

From INSTITUTE OF ENVIRONMENTAL MEDICINE,  
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# CARDIOVASCULAR AND METABOLIC EFFECTS OF LONG-TERM TRAFFIC NOISE EXPOSURE

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**Karolinska  
Institutet**

Stockholm 2012

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ISBN 978-91-7457-828-7

## ABSTRACT

Traffic noise is an increasingly common environmental exposure affecting large parts of the European population. Since the auditory system is directly linked to the sympathetic nervous and the endocrine systems, noise may induce a stress response, influencing several physiological, metabolic and immunological processes. Previous epidemiological studies suggest harmful effects of traffic noise on the cardiovascular system; however, the overall picture is inconclusive. The primary aim of this thesis was to investigate the long-term effects of traffic noise on cardiovascular and metabolic outcomes. A secondary aim was to apply and evaluate digital noise maps produced in Sweden in accordance with the European Environmental Noise Directive (END) for assessments of residential traffic noise exposure.

The long-term effects of aircraft noise on hypertension, obesity and Type 2 diabetes were investigated using questionnaire and clinical data from a cohort within the Stockholm Diabetes Prevention Program. Aircraft noise exposure was assessed by Geographic Information Systems and based on the participants' residential history. After exclusion of subjects who used tobacco prior to the clinical examinations, the risk of hypertension related to aircraft noise exposure was increased in males (RR per 5 dB(A)  $L_{den}$  1.21; 95% CI 1.05-1.39) but not in females (RR 0.97; 0.83-1.13). Stronger associations were seen among noise annoyed (RR 1.42; 1.11-1.82). Regardless of sex, long-term exposure to aircraft noise also showed statistically significant associations with waist circumference: 0.62 cm (0.54-0.70) per 1 dB(A)  $L_{den}$ . Also, females exposed at  $\geq 50$  dB(A)  $L_{den}$  had a twofold increased risk of Type 2 diabetes, although adjustments for contextual confounding reduced the estimates.

A sub-population of the National Environmental Health Survey 2007 (NEHS07) was used to evaluate the Swedish END maps of road traffic and railway noise. The observed proportion of annoyed subjects was plotted as a function of noise exposure and compared to already established exposure-response functions. Generally, there was a good agreement between observed and predicted proportions of annoyed, suggesting that the noise maps are useful for assessments of residential traffic noise exposure. The best agreement was found when the noise estimates derived from the maps were adjusted for how the dwellings were located within the buildings.

Cross-sectional analyses were performed based on the NEHS07 of associations between neighborhood traffic load,  $L_{den}$  levels of road traffic and railway noise, respectively, and prevalence of self-reported hypertension and cardiovascular disease. Neither traffic load nor road traffic noise was associated with the cardiovascular outcomes; however, there was a borderline significant association between railway noise and cardiovascular disease. Methodological limitations make these results difficult to interpret.

In conclusion, our findings suggest adverse effects of long-term traffic noise exposure on cardiovascular as well as metabolic outcomes. Thus, traffic noise may have detrimental public health effects and research in this area should be prioritized.

## LIST OF PUBLICATIONS

- I. Eriksson C, Rosenlund M, Pershagen G, Hilding A, Östenson CG, Bluhm G. *Aircraft noise and incidence of hypertension*. *Epidemiology* 2007;18(6):716-21.
- II. Eriksson C, Bluhm G, Hilding A, Östenson CG, Pershagen G. *Aircraft noise and incidence of hypertension – Gender specific effects*. *Environmental Research* 2010;110(8):764-72.
- III. Eriksson C, Hilding A, Pyko A, Bluhm G, Pershagen G, Östenson CG. *Long-term effects of aircraft noise on body mass index, waist circumference and Type 2 diabetes*. Manuscript.
- IV. Eriksson C, Nilsson ME, Stenkvist D, Bellander T, Pershagen G. *Residential traffic noise exposure assessment – application and evaluation of European Environmental Noise Directive maps*. *Journal of Exposure Science and Environmental Epidemiology*, 2012, 4 July, 1-8.
- V. Eriksson C, Nilsson ME, Willers SM, Gidhagen L, Bellander T, Pershagen G. *Traffic noise and cardiovascular health in Sweden: The Roadside study*. *Noise & Health*, July-August 2012;14(58):140-47.

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## LIST OF ABBREVIATIONS

ACTH	Adrenocorticotrophic hormone
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CRH	Corticotrophin releasing hormone
CVD	Cardiovascular disease
DALY	Disability adjusted life years
dB	Decibel
DBP	Diastolic blood pressure
EC	European Commission
END	European Environmental Noise Directive
EU	European Union
FBN	A Swedish aircraft noise indicator, weighted by time of day
FHD	Family history of diabetes
GIS	Geographic Information Systems
HPA-axis	Hypothalamic-Pituitary-Adrenal axis
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IHD	Ischemic heart disease
$L_{Aeq,24h}$	Equivalent sound pressure level for 24 hours
$L_{Aeq,16h}$	16h average day-time sound pressure level
$L_{dn}$	Day-night average sound pressure level
$L_{den}$	The EU day-evening-night noise indicator
$L_{night}$	The EU night noise indicator
MI	Myocardial infarction
NEHS07	National Environmental Health Survey 2007
NGT	Normal glucose tolerance
NO <sub>2</sub>	Nitrogen dioxide
OGTT	Oral glucose tolerance test
OR	Odds ratio
PM <sub>10</sub>	Particulate matter with a diameter of 10 micrometer or less
RR	Relative risk
SAM-axis	Sympathetic-Adrenal-Medullary axis
SBP	Systolic blood pressure
SDPP	Stockholm Diabetes Prevention Program
SES	Socioeconomic status
SMHI	Swedish Meteorological and Hydrological Institute
TL	Traffic Load
WHO	World Health Organization

# 1 BACKGROUND

## 1.1 TRAFFIC NOISE

### 1.1.1 Definition, sources and public health impact

Community noise has been defined by the World Health Organization (WHO) as “noise emitted from all sources except noise at the industrial workplace” [1]. The main outdoor sources are traffic noise, i.e. noise from roads, railways and aircrafts, but also industries, construction and public work, and the neighborhood. In a recent mapping of the traffic noise situation within major cities (>250 000 inhabitants) of the European Union (EU), almost 76 million people were estimated to be exposed to daily traffic noise levels exceeding 55 decibels (dB)  $L_{den}$ , which is an EU benchmark for excessive noise (Figure 1) [2]. The dominating source is road traffic with 67 million exposed, followed by railway and aircraft traffic with 5.6 and 3.2 million exposed, respectively. These numbers may, however, be an underestimation of the total number of exposed since the mappings only considered major cities. In Sweden, a nationwide analysis of the traffic noise situation for the year 2006 indicated that approximately two million people are exposed to traffic noise exceeding 55 dB  $L_{Aeq,24h}$ : 1 730 000 to road traffic, 225 000 to railway and 13 000 to aircraft noise [3].

Despite efforts to restrict the exposure, noise pollution is an increasing environmental health problem. The increased urbanization and a continuous growth of the transport sector are the two main reasons [2]. Furthermore, the health impact of noise is multifold, ranging from general annoyance, communication problems and sleep disorders to more severe health endpoints such as cardiovascular disease. In a recent report from the WHO, an attempt was made to quantify the burden of disease from environmental noise through calculations of the number of healthy life years lost in Europe [4]. Based on existing exposure-response relationships, exposure distributions, background prevalence’s of disease and disability weights of the outcome, the number of disability-adjusted life-years (DALYs) were calculated for some specific health effects. Sleep disturbances and annoyance were found to comprise the main disease burden of noise with 903 000 and 654 000 DALYs lost for each of the endpoints respectively. Also ischemic heart disease (IHD) contributed significantly to the disease burden with an estimated 61 000 life years lost.

