, 36].

Stress hormone studies on community noise exposure have generally been performed using urine and blood measurements [19, 37-43]. Saliva cortisol measurements are easy to perform,
reliably reflect free cortisol levels in blood [44], and have recently been used in a few studies on exposure to road traffic and aircraft noise [45-47]. In two review articles, the evidence on road traffic noise as well as aircraft noise and cortisol was evaluated [3, 38]. Six of the 14 studies reviewed showed an increase in cortisol level related to exposure, but these were mainly based on urine measurements and had small sample sizes. Only two of the studies used saliva cortisol measures, and the results were inconclusive [45, 46]. Thus, the association between community noise exposure and cortisol levels is still unclear.
2 AIMS

The overall objective of this thesis was to examine the association between residential traffic noise exposure and cardiovascular disease.

Specific research questions:

- To assess whether exposure to traffic noise at the residence increases the risk of myocardial infarction
- To examine the relationship between traffic noise and hypertension
- To assess the relation between traffic noise and saliva cortisol levels
- To analyze if the relation between traffic noise and myocardial infarction is affected by air pollution exposure
- To investigate how a combination of environmental stressors, including traffic noise, affects the risk of myocardial infarction
3 MATERIAL AND METHOD

This thesis is based on the two studies SHEEP and HYENA. Paper I and II are based on SHEEP and paper III and IV are based on HYENA.

3.1 SHEEP – STOCKHOLM HEART EPIDEMIOLOGY PROGRAM

The Stockholm Heart Epidemiology Program (SHEEP) is a population based case-control study conducted in Stockholm County between 1992 and 1994. The aim of the study was to investigate risk factors for myocardial infarction. All men and women living in Stockholm County in the ages 45-70 years, with no history of MI, were included in the study base. The cases were selected at the coronary and intensive care units at all emergency hospitals in Stockholm County, hospital discharge registers and from coronary records from the National Register of Death Causes at Statistics Sweden.

The diagnostic criteria for case inclusion were those applied by the Swedish Association of Cardiologists [48] and included certain symptoms according to case history information, specified changes in blood levels of creatine kinase and lactate dehydrogenase, as well as specified ECG-changes and myocardial necrosis detected at autopsy that could be related to the relevant time of disease onset. To be certain that only subjects with first-time MI events were
included in the study, each case was checked for earlier MI’s in the hospital discharge registry from 1975 and onwards.

Controls were randomly selected from the study base matched on age, gender and hospital catchment area. The controls were selected within two days of the case event. Each potential control was checked for previous MI events in the hospital discharge register. As much as five controls per case were originally sampled in order to quickly replace one control with another in case of non-response. This procedure led to that more controls than cases were included, since it sometimes meant that both the initial control and a substitute control were included due to a late response of the initial control.

3.1.1 Study participants

In total, 5,452 study subjects were included; 2,246 cases and 3,206 controls. The 603 cases that died within 28 days of the MI onset were classified as fatal. For fatal cases, the SHEEP-questionnaire was answered by next-of-kin. The questionnaire response rate among cases was 72% for women and 81% for men. The corresponding rates for controls were 70% and 75% [49].

For paper I a selection was made based on the 4,067 study subjects who answered the SHEEP questionnaire. Individuals with an information gap in their address history for more than five years since 1970 or who had lived outside Stockholm County during more than five years were excluded (n=401). This generated the 3,666 study subjects (1,571 cases, including 338 fatal, and 2,095 controls).

For paper II we based the selection on the participants in paper I. However, participants who did not answer crucial questions regarding paper II (job strain, socio economic position) were excluded (n=219). In order to minimize imprecision in the traffic noise exposure assessment all participants living within 200m from a railway track were excluded (n=397), leaving 3050 study participants (1252 cases and 1798 controls) in the study.

Figure 4. Selection of study participants for paper I and II.
3.1.2 Exposure assessment

The SHEEP-questionnaire, distributed in 1992–1994, focused on a large set of potential risk factors for MI, including the physical and psychosocial work environment, social factors, and lifestyle factors such as smoking and physical activity. In order to reduce missing data and non-response a supplementary telephone interview was conducted. A health examination was performed on cases and controls and various biologic parameters related to cardiovascular disease were measured. In order for cases to regain metabolic stability, the examination was performed at least 3 months after the MI onset. The biologic variables in the analysis were based primarily on data from the health examination, but some (for instance BMI and diabetes) were supplemented with questionnaire data for the 10% of the surviving subjects who answered the questionnaire but did not participate in the clinical testing.

Air pollution exposure was assessed based on a methodology developed for previous studies [50-52]. The assessment was based on information from emission databases that contained historical information regarding road traffic and residential heating. The data was then linked to a GIS-system (Geographical Information System) and a dispersion map regarding air pollution with a 25 x 25 m resolution was created (figure 5). In paper I and II we used the time weighted average traffic-generated NO₂ level for all residential addresses of each study subject during 1970 to 1992–1994 as an indicator of the individual long-term exposure to traffic related air pollution at home.

Figure 5. Air pollution distribution for NOₓ in µg/m³ as a daily annual average in the city of Stockholm during the 1990s

Job strain was defined through questions on psychological demands and decision latitude in the Swedish version of the Karasek-Theorell questionnaire [8]. The psychological demands and job
control scores were dichotomized at the 75th percentile with two different approaches. In one variable, a total sum score regarding the questions on psychological demands and decision latitude was created and participants with a sum score >75th percentile were classified as exposed to job strain. In the other variable, the sum score for psychological demands and decision latitude were kept separate and participants who had a sum score >75th percentile in both variables were classified as exposed to job strain. The exposure measurement is described in detail elsewhere [12, 53].

Exposure to road traffic noise was assessed for all addresses of the participants from 1970 until they entered the SHEEP-study in 1992–1994. For each address, a 24-hour average A-weighted sound pressure level ($L_{A_{eq,24h}}$) from road traffic was calculated according to a simplified version of the Nordic prediction model [54]. We collected data regarding crucial parameters such as distance and angles to roads, the number of vehicles on each road, and vehicle speed. The traffic information was received from the municipalities in Stockholm County. Measurements of distance and angles from the most exposed facade to the three nearest roads were performed with maps and area photos (figure 6).

![Figure 6](image_url)

**Figure 6.** Illustration of the method for measuring distance and angles to the three nearest roads from the façade of the house with the highest exposure.

Contributions of distant larger roads (>20,000 vehicles) were assessed separately, using the same method but ignoring effects of shielding buildings. A final exposure estimate that combined the levels from distant and nearby roads was calculated and a time-weighted average (equation specified below) was used to combine levels from several addresses to a single value of road traffic noise exposure for each individual.

$$L_{A_{eq,24h}} - \text{average} = \frac{\sum Y_i}{\sum Y_i}$$

Data on railway noise exposure were of varying quality as well as in different formats and a crude assessment had to be used. Participants who had lived for at least 1 year within 200 m of a railway track were classified as railway noise exposed; remaining subjects were classified as unexposed. In paper II all participants living within 200 m from a railway track at their last
address were excluded from the analyses (12% of the study population) to reduce imprecision in the traffic noise exposure assessment.

We used a job-exposure matrix (JEM) to assess occupational noise exposure. The matrix is described in detail elsewhere [55]. Briefly, the JEM was derived from measurements performed by occupational medicine clinics and occupational health services units in Sweden during the period 1970-2004. The JEM included 320 occupations, and was based on up to 35 different measurements per occupation. In case of missing data, an expert judgment was performed. Estimated exposure for each occupation was coded as <75 dB, 75-84 dB, or ≥85 dB (L_{Aeq,8h}) based on the consensus of three occupational hygienists. We used the JEM together with questionnaire information on type and duration of occupation to calculate the level and duration of each subject’s occupational noise exposure. Subjects were classified as noise exposed if they had an occupational exposure ≥75 dB for more than 1 year.

In 2003, a supplementary questionnaire was distributed to enhance the noise exposure assessment. This included questions on hearing impairment, window insulation, bedroom orientation, and noise annoyance. If the case or control had died, the questionnaire was sent to the next-of-kin. The questionnaire response rate among cases was 66% for women and 68% for men, and for controls, 76% for women and 79% for men.

### 3.1.3 Statistical approach

For paper I and II odds ratios and 95% confidence intervals were calculated using unconditional logistic regression analyses. Interaction effects in paper II were calculated on the additive scale. Trend tests in both papers were performed assuming a linear increase across categorical variables. Regression coefficients were adjusted for the matching variables age (five categories), sex and catchment area (ten categories) and for a number of selected covariates. A covariate was selected if the inclusion of this variable in the preliminary model changed the crude estimate for noise exposure by 10% or more.

The covariates included in the fully adjusted regression model in paper I were diabetes (dichotomous), physical activity (dichotomous), and smoking (5 categories). In addition, we also adjusted for air pollution (continuous) and occupational noise exposure (dichotomous), although these changed the crude estimate for road traffic noise exposure by only 7% and 3%, respectively.

The covariates included in the fully adjusted regression model for paper II were physical activity (dichotomous), socioeconomic position (three categories) and smoking (five categories). We also adjusted for air pollution (continuous), although this changed the regression coefficient for road-traffic noise exposure by only 7%.

Diabetes was not included as a covariate in the final model in paper II despite the fact that it changed the estimate by 10%, because of the possibility that it constitutes an intermediate step in the causal chain between noise exposure and myocardial infarction.

The statistical analyses in paper I was performed with STATA 8.2 and for paper II with STATA 11.0 (Stata Corp., College Station, TX).
3.2 HYENA – HYPERTENSION AND EXPOSURE TO NOISE NEAR AIRPORTS

The HYENA study was conducted as an EU-project including research teams from six European countries. The aim was to investigate health effects associated with exposure to aircraft noise at the residence. Hypertension was the main outcome, but annoyance, acute blood pressure effects, blood pressure dipping, medication use and cortisol levels were also investigated. The study focused on seven airports: Heathrow (United Kingdom), Tegel (Germany), Schiphol (The Netherlands), Arlanda and Bromma (Sweden), Athens (Greece) and Malpensa (Italy). Men and women 45-70 years of age living in selected areas surrounding these airports were invited [56].

3.2.1 Study participants

In the main study, constituting the basis for paper III, a total of 4861 subjects (2404 men and 2457 women) were included. The participation rate differed between countries, from about 30% in Germany, Italy and the UK, to 46% in the Netherlands, 56% in Greece and 78% in Sweden. In order to investigate the possibility of selection bias, a non-responder analysis was performed. Participants who had lived at their address for less than 5 years or lived at their address less than 6 months a year were excluded as well as subjects who were too ill to participate or could not comprehend the questionnaire.

For paper IV, a sample was drawn from the HYENA main study. All participants were eligible for saliva sampling except shift workers, since cortisol levels can vary with the work schedule. Participants with the highest and lowest levels of exposure to aircraft noise in each country were selected, to increase contrast in exposure.

Figure 7. Location of airports included in the HYENA-study.
The participation rate for the cortisol-study was high in Sweden, UK and the Netherlands (99, 98 and 85%), lower in Italy (49%) and Germany (26%) and was not recorded in Greece. The final sample consisted of 439 participants (209 men and 230 women).

3.2.2 Exposure assessment

All participants were interviewed at home by a nurse with a standardized questionnaire that focused on known risk factors for cardiovascular disease. These risk factors included socioeconomic position, health status and lifestyle factors such as diet, physical activity and smoking habits. The questionnaire also contained questions regarding annoyance and coping strategies for noise exposure. During the interview session, the participants underwent blood pressure measurements and height and weight were assessed to calculate body mass index (BMI). The blood pressure measurement was performed with a validated automated blood pressure instrument in order to minimize observer errors. Blood pressure was measured three times: the first measurement was recorded immediately before the interview, after a 5-minute rest, the second one minute after the first one and the third measurement was taken after the interview. The mean level of the first two readings was used to define the blood pressure.

The annoyance variables included in the questionnaire were categorized in accordance with the International Commission on Biological Effects of Noise (ICBEN) on an 11-category scale (0-10). In the analyses regarding annoyance in paper IV, the annoyance variable for aircraft noise was classified in three categories (low: 0-3, moderate: 4-7 and high: 8-10).

The noise exposure assessment was coordinated between centers to ensure that a similar approach was used in each participating country. Aircraft noise exposure was assessed for each participant’s home address using noise maps [56]. The home addresses were transformed into coordinates and marked on a GIS-map (geographic information system map) using aircraft noise data from the year 2002 in contours with 1dB intervals. The INM-model (Integrated Noise Model) served as standard model for aircraft noise and was used in the study areas of Germany, the Netherlands, Sweden, Italy, and Greece to calculate the aircraft noise levels [57]. In the United Kingdom the Ancon model was applied [58].
Figure 8. GIS-map with exposure assessments made for aircraft noise exposure $\geq 55$ L$_{den}$, INM-model, at the international Stockholm Arlanda airport, 2-runway-system.