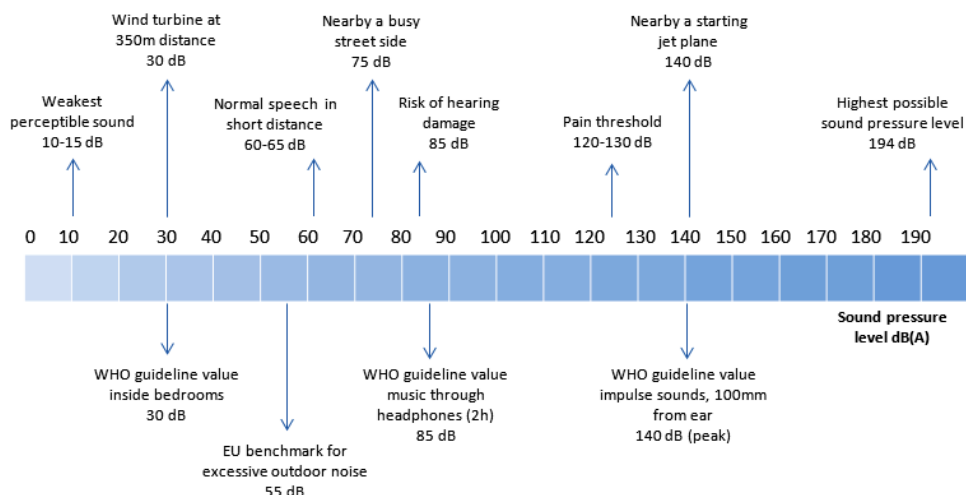


Figure 1. The decibel scale, including some WHO and EU reference values.

### 1.1.2 Former research on cardiovascular and metabolic effects

#### *Cardiovascular disease*

Cardiovascular effects of long-term traffic noise exposure is a relatively novel field of research. A community cardiovascular survey from 1977, investigating the medical effects of aircraft noise around Schiphol airport, Amsterdam, was among the first epidemiological studies to link residential noise exposure to cardiovascular outcomes [5]. In this study, it appeared that in areas with more aircraft noise, more people took cardiovascular drugs and, furthermore, the prevalence of hypertension was increased. In 1989, results from the cross-sectional Luebeck Blood Pressure Study indicated an association between road traffic noise and prevalence of hypertension in men [6]. Males classified as “high exposed” were found to have a 32% increased risk of hypertension in relation to those classified as “low exposed”.

During the last decades, the number of studies investigating cardiovascular outcomes in relation to traffic noise has increased. The main outcomes that have been studied are cardiovascular medication, blood pressure (BP), hypertension and IHD, primarily myocardial infarction (MI). In the WHO Night Noise Guidelines for Europe from 2009, findings from 60 epidemiological studies on traffic noise and cardiovascular outcomes were reviewed [7]. For medication use, it was concluded that the available studies supported the hypothesis of an increased cardiovascular risk in noise-exposed subjects. However, for BP and hypertension, it was stated that there were no consistent patterns in the adult population, although studies on aircraft noise and hypertension tended to show higher risks in exposed areas. With regard to IHD, the available studies did not indicate much of a higher risk for subjects who live in areas with an exposure of less than 60 dB(A), but showed that a higher IHD risk was relatively consistently found amongst the studies for higher noise levels.

Although some of the more recent studies have indicated positive associations [8-12], the overall picture of the research on traffic noise and cardiovascular outcomes appear inconclusive. In particular, there are uncertainties with regard to the estimations of quantitative exposure-response relationships, but also concerning the identification of vulnerable groups, potential gender differences and the interactive effects between noise and air pollution [13]. To a large extent, the apparent inconsistencies of the results among the epidemiological studies on traffic noise and cardiovascular outcomes can be attributed to methodological limitations [4].

In 2009, Babisch and van Kamp made an attempt to derive an exposure-response relationship for the association between aircraft noise and hypertension, based on a meta-analysis of five studies considered reasonably valid (including the results from paper I in this thesis). [14]. A linear trend coefficient of 1.13 (95% CI 1.00-1.28) per 10 dB(A) day-night average sound level ( $L_{dn}$ ) was calculated, however, since there were large methodological differences between the studies, no conclusions regarding possible threshold values could be drawn and the results should be interpreted with caution. Concerning road traffic noise and hypertension, the evidence is not as limited. A meta-analysis from 2012 aggregated data from 24 observational studies in order to derive a quantitative exposure-response association [15]. The results showed a positive



and statistically significant association with an OR of hypertension of 1.034 (95% CI 1.011-1.056) per 5 dB(A) increase in the 16h average noise level ( $L_{Aeq,16h}$ ). With regard to IHD, no exposure-response association has been derived for aircraft noise since there are few available studies. However, in 2010, Huss et al. reported a significantly increased risk of mortality from MI among subjects who had lived 15 years or more in areas exposed to aircraft noise  $\geq 60$  dB(A)  $L_{dn}$  in comparison to those living in areas with noise levels  $< 45$  dB(A); hazard ratio 1.5 (95% CI 1.00-2.2) [9]. For road traffic, a meta-analysis conducted in 2008, pooling data from two descriptive and five analytical studies, revealed an OR for MI of 1.17 (95% CI 0.87-1.57) per 10 dB(A) increase in  $L_{Aeq,16h}$ . [16]. No exposure-response associations have, so far, been derived for railway noise since only a few studies are available [8, 17, 18].

Some groups in the population may be more vulnerable to traffic noise. For example, studies have indicated that elderly people and those who are annoyed by the noise appear to be at a particularly high risk of noise-induced cardiovascular disease [9, 19]. Lifestyle related factors, such as socioeconomic status, smoking, physical activity, job strain and psychosocial distress, may also be of importance but the evidence of their modifying effects is limited. In addition, noise sensitivity and attitudes towards the noise source have been suggested to modify the effect of noise [20, 21]. Potential gender differences in noise effects have been studied to some extent but no clear patterns have emerged: some investigations suggest an effect predominately among males [17-19, 22, 23], others observe higher risks among females [12, 24, 25], and yet others do not detect any differences between the sexes [10, 17, 26-28]. Clearly, these uncertainties make further investigation important.

Noise and air pollution have both been hypothesized to increase the risk of cardiovascular disease, although generally through different mechanisms. While noise is believed to prompt a physiological stress response, air pollution may induce vascular and systemic inflammation, thereby promoting atherosclerosis and thrombosis [29, 30]. Because noise and air pollution largely stem from the same source (road traffic), they are likely to be correlated. However, the size of the correlation can vary substantially, depending for example on the air pollutants being studied, the methods of assessment (measurements versus modeling) and study area characteristics (rural versus urban structure) [31, 32]. Separate assessments of both exposures, as well as of their correlation, are vital in order to disentangle their effects. However, relatively few studies have considered both exposures jointly [8-10, 12, 26, 28].

Many of the studies on traffic noise and cardiovascular health have suffered from methodological limitations, for instance relating to study design, power, exposure and outcome assessments and residual confounding. There is an apparent lack of large-scale longitudinal studies with objective and standardized assessments of both the exposure and outcomes, as well as with a careful adjustment for potential confounding factors. Additionally, few studies have adjusted for contextual confounding, such as neighborhood socioeconomic status. Area-based socioeconomic factors may constitute strong confounders in studies on environmental factors and health [33] and could thus have biased previous findings.

### *Metabolic outcomes*

Metabolic effects of long-term traffic noise exposure have so far not been investigated systematically. No previous longitudinal studies are available, however, two cross-sectional studies have considered metabolic parameters in relation to aircraft noise [25, 34]. Matsui et. al. found significant *decreases* of lipid concentrations with an increase of aircraft noise level among 29 000 residents living around military airfields in Okinawa, Japan [34]. Contradicting findings was found in the study by Rhee et. al. [25], investigating the effect of military aircraft noise on the prevalence of hypertension, where a higher prevalence of Type 2 diabetes were reported among subjects exposed to fighter jet noise than in a control group. The exposed group also had a significantly higher BMI, but there were no differences in other metabolic related outcomes, such as fasting glucose or total cholesterol.

Although the epidemiological evidence of an effect of noise exposure on metabolic outcomes is virtually non-existing, there are clear biological mechanisms for a possible detrimental effect of noise on the metabolic system (see section 1.4 below) which motivates an expansion of the research in this area.

### **1.1.3 The European Environmental Noise Directive (END)**

In 2002, a new directive on noise was issued by the European Commission (EC), relating to the assessment and management of environmental noise [35]. This is often referred to as the European Environmental Noise Directive (END). The aim was to define a common approach intended to avoid, prevent or reduce the harmful effects of exposure to environmental noise, in the Directive defined as traffic and industrial noise, and to provide a basis for developing community measures to reduce noise emitted by the major sources. In practice, the Member States were obliged to determine the exposure to environmental noise through noise mappings by common assessment methods [36], ensure that the information on environmental noise and its effects were made available to the public, and adopt action plans based on the noise mappings to prevent and reduce the noise exposure. The END also issued a request for the use of common noise indicators; the  $L_{den}$  (the A-weighted 24-hour equivalent continuous sound pressure level, with an addition of 5 dB for evening noise events and 10 dB for night-time noise events) and  $L_{night}$  (the A-weighted long-term night sound pressure level); although, the Member States were allowed to use existing national noise indicators until the use of common assessment methods for the determination of the END indicators were made available.

The first phase of the strategic noise mappings were reported to the EC in 2007, and related to mappings of agglomerations with more than 250 000 inhabitants, major roads with more than six million vehicle passages per year, major railways with more than 60 000 train passages per year, and major airports within the territories [35]. In Sweden, noise mappings were performed in three cities, Stockholm, Gothenburg and Malmö, and additionally, around major roads, railways and airports. A second wave of mappings shall be reported during 2012 and relates to all agglomerations with more than 100 000 inhabitants, roads with more than three million vehicle passages per year and railways with more than 30 000 passages per year. Additionally, to enhance the reliability and comparability of noise data in Europe, the EC is advancing the

preparation of common noise assessment methods by developing common noise assessment methods in EU [37].

Because of the standardized methodology, the END noise maps could provide valuable exposure information in noise and health research. Previous epidemiological studies on traffic noise and cardiovascular outcomes have used various and disparate methods to assess noise exposure [7]. Often, national calculation models and local noise indicators have been used. Also, the quality and accuracy of input traffic data have differed, resulting in difficulties to compare the findings. Implementation of the standardized END maps in epidemiologic research on noise and health could remedy some of the difficulties; however their usefulness for assessment of residential traffic noise exposure needs to be systematically evaluated.

## **1.2 CARDIOVASCULAR DISEASE**

Cardiovascular diseases (CVD) include diseases of the heart, vascular diseases of the brain and diseases of blood vessels [38]. Many of the CVDs are due to atherosclerosis, which is a thickening of the artery wall caused by an accumulation of fatty materials such as cholesterol. Atherosclerosis is a complex process that develops over many years. Fatty deposits (plaque) cause the inside surface of the vessels to become irregular and narrow, which makes it harder for blood to flow through. Consequently, the vessels become stiffer, resulting in raised blood pressure. Built-up fatty deposits on the inner walls of blood vessels may cause a blockage, preventing the blood from flowing to the heart and brain. Alternatively, the plaque can rupture and trigger the formation of a blood clot which may lead to a thrombosis. CVDs caused by atherosclerosis include ischemic heart disease or coronary artery disease (e.g. MI), cerebrovascular disease (e.g. stroke) and diseases of the aorta and arteries, including hypertension and peripheral vascular disease. Other CVDs include congenital heart disease, rheumatic heart disease, cardiomyopathies and cardiac arrhythmias.

CVDs are the leading cause of death and contribute to one third of the global mortality [38]. In 2008, the WHO estimated that 17.3 million people died from CVDs, 7.3 million of these were due to coronary heart disease and 6.2 million were due to stroke. Counted as DALYs, the CVDs account for 151 377 million life years lost. Over 80% of the CVD deaths occur in low- and middle-income countries with an almost equal distribution between men and women. A prognosis from the WHO indicates that CVDs will remain the leading cause of death, and by 2030, almost 23.6 million people will die from these diseases. In Sweden, however, the risk of dying from a heart disease almost halved between 1987 and 2006, and the trend persists [39]. The decline in CVD mortality is primarily caused by improved treatment methods, but may also be attributed to a reduced risk of falling ill, which in turn may be related to a lower prevalence of smoking as well as a lowering of both blood lipids and blood pressure. Still, however, CVDs are the most common cause of death in Sweden, accounting for 42% of the annual deaths.

Risk factors for atherosclerosis, as well as CVD, are divided into behavioral, metabolic and other risk factors [38]. The four most important behavioral risk factors are tobacco use, physical inactivity, unhealthy diet (rich in salt, fat and calories), and harmful use of

alcohol. The metabolic risk factors include raised blood pressure (hypertension), raised blood sugar (diabetes), raised blood lipids (e.g. cholesterol) and overweight or obesity. Poverty or low educational status, age, gender, genetic predisposition and psychological factors, such as stress or depression, are amongst the other risk factors.

Hypertension is a highly prevalent risk factor for CVD and is becoming an increasingly common health problem [40]. Between 1980 and 2008, the worldwide number of people with uncontrolled hypertension rose from 600 million to nearly one billion [41], and the overall prevalence of hypertension in adults ( $\geq 25$  years) is estimated to approximately 40%. Furthermore, hypertension is estimated to cause 7.5 million annual deaths, which accounts for 57 million DALYs [38]. The risk increase of CVD starts already at a BP of 115/75 mmHg, however, the definition of hypertension grade 1 (i.e. mild hypertension), is systolic blood pressure (SBP) 140-159 and/or diastolic blood pressure (DBP) 90-99 mmHg. Subsequently, hypertension grade 2 (“moderate”) is defined as SBP 160-179 and/or DBP 100-109 mmHg, and hypertension grade 3 (“severe”) equals SBP  $\geq 180$  and/or DBP  $\geq 110$  mmHg [42]. In the Swedish adult population ( $\geq 20$  years), 1.8 million people (27%) are estimated to have a high blood pressure. Of these, 60% have mild, 30% moderate and 10% severe hypertension [43]. In general, Swedish studies show a reduction in mean BP, which mainly can be attributed to improved treatment methods, and possibly, changes in the salt intake [39].