Figure 9. GIS-map with exposure assessments made for aircraft noise exposure $\geq 55$ dB L$_{Aeq,24h}$, INM-model, at the small domestic Stockholm Bromma airport.
Local models were used in each country for road traffic noise since no uniform traffic data were available. The Good Practice Guide for Strategic Noise Mapping was applied to merge the data between countries [59]. Road traffic noise levels in all countries had a 1-dB resolution, except for the United Kingdom, where 5-dB classes were used. The midpoints of these classes were chosen for the analyses using continuous exposure data.

The participants selected for saliva sampling were instructed to collect three samples. The first sample was to be taken 30 min after awakening (which usually corresponds to the peak excretion of cortisol), the second sample immediately before lunch, and the third sample just before going to bed in the evening. Detailed instructions were provided in order to ensure that the samples were taken in a similar fashion for all participants in each country and that the samples would be marked properly. Participants were instructed to write the date and time on the label of the test tube, and put it in the refrigerator. The samples were collected by a nurse or put in an envelope and mailed to the laboratory in each of the participating countries responsible for the cortisol sampling. The samples were then centrifuged and frozen. When all samples had been collected, the saliva tubes were sent to a laboratory at Karolinska Institutet (Stockholm, Sweden) for analysis.

Cortisol levels in saliva were determined by the Spectria cortisol coated tube radioimmunoassay kit (Orion Diagnostica, Espoo, Finland). All samples from each subject or group of subjects were analyzed simultaneously in duplicate. The within- and between-assay coefficient of variation never exceeded 5.0% and 10.0%, respectively. Cortisol was analyzed and compared for 30 samples at the Department of Physiological Psychology, University of Düsseldorf, Germany [60]. There was a very high correlation (0.98) but a slight difference in level, with systematically lower levels in the Stockholm laboratory. The difference was 12.5% (95% CI 1.5–22.3%).

### 3.2.3 Statistical approach

In paper III logistic regression models were used to calculate the association between traffic noise exposure and hypertension. All analyses were adjusted for country, age, BMI, alcohol intake, education and exercise. The statistical software SAS (SAS institute inc. Cary, NC, USA) and EGRET (Cytel Software Corporation, Cambridge, MA, USA) were applied.

In paper IV linear regression models were used to assess the relation between traffic noise exposure and saliva cortisol levels. The analyses were adjusted for traffic noise exposure (air or road), country, age, sex, employment status, occupational status, medication use, BMI, alcohol intake, diet, remedy during night and other noise sources. In paper IV a covariate was selected as a confounder if the inclusion of this variable changed the regression coefficient in the crude model by 10% or more. A full model was applied and covariates that affected the full model less than 3% were excluded in the final model. The analyses were conducted using the statistical software STATA 8.2 (Stata Corp., Collage Station, TX, USA). In both papers tests for heterogeneity between countries were performed and no significant difference was found, indicating that combined analyses could be used.
4 RESULTS

The results presented below mainly focus on the tables and figures published in paper I-IV. However, some further analyses have been performed and these results are also presented below.

4.1 ROAD TRAFFIC NOISE, AIR POLLUTION AND MYOCARDIAL INFARCTION

The results from the SHEEP-study indicate an increased risk of myocardial infarction related to road traffic noise exposure at the residence. In table 1, traffic noise exposure of 50 dBA or higher tended to be associated with an increased risk of MI OR 1.12 (95% CI 0.95–1.33). Similar results were found for fatal and nonfatal cases as well as for men and women (data not shown). In addition, a dose-response relationship between road traffic noise and MI was suggested.

Table 1. Association (OR) between long-term road-traffic noise exposure (L_{Aeq,24h}) and myocardial infarction in a population based case-control study from Stockholm.

<table>
<thead>
<tr>
<th>Road-traffic noise (dB)**</th>
<th>Controls</th>
<th>All cases</th>
<th>Fatal cases</th>
<th>Non-fatal cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>OR*</td>
<td>95% CI*</td>
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<tr>
<td>Dichotomous</td>
<td></td>
<td></td>
<td></td>
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<td>923</td>
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<td>-</td>
</tr>
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<td>683</td>
<td>543</td>
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<td>60</td>
<td>1.21</td>
<td>0.81-1.79</td>
</tr>
<tr>
<td>≥65</td>
<td>10</td>
<td>10</td>
<td>1.26</td>
<td>0.48-3.30</td>
</tr>
</tbody>
</table>

**Time-weighted average of road-traffic sound levels (L_{Aeq,24h}) for each of the subject’s addresses during the study period (from 1970 to 1992-1994).
*Odds ratios and 95% confidence intervals adjusted for matching criteria (sex, catchment area and age) and for smoking, physical inactivity, diabetes, air pollution and occupational noise exposure.
In figure 10 associations (ORs) between road traffic noise exposure and MI is shown for different subsamples of subjects. The samples were defined by excluding participants where there is a possibility of misclassification regarding noise exposure, such as those with railway noise exposure (743 subjects), aircraft noise exposure (17), ventilation noise annoyance (147), neighbor-noise annoyance (289) and hearing impairment (297).

The exclusion of subjects exposed to railway noise resulted in a significantly increased risk of MI associated with exposure to road traffic noise, OR 1.23 (1.01–1.50). Other exclusions appeared to have a more modest impact on the risk estimates. When excluding all 1207 persons exposed to other noise sources or with hearing impairment, the MI risk associated with noise exposure from road traffic was markedly elevated (1.38; 1.11–1.71).

**Figure 10.** Associations (OR, 95% CI) between road traffic noise exposure (cut-off $\geq 50$ dB $L_{A_{eq,24h}}$) and MI for subgroups defined by excluding persons with noise exposure from other sources or reported hearing loss in a case-control study from Stockholm. All models were adjusted for matching variables (age, sex and catchment area) and for diabetes, physical inactivity, smoking, air pollution and occupational exposure.
In Figure 11, the association between road traffic noise exposure and MI was analyzed in relation to risk factors included in the SHEEP-questionnaire in order to identify any possible effect modification. There was a tendency towards a higher risk among former smokers and low-level white collar workers. In addition, an increase in risk was also suggested in subjects with job strain and hypertension.

Figure 11. Associations (OR, 95% CI) between (MI) road-traffic noise exposure (cut-off: ≥50 dB $L_{Aeq,24h}$) and myocardial infarction by various MI-risk factors in a case-control study from Stockholm. All models were adjusted for matching variables (age, sex and catchment area) and for diabetes, physical inactivity, smoking, air pollution and occupational noise exposure.
Furthermore, we analyzed the association between road traffic noise exposure and MI in relation to the questions in the supplementary questionnaire regarding noise exposure (figure 12). An increased risk of myocardial infarction was found for participants mainly annoyed by traffic noise in their bedroom (OR 1.61; 1.02–2.54). However, no elevated risk was found in participants reporting sleep disturbance due to noise.

**Figure 12.** Associations (OR 95% CI) between road traffic noise exposure (cut-off: ≥50 dB_{A_{eq,24h}}) and myocardial infarction by noise-related factors in a case-control study from Stockholm. All models were adjusted for matching variables (age, sex and catchment area) and for diabetes, physical inactivity, smoking, air pollution and occupational noise exposure.
Figure 13 shows the association between long-term individual exposure to air pollution (NO₂) and noise from road traffic (dB L_{A_{eq,24h}}). The correlation was high (r=0.6) between the two variables. We used a cut-off value of 42 dBA in the noise exposure assessment, and no detailed estimation was performed below this level.

Further analyses of the correlation between road traffic noise exposure and air pollution from traffic, based on a sample of the study population, indicated a higher correlation along roads with a high amount of traffic in the city center (r=0.91) than in suburban areas with less traffic (0.41).
In Figure 14, associations between myocardial infarction and road traffic noise exposure as well as air pollution is shown. The estimates for road traffic noise exposure indicate an increase in risk of about 40%, on average. Air pollution exposure (NO₂) did not seem to be associated with an increased risk of myocardial infarction, except possibly in the subgroup of cases that died outside of hospital (7% of the cases). Adjustments were made for air pollution in the analysis between road traffic noise exposure and myocardial infarction and vice versa.

**Figure 14.** Odds ratios and 95% CIs for myocardial infarction in relation to road traffic noise exposure (dB L_{A,eq,24h}) and air pollution (NO₂) in a case-control study in Stockholm.
4.2 TRAFFIC NOISE AND MYOCARDIAL INFARCTION IN RELATION TO OCCUPATIONAL NOISE AND JOB STRAIN

In table 2, associations between different environmental stressors and myocardial infarction were investigated with data from the SHEEP-study. A significant association with myocardial infarction was seen for job strain as well as for road traffic noise exposure. Occupational noise exposure displayed a non significant increase in risk.

Table 2. Logistic regression analysis with odds ratios and confidence intervals for job strain, road traffic noise and occupational noise exposure in association with myocardial infarction. Data from a case-control study conducted in Stockholm County 1992-1994.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Exposed n</th>
<th>ORb</th>
<th>95% CIb</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Road traffic noise dB(L_{Aeq24h})</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 75th percentile (51.8 dBA)</td>
<td>708</td>
<td>1.23</td>
<td>1.01-1.51</td>
</tr>
<tr>
<td><strong>Job strain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 75th percentile in an overall sum score</td>
<td>836</td>
<td>1.39</td>
<td>1.17-1.65</td>
</tr>
<tr>
<td>including both psychological demand and</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>decision latitude</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 75th percentile in each of the separate sum</td>
<td>218</td>
<td>1.59</td>
<td>1.18-2.13</td>
</tr>
<tr>
<td>scores for psychological demand and decision</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>latitude</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Occupational noise</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;75 dBA</td>
<td>1219</td>
<td>1.17</td>
<td>0.98-1.41</td>
</tr>
</tbody>
</table>

a Number of exposed participants in each category out of the 3050 participants included in the study population.
b Odds Ratios and 95% Confidence Intervals for the association between road traffic noise exposure, occupational noise exposure and job strain and first event of myocardial infarction. All analyses adjusted for age, sex, hospital catchment area, physical inactivity, smoking, air pollution and socioeconomic position.
In figure 15, participants exposed to road traffic and occupational noise displayed an increased risk of MI, OR 1.43 (95% CI 1.05-1.93). In subjects exposed to road traffic or occupational noise in combination with job strain a tendency towards an interaction effect was suggested OR 1.84 (95% CI 1.33-2.54) and OR 1.66 (95% CI 1.27-2.16), however this interaction effect was not statistically significant.

**Figure 15.** Associations (OR, 95% CI) between road-traffic noise exposure (>/<75th percentile 51.8 dB L_{Aeq,24h}), occupational noise exposure (>/< 75dB L_{Aeq,8h}) and job strain (>/< the 75th percentile in an overall sum score including both psychological demand and decision latitude) in relation to myocardial infarction. All analyses adjusted for age, sex, hospital catchment area, physical inactivity, smoking, air pollution and socioeconomic position.
Figure 16 shows associations for risk of myocardial infarction when exposed to one, two or three of the noise and job strain exposures under study. A significant trend for linear increase of each additional exposure 1-3 was observed. The risk appeared particularly high in those with all three risk factors OR 2.27 (95% CI 1.41-3.64). A total of 676 participants out of 3050 (22%) were exposed to two or three factors in combination.

Figure 16. Associations (OR, 95% CI) for myocardial infarction (MI) in individuals with or without road traffic noise (>/<75th percentile 51.8 dB(LA,<24h)), occupational noise (>/< 75dB(Aeq,8h)) and job strain (>/< the 75th percentile in an overall sum score including both psychological demand and decision latitude). The first category 0/3 is the reference group with low exposure to all three factors. The three following categories 1/3, 2/3 and 3/3 contain study participants exposed to one, two or all three of the factors investigated. All analyses adjusted for age, sex, hospital catchment area, physical inactivity, smoking, air pollution and socioeconomic position.
4.3 TRAFFIC NOISE EXPOSURE AND HYPERTENSION

The results from the HYENA-study pointed to an increased risk of hypertension among participants exposed to air traffic and road traffic noise exposure at the residence. However, the increase was modest and there were no clear dose-response relationships.

In figure 17, ORs for hypertension in relation to aircraft noise during the day ($L_{A_{eq,16h}}$) and night ($L_{night}$) are presented. An increased risk was indicated among participants exposed to aircraft noise levels >50 dBA at daytime and >40 dBA at nighttime. However, a clear dose-response relationship was lacking. There were no clear differences in risk between men and women.