### 1.3 OBESITY AND TYPE 2 DIABETES

#### *Obesity*

Overweight and obesity is defined by the WHO as “abnormal or excessive fat accumulation that may impair health” [44]. Generally, it is caused by an energy imbalance between the calories consumed and the calories expended. An often used measure of generalized overweight and obesity is the body mass index (BMI), calculated as a person’s weight in kilograms divided by the squared height ( $\text{kg/m}^2$ ). BMI may be used on population level to monitor trends of overweight and obesity over time, but should be used with caution on an individual level because it does not distinguish between factors such as sex, age, ethnicity or body composition. The definition of overweight is a BMI  $\geq 25$  and the definition of obesity is a BMI  $\geq 30$ . Other measures of overweight and obesity include waist circumference or the waist-hip ratio, which are measures of centralized, or abdominal, obesity [45]. These indices are correlated with BMI but the level of association varies, suggesting that they provide partly different information and thus are not exchangeable. Both waist circumference and the waist-hip ratio have been associated with an increased risk of CVD, Type 2 diabetes and overall mortality. Since the waist and hip circumferences are specific to populations with different body size, ethnic or country-specific cutoffs have been established. According to the WHO, the waist circumference cutoffs for the European population related to an *increased risk* of metabolic complications are  $>94$  cm for males and  $>80$  cm for females. Cutoffs associated with a *substantially increased risk* of metabolic complications are  $>102$  cm and 88 cm for males and females, respectively. For the waist-hip ratio, the cutoffs for a *substantially increased risk* of metabolic complications are  $\geq 0.90$  for males and  $\geq 0.85$  for females [45].

Obesity is rising steadily around the world and has more than doubled since 1980 [44]. In 2008, the WHO estimated that more than 1.4 billion adults ( $\geq 20$  years) were overweight, and of these, over 500 million were obese (200 million men and 300 million women). Thus, more than 10% of the world's population suffers from obesity. The main reasons for this global increase are changes in dietary habits and physical activity patterns. An increasing intake of energy-dense foods, which are high in fat, salt and sugars but low in vitamins, minerals and micronutrients, in combination with a decreased physical activity have led to an epidemic like increase in the number of overweight and obese persons. Each year, approximately 2.8 million adults die as a result of overweight or obesity, which makes it the fifth leading cause of death. Furthermore, overweight and obesity accounts for and a large proportion of the overall global disease burden, because of its relation to diseases such as diabetes, IHD and cancer. In the Swedish population, half of all males and a third of the females are overweight [39]. Approximately 10% are obese.

### *Type 2 diabetes*

Diabetes is an endocrine disease which is characterized by elevated levels of blood glucose, either because of a reduced production of insulin from the pancreas (Type 1 diabetes) or because of a combination of a reduced sensitivity to insulin in the tissues and an impaired secretion of insulin (Type 2 diabetes) [46]. The hormone insulin is produced in the pancreas and plays a crucial role in glucose regulation since it signals to the body's muscle and fatty tissues to take up sugar, i.e. glucose, from the blood. Type 2 diabetes is most often a result of an extended period of unhealthy diet and physical inactivity, leading to overweight and obesity. The disease may be undetected for several years since the early symptoms usually are not obvious. Typically, intermediate conditions of impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG) occur in the transition between a normal glucose regulation and manifest Type 2 diabetes. These stages of prediabetes, as well as the manifest disease, can be identified by an oral glucose tolerance test (OGTT) [47]. The OGTT is usually administered in the morning, after an overnight fast, and the person being tested should refrain from using any kind of tobacco or drinking caffeine containing drinks, such as coffee, before or during the test. To estimate levels of plasma glucose, blood sampling is performed before (0h=fasting glucose) and 2h after ingestion of 75g of glucose [48]. Patients are then classified according to the WHO categorization of glucose tolerance, described in *Table 1* below.

**Table 1.** Categorization of glucose tolerance according to the World Health Organisation (WHO 2006). Levels of plasma glucose before (0h=fasting) and 2h after glucose ingestion.

	0h (mmol/l)	2h (mmol/l)
<b>NGT</b>	<6.1	<7.8
<b>IFG</b>	6.1 ≤ glucose <7.0	<7.8
<b>IGT</b>	<6.1	7.8 glucose <11.1
<b>IFG+IGT</b>	6.1 ≤ glucose <7.0	7.8 glucose <11.1
<b>Diabetes</b>	≥7.0 and or...	≥11.1

NGT=Normal Glucose Tolerance. IFG=Impaired Fasting Glucose. IGT=Impaired Glucose Tolerance.

Globally, it is appraised that more than 300 million people have diabetes [46]. The majority of these (90%) have Type 2 diabetes. According to estimates from 2004 made by the WHO, 3.4 million people died from consequences of having high blood sugar and the number is projected to double by 2030. Consequences of diabetes include damage to the heart, blood vessels, eyes, kidneys and nerves and the overall risk of dying among people with diabetes is at least double to those without diabetes; the primary causes of death being heart disease and stroke. The number of people with diabetes in Sweden has been estimated to approximately 365 000 and despite of an unchanged risk of becoming ill, the number of persons with diabetes is increasing [39]. Between 1980 and 2005, the prevalence of diabetes increased from 2.5 to 3.7% among Swedish males and from 2.1 to 2.6% among the females. This increase is believed to be caused mainly by better treatment methods and earlier diagnoses of patients with diabetes, which increases their survival.

To a large extent, diabetes and CVDs share disease etiology, relating to the life-style. In fact, a considerable amount of the disease burden could be prevented by simple life-style measures, such as improvements of diet, increases in the physical activity and reductions of stress, smoking and alcohol. Other risk factors, for example genetic predisposition and social inequalities, may be more difficult to target.

## **1.4 BIOLOGICAL MECHANISMS OF NOISE EFFECTS**

### **1.4.1 “The general stress hypothesis”**

The main biological mechanism underlying cardiovascular and metabolic effects of noise exposure is a physiological stress response [4]. Our hearing system help us to quickly react in dangerous situations. Through its subcortical connections, the auditory system is directly linked to the sympathetic branch of the autonomic nervous system as well as to the endocrine system. These links are always open, even during sleep, and exposure to loud noise may thus trigger a stress response, thereby affecting a number of physiological, metabolic and immunological processes [49-52].

Generally, stress is induced by two different systems, the Sympathetic-Adrenal-Medullary (SAM) axis and the Hypothalamic-Pituitary-Adrenal (HPA) axis [53]. The SAM-axis is primarily triggered during acute stressors and results in the secretion of catecholamines, i.e. adrenaline and noradrenaline, from the adrenal medulla. This mechanism prepares the body for “fight-or-flight”, by mobilizing energy to the muscles, heart and brain and reducing blood flow to the internal organs. The HPA-axis is more involved in the long-term effects of both acute and chronic stress and is characterized by a “defeat reaction”, associated with a lack of control, helplessness and feelings of distress, anxiety and depression. The endocrine response of the HPA-axis stems from hypothalamus which releases various regulatory neuropeptides, e.g. corticotrophin releasing hormone (CRH). CRH activates a cascade of releasing hormones from the pituitary gland, amongst these, the adrenocorticotrophic hormone, ACTH. The target organ for ACTH, in its turn, is the adrenal cortex and from here, the glucocorticoid hormone cortisol is secreted [54, 55].

Over- or under activity in any of these stress systems may be detrimental to health. For example, lasting elevated levels of catecholamines have been shown to contribute to the development of atherosclerosis, thereby increasing the risk for hypertension and IHD [56]. Additionally, because the HPA-axis may continue to be activated long after the stressor has been removed, it is of special interest for long-term cardiovascular and metabolic effects of traffic noise exposure. Cortisol is an important regulatory hormone of the lipid and glucose metabolism and a prolonged dysfunction of its feedback mechanism may result in several health effects, including hypertension, centralization of body fat, dyslipidemia and insulin resistance [54, 55, 57-61].

### **1.4.2 Sleep disturbances**

Cardiovascular and metabolic effects of noise exposure may also be mediated via sleep disturbances [7, 62]. Sleep disturbances are one of the most common complaints related to noise exposure and have major impact on health and general wellbeing. Furthermore, clear exposure-response associations have been established between night-time noise and self-reported sleep disturbance [63]. At a comparable noise level, aircraft noise is associated with more sleep disturbances than road traffic, and road traffic noise is associated with more sleep disturbances than railway noise. However, since road traffic noise is more common, it gives rise to more sleep disturbances in the general population than aircraft or railway noise.

*Immediate effects* of traffic noise on sleep include arousal responses, which are often accompanied by activations of the autonomic nervous system, sleep stage changes, awakenings, body movements and total wake time [4]. Autonomic arousals are transient elevations of the activity of the sympathetic nervous system (described above), leading to increased ventilation, peripheral resistance and blood pressure as well as to alterations of the heart rate [52, 64]. Noise exposure during night has also been shown to affect the awakening cortisol response [61, 65]. In addition, there are *after-effects* of noise exposure during the night, including sleepiness, reduced daytime performance and deterioration of cognitive functions, and *long-term effects*, such as chronic sleep disturbance, influence on inflammatory markers and effects on metabolic and endocrine functions [7].

Several hormones may mediate the association between sleep deprivation and effects on the metabolic system. Two of the most important hormones are leptin and ghrelin, which have opposing functions in the regulation of appetite and energy expenditure [66-68]. Short sleep has been associated with significantly decreased levels of leptin and increased levels of ghrelin, leading to an increased appetite and reduced energy expenditure. Furthermore, sleep debt may also affect the carbohydrate metabolism and has been associated with impaired glucose tolerance [69]. Thus, noise-induced sleep loss may be an important risk factor for several metabolic outcomes, including obesity and Type 2 diabetes.

## 2 OBJECTIVES

### 2.1 OVERALL

The overall objective of this thesis was to investigate the long-term effects of traffic noise exposure on cardiovascular and metabolic outcomes, including hypertension, BMI, waist circumference and Type 2 diabetes. A secondary aim was to apply and evaluate digital noise maps, produced in Sweden in accordance with the END [35], for assessments of residential traffic noise exposure to be used in noise and health research.

### 2.2 STUDY SPECIFIC

- Paper I: To investigate the influence of long-term aircraft noise exposure on the cumulative incidence of hypertension among men.
- Paper II: To investigate gender specific effects of long-term aircraft noise exposure on the cumulative incidence of hypertension.
- Paper III: To investigate the influence of long-term aircraft noise exposure on metabolic outcomes, including BMI, waist circumference, prediabetes and Type 2 diabetes, and to assess the modifying effects of sleep disturbances.
- Paper IV: To apply and evaluate Swedish END maps for assessments of residential traffic noise exposure.
- Paper V: To investigate cardiovascular effects of living near noisy roads and railways, and to elucidate the modifying effects of air pollution.



## 3 METHODS

### 3.1 THE STOCKHOLM DIABETES PREVENTION PROGRAM

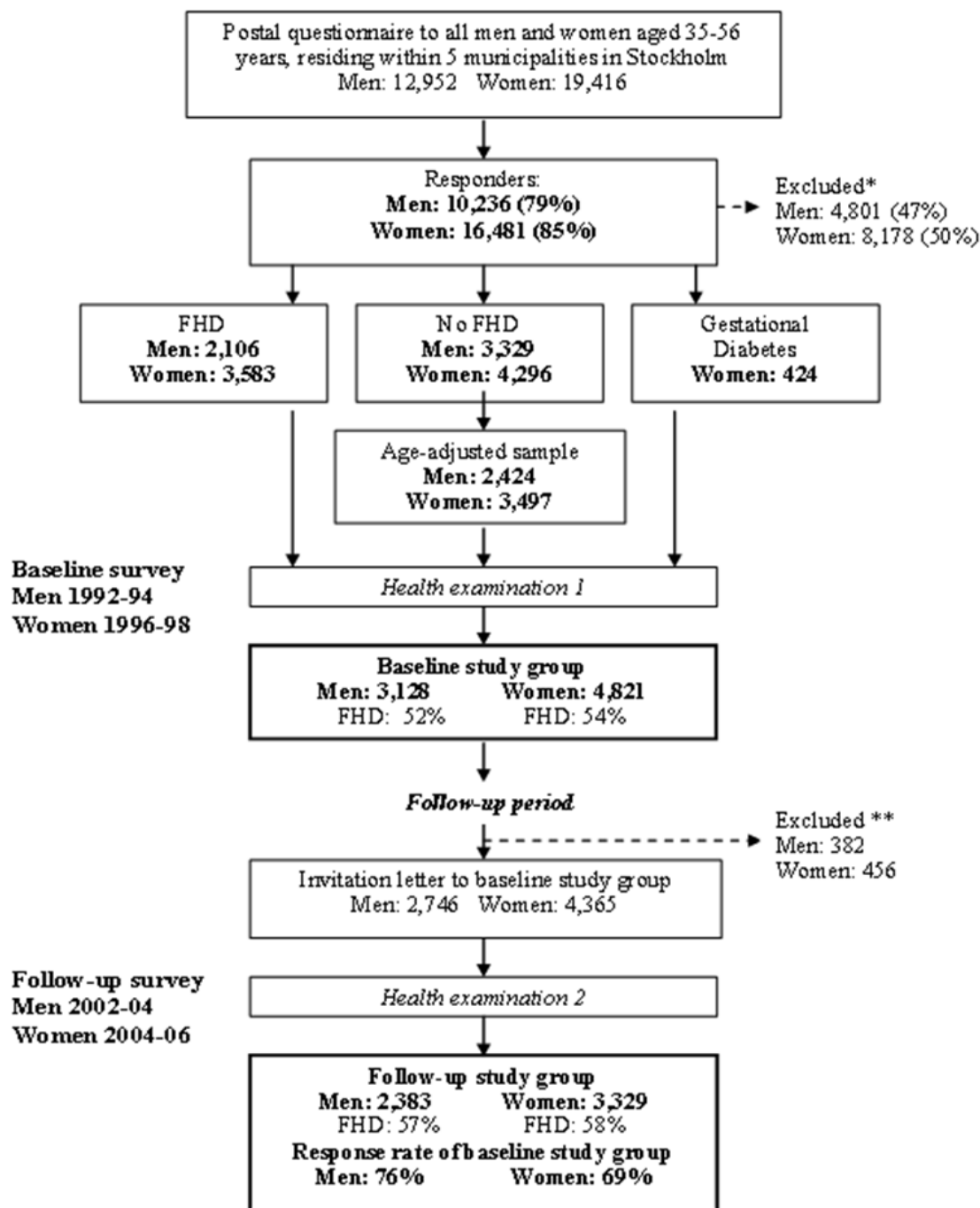
The first three papers of this thesis are cohort studies based on a diabetes preventive intervention study, the Stockholm Diabetes Prevention Program (SDPP). SDPP was performed in five municipalities in Stockholm County between 1992 and 2006 [70]. The aim of the program was to study risk factors for Type 2 diabetes as well as to suggest and implement actions to prevent the disease. Community based interventions were performed in three of the municipalities: Sigtuna, Upplands Väsby (women only) and Värmdö. The preventive measures were primarily focused on three factors of importance for the developments of Type 2 diabetes: diet, physical activity and overweight. The remaining two municipalities, Upplands Bro and Tyresö, served as reference group.

#### 3.1.1 Study population

At the initial stage of the SDPP, all men and women aged 35 to 56 years living in the five municipalities (n=32 368) were sent a short postal questionnaire asking about their family history of diabetes (FHD) (*Figure 2*). FHD was defined as known diabetes in at least one first-degree relative (mother, father, sister or brother) or at least two second-degree relatives (grandparents, uncle or aunt). Of the respondents, all subjects with a positive FHD (n=5 689) together with an age-adjusted sample of those without diabetes heredity (n=5 921) and, additionally, women with gestational diabetes (n=424) were invited to a baseline survey. However, subjects with already known diabetes, a foreign origin or an unclear or insufficient family history of diabetes were excluded. Of the 12 034 subjects who were invited, 7 949 responded (3 128 men and 4 821 women). These constitute the baseline-study group.