**Figure 17.** ORs of hypertension in relation to aircraft noise (5-dB categories). $L_{A_{eq,16h}}$ (A) and $L_{night}$ (B) separately included in the model. All analyses were adjusted for country, age, sex, BMI, alcohol intake, education, and exercise. The error bars denote 95% CIs for the categorical (5-dB) analysis. The curves show the ORs and corresponding 95% CIs for the continuous analysis.
Figure 18 shows the ORs for hypertension in men and women in relation to daily annual average road traffic noise exposure ($L_{A_{eq,24hr}}$). An increase in risk for hypertension was found for men in relation to road traffic noise exposure. However, no clear dose-response relationship was observed. No association between road traffic noise exposure and hypertension was found for women.

Figure 18. ORs of hypertension in women (A) and men (B) in relation to road traffic noise ($L_{A_{eq,24hr}}$; 5-dB categories) separately included in the model. All analyses were adjusted for country, age, BMI, alcohol intake, education, and exercise. The dotted line denote 95% CIs for the categorical (5-dB) analysis. The curves show the ORs and corresponding 95% CIs for the continuous analysis.
In the country specific analyses the differences in risk among countries was explored. There was no statistically significant heterogeneity among countries in the association between aircraft noise and hypertension; therefore a combined analysis could be used. The strongest association between aircraft noise exposure at night and hypertension was suggested in the United Kingdom and Italy (figure 19, A).

Non-responder analyses were performed in order to evaluate the effect of low response rates. No difference in exposure to aircraft noise was indicated between responders and non-responders. However, a difference was indicated among responders and non-responders in relation to road traffic noise exposure with more non-responders in the group exposed to high levels of road traffic noise. The questionnaire distributed to a sample of the non-responders showed no difference in the prevalence of self reported hypertension between responders and non-responders.

Figure 19. Forest plot showing country-specific ORs for hypertension per 10-dB increase in noise exposure, in relation to L_{night} for aircraft noise (A), and L_{Aeq,24h} for road traffic noise (B). All analyses were adjusted for country, age, BMI, alcohol intake, education, and exercise.
4.4 AIR TRAFFIC NOISE AND MORNING SALIVA CORTISOL

In the HYENA study, associations between aircraft noise and saliva cortisol were investigated. In figure 20, the cortisol levels in the morning sample showed a roughly normal distribution. There were two “outliers” included in the data, one in the United Kingdom (99.8) and one in Sweden (89.0). However, these values were still within the normal range and were therefore included in the subsequent analyses.

![Figure 20](image)

**Figure 20.** Distribution of cortisol for morning saliva samples from 439 participants exposed to aircraft noise in six European countries.

The median levels of cortisol nmol/l for morning, lunch, and evening samples were comparable across countries (Figure 21). However, in Greece there was a lower median level for the morning sample.

![Figure 21](image)

**Figure 21.** Median saliva cortisol level for each country for morning, lunch and evening saliva samples in six European countries.
Figure 22 shows linear regression coefficients and 95% CIs for cortisol level in saliva from the morning sample in relation to aircraft noise levels ($L_{Aeq,24h}$). A significant association between aircraft noise exposure and morning saliva cortisol was found in women, where the difference in means > 60 dBA were 6.07 (95% CI, 2.32–9.81) nmol/L, corresponding to a 34% increase in morning saliva cortisol level. Furthermore, a dose-response relationship was suggested. No similar effect was seen for men. Separate analyses excluding the previously mentioned outliers (Figure 20) did not change the results.

In country-specific analyses, the number of investigated participants for either sex in each country was small, leading to substantial statistical uncertainty of the estimates. The strongest association between aircraft noise exposure and cortisol among women was found in the United Kingdom and the Netherlands. However, no statistically significant heterogeneity between countries was indicated.
In table 3, analyses regarding noise exposure and annoyance are presented. Women exposed to aircraft noise > 60 dB had an increase in morning saliva cortisol level regardless of whether they considered themselves as annoyed or not. A 25% increase (4.86 nmol/L; 95% CI, -0.46 to 10.18 nmol/L) in mean saliva cortisol was observed for those who reported low annoyance, 52% increase (9.96 nmol/L; 95% CI, 3.30–16.62 nmol/L) for moderately annoyed participants, and a 30% increase (5.73; 95% CI, 0.05–11.40 nmol/L) for highly annoyed study subjects compared to participants with an exposure < 50 dB and who reported low annoyance. We found no rise in saliva cortisol level among participants who reported moderate or high annoyance in the lowest exposure group, < 50 dB.

### Table 3. Linear regression coefficients for the association between residential aircraft noise exposure and morning saliva cortisol in relation to annoyance among women in six European countries.

<table>
<thead>
<tr>
<th>Annoyance scale 0-10</th>
<th>n</th>
<th>Coef (CI 95%)</th>
<th>n</th>
<th>Coef (CI 95%)</th>
<th>n</th>
<th>Coef (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;50</td>
<td></td>
<td>50-60</td>
<td></td>
<td>&gt;60</td>
<td></td>
</tr>
<tr>
<td><strong>Daytime</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3</td>
<td>116</td>
<td>-</td>
<td>34</td>
<td>3.84 (-2.02, 9.70)</td>
<td>27</td>
<td>5.98 (-0.72, 12.68)</td>
</tr>
<tr>
<td>4-7</td>
<td>44</td>
<td>-5.31 (-10.52, 0.10)</td>
<td>41</td>
<td>-0.21 (-5.32, 4.90)</td>
<td>31</td>
<td>1.35 (-4.79, 7.49)</td>
</tr>
<tr>
<td>8-10</td>
<td>14</td>
<td>-3.87 (-13.42, 5.68)</td>
<td>68</td>
<td>1.68 (-3.56, 6.92)</td>
<td>65</td>
<td>7.93 (2.61, 13.25)</td>
</tr>
<tr>
<td><strong>Nighttime</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3</td>
<td>137</td>
<td>-</td>
<td>74</td>
<td>2.78 (-1.52, 7.09)</td>
<td>50</td>
<td>4.86 (-0.46, 10.18)</td>
</tr>
<tr>
<td>4-7</td>
<td>22</td>
<td>-0.02 (-7.97, 7.94)</td>
<td>20</td>
<td>0.73 (-6.07, 7.53)</td>
<td>27</td>
<td>9.96 (3.30, 16.62)</td>
</tr>
<tr>
<td>8-10</td>
<td>15</td>
<td>-6.95 (-16.01,2.10)</td>
<td>49</td>
<td>4.28 (-1.12, 9.68)</td>
<td>45</td>
<td>5.73 (0.05, 11.40)</td>
</tr>
</tbody>
</table>