The baseline survey was performed between 1992 and 1994 for men and between 1996 and 1998 for women. Each participant answered an extensive questionnaire and took part in a clinical health examination. Eight to ten years later, the participants were invited to a follow-up survey. Some subjects were, however, not contacted again (including those who had been diagnosed with diabetes at the baseline examination, had moved outside of Stockholm County or were deceased), thus resulting in 7 111 invited subjects. The follow-up survey followed the same procedures as at baseline and included a total of 5 712 subjects (2 383 men and 3 329 women).

The number of participants who were invited to and took part in the follow-up survey differs between paper I and II due to some late corrections of the SDPP database. The corrections all relate to the exclusion criteria; for example, a change in the definition of diabetes during the study period led to additional exclusions of ten males who should have been classified with Type 2 diabetes at baseline.



**Figure 2.** Design of the Stockholm Diabetes Prevention Program.

\*Excluded due to already known diabetes, foreign origin, unclear or insufficient family history of diabetes (FHD). \*\*Excluded due to diagnosis of diabetes at baseline examination, moved outside of Stockholm County, or deceased.

Paper I included only males since data on females were not available at the time. Our study population was restricted to 2 027 subjects who finalized both surveys, had complete exposure data (see below), were not treated for hypertension, and had a blood pressure below 140/90 mmHg at enrollment (65% of baseline study group).

Paper II was designed to assess potential gender differences and thus included both men and women. The same restrictions of the cohort as in paper I was made, although slightly stricter with regard to hypertension. Subjects with no treatment for hypertension but missing data on blood pressure (BP) at baseline were excluded. Similarly, subjects with no diagnosis of hypertension but missing data on BP at the follow-up examination were also excluded. In total, our study group included 4 851 subjects, 1 989 men and 2 862 women (64% and 59%, respectively, of the baseline groups).

In paper III, we restricted the analyses to subjects who completed both surveys, had complete exposure data and had a normal glucose tolerance at baseline. This included 5 411 subjects, 2 213 men and 3 198 women (71% and 66%, respectively, of the baseline study groups).

### **3.1.2 Assessment of exposure**

For subjects living near Stockholm Arlanda Airport, we assessed residential aircraft noise exposure using Geographic Information Systems (GIS). The assessments were based on residential history of our participants and address data were obtained from the Swedish Population Register as well as through information in the questionnaires. Subject with missing or unclear address information for a time-period of five years or more were excluded.

The addresses were sent to the Swedish mapping, cadastral and land registration authority and geocoded through matching with the national Real Property Register. The coordinates were delivered in the Swedish national reference system at the time, RT90 2.5GonV. A few of the addresses ( $n=60$ ) could not be matched to the register (mainly farms without a proper street address) and for these, we performed a manual assessment using a GPS (Garmin personal navigator GPS 72, accuracy 10m). Ten addresses were not possible to locate and were therefore excluded.

The data on aircraft noise exposure differed between the first and the two following studies. For paper I, we obtained exposure data based on air traffic statistics for 1997 from the Swedish Civil Aviation Administration, current LFV-group, Swedish Airport and Air Navigation Services (*Figure 3*). The noise levels were estimated by the Swedish aircraft noise calculation model, SWERIM [71], and is expressed as time-weighted equal energy levels, FBN (the Swedish standard aircraft noise indicator used at the time), and as maximum noise levels. In principal, the FBN is based on the 24-hour equivalent sound pressure level ( $L_{Aeq,24h}$ ), weighted by time of day, i.e. with evening noise events (07.00<sub>PM</sub> – 10.00<sub>PM</sub>) multiplied by a factor 3 (equivalent to 4.8 dB) and night-time noise events (10.00<sub>PM</sub> – 07.00<sub>AM</sub>) by a factor 10 (equivalent to 10 dB). The maximum aircraft noise levels are based on the maximum sound pressure level ( $L_{Amax}$ ) occurring at least three times during the average 24-h period in one year.

The FBN levels were provided in 5 dB resolution, ranging from 50 to 65 dB(A). Each address was superimposed on the map and classified in one of five exposure categories: <50 (reference category), 50-55, 55-60, 60-65 and >65 dB(A). For participants with more than one address (approximately 25%), we estimated a linear time-weighted exposure. Only three participants were classified in the highest exposure group and were therefore included in the 60-65 category. In total, 411 subjects (20% of the total population) were exposed to FBN levels equal to or above 50 dB(A) during the study period.

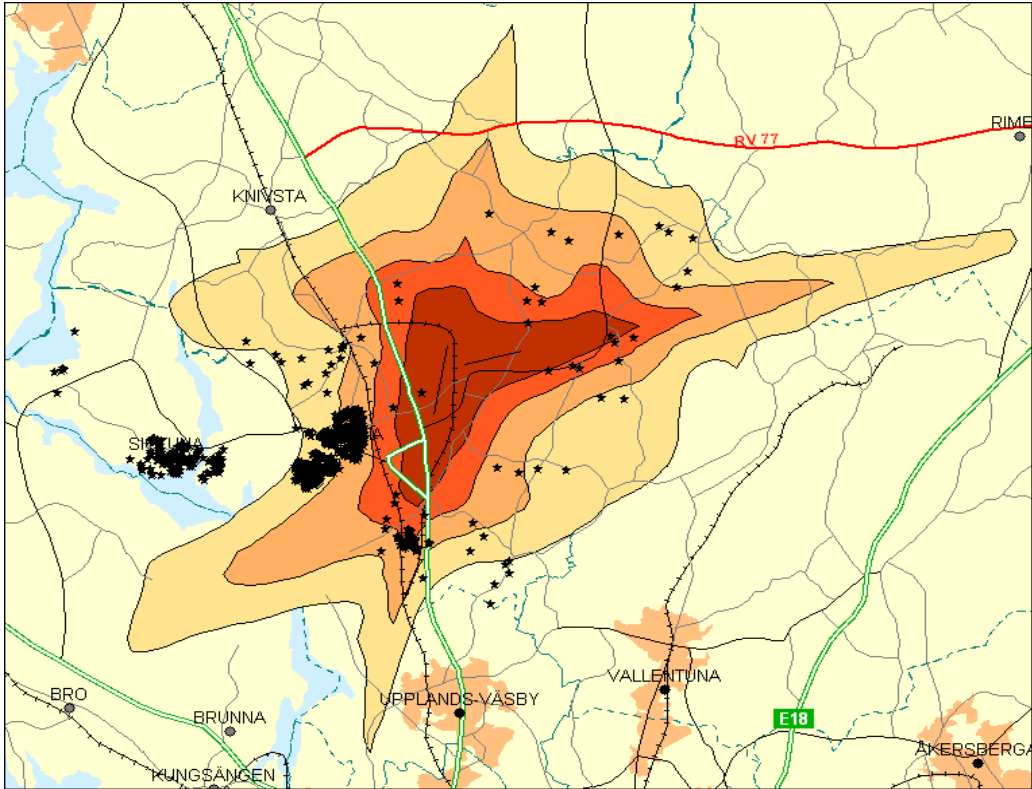
The assessment of maximum aircraft noise levels followed the same procedure. Noise levels were provided in 1 dB resolution with the range 70 to 85 dB(A) and each address was classified in one of the categories <70 (reference category), 70-72, 73-75 and >75 dB(A). A total of 311 subjects (15%) were exposed to maximum aircraft noise levels equal to or above 70 dB(A).

In paper II and III, we aimed at enhancing the comparability with other studies by applying an internationally approved model for aircraft noise calculations, the Integrated Noise Model version 6.1 [72], and by using a standardized indicator of exposure, the  $L_{den}$  [35].  $L_{den}$  is defined as the A-weighted 24-hour equivalent continuous sound pressure level, with an addition of 5 dB for evening noise events (In Sweden defined as the period 19.00-23.00 hours) and 10 dB for night-time noise events (In Sweden: 23.00-07.00 hours). Due to a slight difference in the weighting of the evening noise events, the  $L_{den}$  level differs from the FBN with approximately 1 dB.

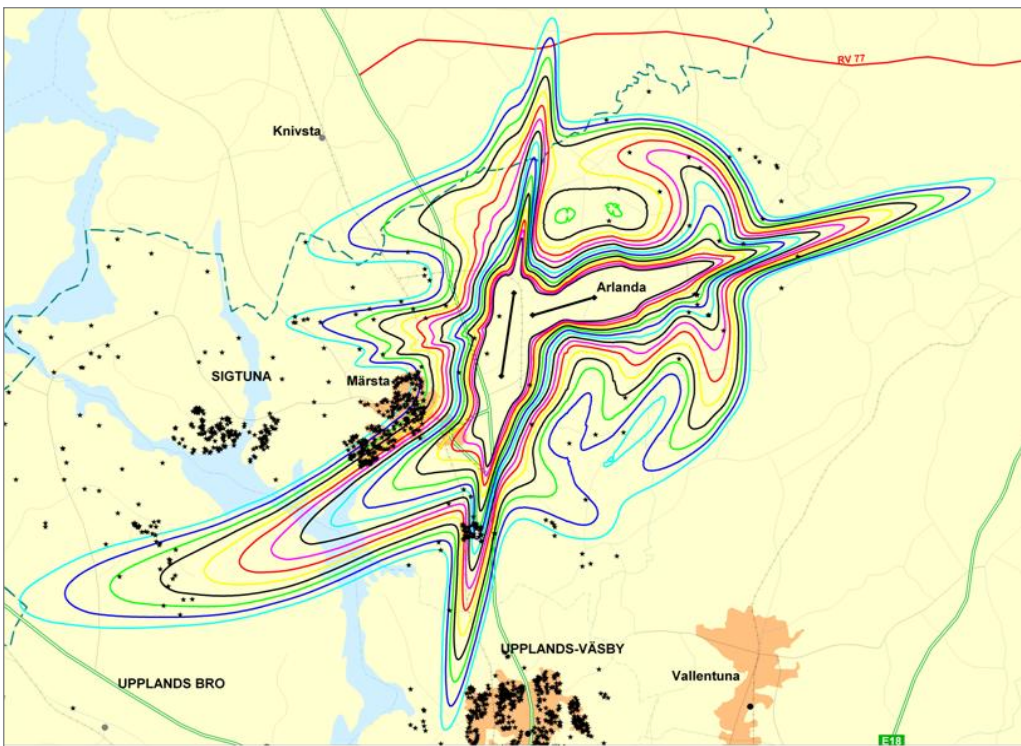
Furthermore, we also aimed to account for a decline in the noise exposure which occurred at Arlanda during the latter part of the study period as a consequence of the introduction of new quieter aircrafts. We therefore used the average noise level between 1997 and 2002 as an indicator of exposure for the complete study period (*Figure 4*). The estimates were based on radar tracks from 2002 and several adjustments were made according to the prevailing traffic situation for the time-period of interest, mainly concerning aircraft types, flight routes and runway distribution. Some additional changes occurred in 2003 when a third runway was opened, altering the flight patterns. However, these changes have not been taken into account since they occurred late during the study period.

The  $L_{den}$  levels were provided in 1 dB resolution ranging from 50 to 65 dB(A). Each subject was assigned their exact exposure level and further classified in one of four categories: <50 (reference category), 50-54, 55-59 and  $\geq 60$ . In total, 605 subjects were exposed to  $L_{den}$  levels  $\geq 50$  dB(A), 294 men and 311 women, corresponding to 13% of the total population. Exposure to road traffic and railway noise was not assessed objectively but only as self-reported noise annoyance.

The exposure assessments for aircraft noise were made using MapInfo Professional, version 9.0.



**Figure 3.** Study participant addresses and average aircraft noise propagation around Stockholm Arlanda Airport for year 1997, FBN 50-65 dB(A).



**Figure 4.** Study participant addresses and average aircraft noise propagation around Stockholm Arlanda Airport for the time-period 1997-2002,  $L_{den}$  50-65 dB(A).

### 3.1.3 Assessment of outcome

In paper I and II, the primary outcome was cumulative incidence of *hypertension* from baseline to follow-up. Paper III investigated metabolic outcomes, including difference in *BMI* and *waist circumference* and cumulative incidence of *prediabetes* and *Type 2 diabetes* from baseline to follow-up.

The outcome assessments were based on the questionnaires as well as on the clinical examinations. The questionnaire focused on health (hearing, cardiovascular, psychosocial), lifestyle (tobacco use, diet, alcohol consumption, physical activity), work-related issues (education, occupation, shift-work, job strain) and social contacts (relationships, personal interests, life-events). The follow-up questionnaire also included questions on noise annoyance, from road, rail, aircraft, ventilation and neighbors, and noise sensitivity (three grade scale). The health examinations were carried out by trained nurses at a primary healthcare centre and included measurements of blood pressure, weight, height, waist and hip circumferences, as well as an OGTT. The examinations were carried out in the morning and all participants were asked to refrain from eating or using any kind of tobacco from 10<sub>PM</sub> the night before examination.

In paper I and II, we defined subjects as cases if they had been diagnosed with hypertension by a physician during the study period, or, if they had SBP  $\geq 140$  mmHg and DBP  $\geq 90$  mmHg at the follow-up examination. Blood pressure was measured once, in a sitting position after about five minutes rest, with a triple cuff hand aneroid sphygmomanometer, Conformité Européenne, CEO123 (Welch Allyn, NY, USA). The cut-off for blood pressure was set in accordance with the World Health Organization's definition of hypertension grade I [73].

In paper III, the anthropometric measurements (weight, height, waist and hip) were carried out with the participants wearing light clothes and no shoes. For each individual, BMI was calculated as the weight divided by the squared height ( $\text{kg/m}^2$ ). The OGTT was performed in order to identify subjects prediabetes as well as manifest Type 2 diabetes. Levels of plasma/serum glucose (mmol/l) were measured before (i.e. fasting glucose) and two hours after glucose ingestion and the categorization was made according to the WHO criteria (Table 1) [47]. The participants were defined as having prediabetes if they had an IFG and/or IGT at the follow-up examination and as having Type 2 diabetes if they had been diagnosed with diabetes by a physician during the study period, or, if they were detected with diabetes at the follow-up examination.

### 3.1.4 Statistical analyses

Differences in background characteristics according to level of exposure were investigated by Chi-square tests for categorical variables and Student's t-test or one-way ANOVA for continuous variables in all three papers.

In paper I and II, associations between aircraft noise and cumulative incidence of hypertension were assessed through relative risks (RR) and 95% confidence intervals (95% CI), using binomial regression models with the log-link function [74-76]. In a few instances, the model did not converge and we then used log-Poisson models, which

provide consistent but not fully efficient estimates of the RR and its CI [77]. Analyses were performed both for the population as a whole and for a sub-population, excluding participants who, contrary to instructions, had smoked or used snuff prior to or during the blood pressure measurements.