All analyses adjusted for road traffic, country, age, employment status, occupational status, medication use, BMI, alcohol intake, diet, remedy during night and other noise sources in the living environment.

a Annoyance is classified from a 11-point ICBEN-scale (0-10)
b Linear regression coefficients for morning saliva cortisol in nmol/L
Employed women had higher morning saliva cortisol levels than retired women (Table 4). This was particularly evident among those with high exposure to aircraft noise. Women exposed to aircraft noise > 60 dB and who were currently employed had an 83% higher mean morning saliva cortisol level (16.23 (95% CI, 9.29–23.17) nmol/L) compared with retired women exposed to aircraft noise level at ≤ 50 dB. Retired women exposed to aircraft noise > 60 dB had an increase of 27% (5.38 (95% CI, –0.57 to 11.33) nmol/L). Additional analysis restricted to participants ≥ 55 years of age showed a similar increase, indicating that the effect is not explained by age differences. It should be noted that these analyses included a small sample of individuals in each group, leading to substantial uncertainties in the estimates.

### Table 4

Linear regression coefficients for the relation between residential aircraft noise exposure and morning saliva cortisol levels in relation to employment status among women in 6 European countries.

<table>
<thead>
<tr>
<th>Aircraft noise dBA</th>
<th>n &lt;50</th>
<th>n 50-60</th>
<th>n &gt;60</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Employ. Status</strong>a</td>
<td>Coefb (CI95%)</td>
<td>Coefb (CI95%)</td>
<td>Coefb (CI95%)</td>
</tr>
<tr>
<td>Retired</td>
<td>33</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Other</td>
<td>17</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>Employed</td>
<td>47</td>
<td>28</td>
<td>17</td>
</tr>
</tbody>
</table>

All analyses adjusted for road traffic, country, age, occupational status, medication use, BMI, alcohol intake, diet, remedy during night and other noise sources in the living environment.

a Employment status is classified categorically. "Retired" includes retired participants. "Other" includes participants on sick leave, unemployed subjects, housewives and students etc. "Employed" includes both full-time and part-time employment as well as self-employed working from home.

b Linear regression coefficients for morning saliva cortisol level in nmol/l

c Reference category. Arithmetic mean cortisol level in the reference category=19.67 nmol/l
5 DISCUSSION

5.1 GENERAL DISCUSSION

The overall objective of this thesis was to examine the association between residential traffic noise exposure and cardiovascular disease. Our findings provide evidence supporting an increased risk of MI, hypertension and elevated levels of cortisol associated with traffic noise exposure at the residence in line with previous studies [3, 4, 38].

In the SHEEP-study an increased risk of MI was indicated, with a suggestive dose-response trend. This increased risk was observed in as low levels as >/<= 50 dBA in contrast to the studies by Beelen and Babisch, that observed an effect in higher categories of noise exposure [33, 34]. In the presence of other environmental stressors, such as job strain and occupational noise exposure the risk of MI associated with road traffic noise exposure increased. The highest risk was seen among participants with all three exposures, indicating that each exposure has the potential to increase the risk of MI. This gives further support for the hypothesis that traffic noise increases the risk of MI. Associations between occupational noise exposure or job strain in relation to MI have been observed in previous investigations [9, 11, 61-63]. However, no previous study has investigated the relationship between all three risk factors in association with MI.

In the HYENA-study an increased risk of hypertension was suggested in participants with outside exposure to aircraft noise at night of more than 40 dB. This is in line with previous studies observing an association between aircraft noise exposure and hypertension [28, 64]. In addition, an increased risk of MI in relation to traffic noise exposure in the SHEEP-study was found in participants who reported annoyance by traffic noise mainly in the bedroom. Earlier studies have suggested an association between sleep disturbance and an increased risk of myocardial infarction [65, 66] as well as between sleep disturbance and stress [67, 68], indicating that the stress-related effect regarding noise exposure at night may be mediated by sleep disturbance.

An increased level of cortisol was found in morning saliva among women exposed to high levels of aircraft noise. Previous studies regarding traffic noise and cortisol have been inconclusive [3, 37, 38, 45, 46, 69, 70] However, they often included few subjects or did not keep a strict time-line to capture the cortisol level at a specific time-point during the first morning hour. According to a review by Chida et al, that indicated an increase in morning saliva cortisol level among subjects exposed to job strain, assessment of morning cortisol level is a more appropriate measure for assessing HPA-activation following awaking then repeated measurements during the day [71]. This might also be relevant for noise research.

Previous studies regarding traffic noise have suggested that the causal pathway behind the association between traffic noise exposure and MI involves annoyance [4]. It is therefore of interest that the associations between aircraft noise exposure and morning saliva cortisol level was not affected by the degree of annoyance. Furthermore, in another part of the HYENA-study, not included in the thesis, the association between traffic noise and acute blood pressure change during sleep was investigated. A significant increase in blood pressure was observed in relation
to noise exposure events LAmax >35dB indoor [25]. This increase in blood pressure was evident in relation to aircraft noise, road traffic noise and other indoor noise sources. This suggests a direct effect of noise on blood pressure not mediated by annoyance.

The overall correlation between traffic noise exposure and air pollution from traffic was high (r=0.6). It varied between different parts of the county indicating a higher correlation along roads with a high amount of traffic in the city center. This is not surprising since both models are more accurate at high levels of exposure. In addition, at lower levels of exposure in the suburbs other factors, such as topography, prevailing wind direction and presence of obstacles may be more influential. The overall correlation measure might therefore depend on how many of the study participants that live close to roads with a high amount of traffic. In previous studies the correlation between traffic noise and air pollution has varied [70, 72, 73], from low (r=0.32) to high (r=0.89).

Several large epidemiological studies have indicated an association between air pollution and MI [74, 75]. However, in our study there was no statistically significant association between air pollution and MI after adjustment for traffic noise exposure and the estimates for the association between road traffic noise and myocardial infarction did not appear to be affected by adjustments for air pollution. No interaction effect between road traffic noise exposure and air pollution in association with MI was found. It should be pointed out that because of the comparatively high correlation between exposure to air pollution and noise from traffic it is difficult to independently assess the effect of each factor and to evaluate interactions.

The estimate for the association between road traffic noise exposure and myocardial infarction increased and became statistically significant after exclusion of participants living within 200 meters from a railway track. This change in estimate indicates that railway traffic noise may have confounded the estimates. Studies regarding railway noise and cardiovascular endpoints are few [30], but effects of railway noise, such as annoyance and sleep disturbance, are well-documented [76-78]. In our study we lacked sufficient precision in the estimation of railway noise exposure and we were therefore unable to investigate the association between railway traffic noise and myocardial infarction or properly adjust for railway noise exposure in the analyses regarding road traffic. In paper II all analysis were performed on study participants who lived further away than 200m from a railway track (88% of the study population). While, the estimate for the association between road traffic noise exposure and myocardial infarction changed when excluding participants living close to a railway track, the estimates for job strain or occupational noise exposure remained the same.

Diabetes mellitus was included as a covariate in the regression model in paper I since it changed the estimate with 10%. However, because of a growing suspicion that diabetes mellitus may constitute an intermediate step in the causal chain between noise exposure and cardiovascular disease, it was not included in the regression model in paper II. Some studies suggest that stress is related to development of the metabolic syndrome [15, 18], and might thus also affect diabetes occurrence, which is a risk factor for cardiovascular disease. The estimates in our study with regard to noise and MI did not change markedly when including diabetes in the model and our conclusions would have remained the same.

The risk of MI in relation to road traffic noise exposure appeared to be similar in men and women. However, our results on hypertension pointed to a difference in risk between men and
women with regard to road traffic noise exposure, but not for aircraft noise exposure. In addition, an association between aircraft noise and cortisol was only suggested among women. This difference in risk between men and women is difficult to explain and previous studies regarding traffic noise exposure in relation to hypertension or myocardial infarction have been inconclusive regarding sex differences [28, 33, 79, 80].

It is also of interest that women who were employed had a higher cortisol level than did retired women. We found a particularly strong increase in employed women exposed to high levels of aircraft noise. This effect could be a result of disrupted sleep during night and the lack of recovery during the day due to employment. It can also be a result of stressful activities related to employment [81-84] combined with aircraft noise exposure at home.
5.2 METHODOLOGICAL CONSIDERATIONS

Even though the findings in this thesis suggest an increased risk of cardiovascular disease in relation to traffic noise exposure, the estimates indicate a modest increase in risk, vulnerable to chance findings and residual confounding, and with weak or inconsistent dose-response.

This thesis is based on two observational studies with different study designs, one cross-sectional and one case-control study. A major strength of the case-control study was the extensive assessment of road-traffic noise exposure, occupational noise exposure, job strain and air pollution. The detailed road-traffic noise exposure and air pollution assessment for all addresses since 1970 made it possible to estimate the exposure for a longer period (22-24 years) than in previous longitudinal studies[4]. The extensive job exposure matrix covering 320 occupations and based on up to 35 different measurements per occupation enabled a thorough exposure classification of occupational noise exposure. A well-defined and validated method of assessing job strain used in many earlier studies was used [12, 53].

However, in all observational studies errors occur and they can be divided into systematic and random errors.

5.2.1 Systematic error

Systematic error is usually referred to as bias. It does not depend on study size or chance, instead it is a methodological error that is introduced when you select your study participants, determine your outcome or assess the exposure under study. An estimate that has little systematic error may be described as valid. Systematic error can be divided into three categories: selection bias, information bias and confounding.

5.2.1.1 Selection bias

Selection bias occurs when the association between exposure and outcome differs among those who participate in the study and those who do not. In the case-control study SHEEP, the different sources of case identification, the strict diagnostic criteria and the high autopsy rate contributed to a high reliability of case identification. This minimized the risk of self-selection, since a very large part of cases of first event MI in Stockholm County were probably included. The controls were sampled randomly from the population matched on age, sex and catchment area. The high response rate and the fact that the response rate did not differ across case-control status, age or hospital catchment area further minimized the risk of selection bias.

In the cross-sectional study HYENA, the well trained nurses, the validated automatic blood pressure device and the use of a mean level of two measurements for each participant contributed to a high reliability of case identification. However, the low response rate in some countries may have introduced a selection bias. The non-responder analysis showed no difference in the prevalence of self reported hypertension between responders and non-responders or difference in aircraft noise exposure. However, a difference in exposure to road traffic noise among responders and non-responders was suggested, indicating a lower response rate among individuals exposed to high levels of road traffic noise. This could have contributed to the low noise exposure contrast in our study for road traffic noise, making it more difficult to observe an association with hypertension or cortisol.
Information bias occurs when the collected information regarding study participants is faulty and the participants are categorized incorrectly. Such misclassification can be divided into differential and non-differential misclassification. Differential misclassification occurs when the misclassification of exposure is different among those with and without the disease. Likewise, it is also present when misclassification of disease is different among those with and without the exposure. Differential misclassification can either exaggerate or underestimate an effect. In non-differential misclassification, the misclassification does not differ between exposed or unexposed or those with or without a disease. This bias may lead to a diluted effect estimate.

In SHEEP, the exposure to traffic noise was not determined until after the original data collection and it could not have influenced the diagnosis. Therefore, differential misclassification of disease appears unlikely. As previously described, the different sources of case identification, the strict diagnostic criteria and the high autopsy rate contributed to a high reliability of case identification. This minimized the risk of non-differential misclassification of disease.

In HYENA, the procedure regarding recruitment, case identification and exposure assessment was the same for exposed and unexposed participants. However, it can not be completely ruled out that the staff differed in their procedure regarding the blood pressure measurement and the questionnaire-based interviews in exposed and unexposed individuals, since they were not blinded to exposure status. Therefore differential misclassification of disease and exposure to cardiovascular risk factors may exist. The cortisol assessment was performed in the lab, blinded to exposure status and the assessment of cortisol level could therefore not have been influenced by exposure status, and thereby misclassification of outcome was not likely in the cortisol part of the study.

In case-control studies, differential misclassification of exposure due to recall bias is always a concern. In SHEEP the exposure assessment of traffic noise, occupational noise and air pollution were performed with objective calculation models, not influenced by case-control status, and thereby not affected by recall bias. However, the assessment of job strain was based on questionnaire data after disease onset and can therefore be affected by bias. However, a previously published analysis regarding the subjective measures with inferred measures as standards indicated a high validity in the exposure assessment of job strain, particularly regarding decision latitude, making differential misclassification due to recall bias less likely [53]

Road traffic noise exposure in the SHEEP study was assessed by the use of a simplified calculation model and even though this model was found to be of high validity, it is less precise than the full calculation model. In the smallest roads that lacked information regarding traffic flow and speed, imputed values were applied. In addition, road traffic noise exposure was assessed in reference to the façade of the house with the highest amount of exposure. This may differ from the true exposure, especially regarding apartment buildings where the location of the apartment was not established. This misclassification would be expected to primarily result in non-differential misclassification of exposure, leading to a dilution of the associations.

In SHEEP, misclassification of exposure should also be considered regarding occupational noise exposure. The job-exposure matrix is a simplified assessment and in order to obtain a more
precise estimation an individual assessment of occupational noise exposure has to be performed. However, a similar approach with a job exposure matrix has been used in earlier studies and was found to be of high validity [85]. Any possible imprecision in exposure assessment would primarily lead to attenuation of the effect estimates.

In HYENA, the exposure assessment regarding aircraft noise exposure was of high validity and assessed with the same calculation model, in all counties except in The United Kingdom. However, the road traffic assessment was made with different calculation models in most countries and in United Kingdom, road traffic noise could only be assessed in 5 dB-categories. Therefore, substantial non-differential misclassification of road traffic noise exposure is probably present, and may partly explain the lack of association between road traffic noise and hypertension or saliva cortisol levels. The exposure assessment to aircraft noise and road traffic noise was made blinded to outcome status and differential misclassification of exposure was therefore minimized.

5.2.1.3 Confounding

Confounding is present when an observed association between exposure and outcome is distorted due to an extraneous factor that have been mistaken for or mixed with the actual exposure effect. It could lead to an overestimation or an underestimation of the true effect. In order to be classified as a confounder the variable has to have an association with both exposure and outcome.

When studying the association between traffic noise and cardiovascular disease, air pollution is always referred to as a potential confounder since it is correlated with noise exposure from road traffic and has been established as a risk factor for cardiovascular disease. However, in our study air pollution had no major effect on the estimates, primarily because of a weak effect on its own.

Residual confounding has to be considered even if several known risk factors for cardiovascular disease were included in the different analyzes. It is of less concern in studies involving a high increase in risk. However, in our studies the risk associated with cardiovascular endpoints was small, increasing the possibility of residual confounding affecting the estimates.

5.2.2 Random error

Random error is the variability in the data. It is sometimes a result of chance that can be solved with bigger study sizes, but usually random errors are not strictly due to chance and can thereby be eliminated with better information. A study with a small random error can be described as a study with high precision.

Both SHEEP and HYENA had a comparatively high number of participants, leading to random errors of minor importance. However, subgroup analyzes such as several exposure classes, may lead to considerable statistical uncertainty in each group. Furthermore, in the cortisol part of the HYENA study, only 439 participants were recruited. This low number of study participants might introduce random error due to chance and lead to a greater uncertainty regarding the estimates.
6 CONCLUSIONS

The findings in this thesis provide evidence supporting an association between long-term traffic noise exposure at the residence and cardiovascular disease. However, the results show a modest increase in risk, vulnerable to chance findings and a clear overall dose-response result is lacking.

- We found an increased risk of myocardial infarction (MI) following residential exposure to noise from road traffic, particularly after exclusion of those with noise exposure from other sources (to reduce exposure misclassification) or hearing loss. Together with earlier evidence this points to exposure to noise from traffic as a possible risk factor for MI.

- There was a correlation between exposure to air pollution and noise from road traffic. However, the association between road traffic noise and MI did not seem to be affected by air pollution, primarily because of a weak relation between air pollution and MI. The confounding effect by air pollution on the relationship between traffic noise and MI (and vice versa) is study specific. It depends on the correlation between the two exposures, which may differ between highly trafficked streets in city centers and streets in other areas, as well as on the risk associated with either exposure.

- A particularly high risk was observed in subjects exposed to both traffic and occupational noise as well as job strain. This indicates that combined exposure to several environmental stressors may be especially harmful. Although these data need confirmation, it provides some guidance for prioritization of preventive measures.

- Our findings suggest that exposure to aircraft noise may increase the risk of hypertension, even though a clear dose-response relationship was lacking. For road traffic noise an increased risk was seen only in men. Considering also earlier evidence there seems to be substantial support for traffic noise, particularly from aircraft, as a risk factor for hypertension.

- We saw an increased saliva cortisol level in women related to aircraft noise exposure, while no corresponding association was observed among men. The reason for the apparent sex difference is unclear, but it is supported by some earlier data. An increased saliva cortisol level related to noise exposure indicates a stress response, and a potential pathway for cardiovascular effects induced by noise.
7 FUTURE RESEARCH

Finding an association you believe are there can be difficult. It has sometimes been compared with the situation when you trying to tune in a radio station on an old transistor radio. It will take some time before you can hear the radio station loud and clear. We are not there yet regarding the association between traffic noise at the residence and cardiovascular disease. Through the static we can hear people talk, but we can not yet make out what they are saying. We believe we have found an association, but we can not yet establish at what noise levels an increase in risk occurs and what the true dose-response relationship looks like. Further, we can not yet completely rule out that the talking is coming from a different radio station.

We need many more high qualitative studies that investigate the association between long-term exposure to traffic noise at the residence and cardiovascular disease. As a consequence of the EU-directive on environmental noise (Directive, 2002/49/EC, 2002), every country has to produce noise maps showing the distribution of traffic noise in all major cities before 2012. This will contribute to an easier access to qualitative noise data and increase the possibility of conducting health related noise studies.

Further research regarding how the association between traffic noise and cardiovascular disease is affected by traffic generated air pollution and vice versa is also needed. Probably they both have an association with cardiovascular disease, but there is still a possibility that one exposure is confounding the estimates for the other.

Since an association between traffic noise exposure and cortisol has been suggested, it is not far fetched that an association between traffic noise and diabetes/ metabolic syndrome may also exist. This association should be investigated in future studies.
8 SAMMANFATTNING PÅ SVENSKA


Sammanfattningsvis ger våra resultat stöd för att långtidsexponering för vägtrafikbuller i bostaden kan öka risken för hjärtinfarkt. En kombination av vägtrafikbuller, yrkesbuller och yrkesstress ökade risken märkbart. Dessutom antyddes en ökad risk för högt blodtryck och höga morgonvärden av kortisol hos personer utsatta för flygtrafikbuller.
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