Aircraft noise was included in the models both in the categorized form and dichotomized. Potentially important confounders were identified from previous literature. In paper I, these included age (5-year age groups), BMI (<25, 25-30 and >30 kg/m<sup>2</sup>), FHD (negative or positive), glucose tolerance (normal or impaired/diabetes), smoking (never, former and current), physical activity (sedentary/low or moderate/high), annoyance due to noise from other sources (annoyed or not annoyed), and socioeconomic status (SES) based on occupation (low, medium, high) [78]. In paper II, we included all of the above covariates, except glucose tolerance, and additionally shift work (yes or no), alcohol intake (tertiles of total consumption: low, medium and high) and hormone replacement therapy in combination with menopause status for women (pre-menopause, post menopause without hormone replacement therapy and post menopause with hormone replacement therapy). Moreover, the use of moist snuff (snus) was combined with smoking into the variable ‘tobacco use’ (never, former and current). Analyses of effect modification were performed in order to identify potentially vulnerable groups. All covariates mentioned above, and additionally aircraft noise annoyance in paper II, were included in the regression models using interaction terms with the binary exposure variable (<50 vs. ≥50 dB(A)). Wald-tests were used to assess the statistical significance of the interaction terms.

In paper III, we used ordinary linear regression models, estimating regression coefficients (b) and 95% CIs, to assess the associations between aircraft noise and changes in BMI as well as waist circumference. Both outcomes were modeled as the difference between baseline and follow-up and adhered to normal distributions. Associations between aircraft noise and cumulative incidence of prediabetes, Type 2 diabetes and the combination of them both were analyzed using logistic regression models, estimating odds ratios (OR) and 95% CIs.

Aircraft noise was included in the models both as a continuous variable in steps of 1 dB(A), ranging from 47 to 65, and, to account for non-linearity, categorized in three groups (<50, 50-54 and ≥55 dB(A)). Furthermore, we also assessed risk estimates using a binary exposure variable with a cut-off at 50 dB(A).

In this study, we accounted for individual-based as well as area-based confounders. The individual characteristics that were assessed include sex, age (35-39, 40-44, 45-49, 50-55 years), family history of diabetes (Negative or Positive), SES based on occupation (Manual workers, Low-level non-manual workers, Medium and high level non-manuals, and Self-employed and farmers), physical activity (Low, i.e. sedentary lifestyle, Moderate, i.e. occasional exercise, and High, i.e. regular exercise or training), tobacco use (Never, Former and Current smoking or use of moist snuff), alcohol (tertiles of total alcohol consumption: Low, Medium, and High) and annoyance due to noise from other sources, including road, rail or occupational noise (Not annoyed, i.e. seldom/never or a few times per month, or Annoyed, i.e. a few times per week or every day). Furthermore, we also assessed job strain and psychological distress. Job strain

was based on the Swedish version of the Karasek & Theorell demand-decision latitude questionnaire [79, 80]. From the questions, two indices for work related demands and decision latitude were created that were further categorized in tertiles. Job strain was defined as the highest tertile of demand together with the lowest tertile of decision latitude. A similar index was created for psychological distress which was assessed from questions on anxiety, apathy, depression, fatigue and insomnia [81]. This index was categorized in quartiles.

Sleep disturbances (Not disturbed, i.e. never or seldom, or Disturbed, i.e. sometimes or often) and BMI ( $<25$ ,  $25-29$  and  $\geq 30$  kg/m<sup>2</sup>) were considered as possible intermediate factors in the causal pathway between noise exposure and the outcomes and were therefore not included as confounders. We did, however, investigate their relation to the outcomes in the regression modeling, simultaneously adjusting for all other covariates.

Contextual confounding was assessed in terms of area-based mean income (yearly) and proportion of unemployed (%), using data from Statistics Sweden. The analyses were performed using random effects models, clustering on so called “small areas for market statistics”. These areas are selected to be homogenous with respect to socioeconomic characteristics and our five municipalities included 139 such areas.

All of the above mentioned individual-based covariates, and additionally aircraft noise annoyance (Not annoyed, i.e. never/seldom or a few times per month, or Annoyed, i.e. a few times per week or every day), were also investigated with regard to effect modification. The covariates were included in the models as interaction terms with the binary exposure variable ( $<50$  vs.  $\geq 50$  dB(A)), using a Wald-test to assess statistical significance. These results were not adjusted for contextual confounding.

### **3.1.5 Combined analyses**

With the intention of summarizing the long-term effects of aircraft noise exposure on cardiovascular and metabolic health, we performed additional analyses combining four different outcomes. These were 1) *hypertension* (physician diagnosis during the study period or a BP  $\geq 140/90$  mm Hg at follow-up), 2) *generalized obesity* (BMI  $\geq 30$  kg/m<sup>2</sup>), 3) *abdominal obesity* (waist circumference  $\geq 102$  cm for men and 88 cm for women), and 4) *prediabetes or Type 2 diabetes* (physician diagnosis during the study period or identified via the OGTT at follow-up). The cut-offs for BMI and waist circumference were set in accordance with WHO recommendations [45]. Subjects were classified as cases if they developed at least one of the four outcomes during the study period.

The analyses were restricted to subjects who had complete exposure data and were free of the above mentioned diseases at baseline (n=4 182). Relative Risks and 95% CI:s were estimated by log-Poisson models and adjusted both for individual-based and area-based confounders.

All analyses were performed using the statistical software STATA (StataCorp LP, College Station, Texas, USA); IC version 8.0 (paper I), IC version 8.2 (paper II) and SE version 11.0 (paper III).

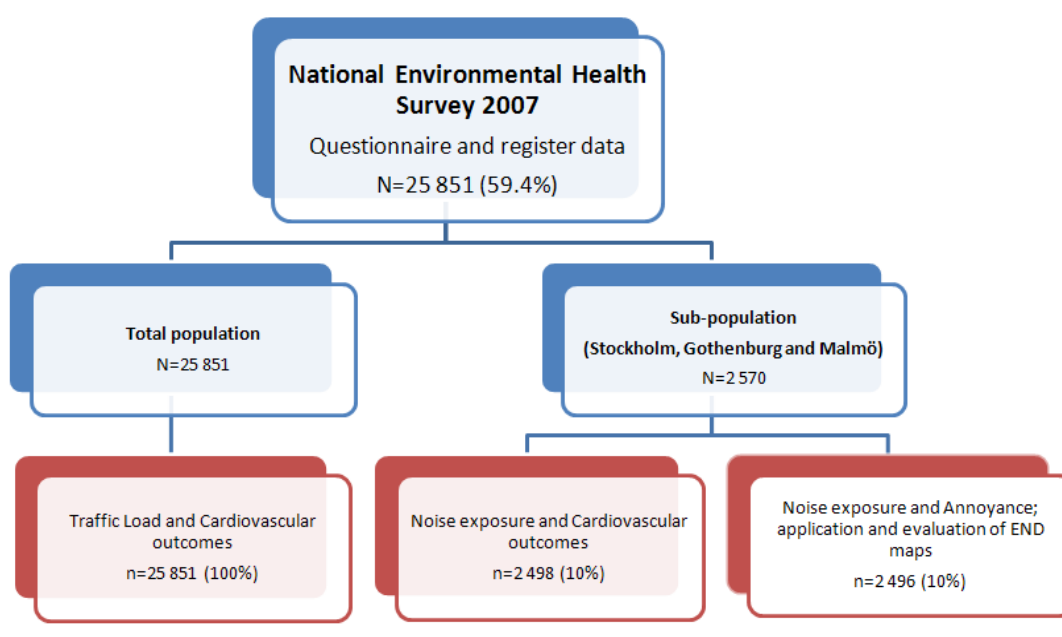


## 3.2 THE NATIONAL ENVIRONMENTAL HEALTH SURVEY 2007

### 3.2.1 Study population

Paper IV and V are based on a National Environmental Health Survey which was performed in Sweden during 2007, the NEHS07 (*Figure 5*). The participants were selected randomly, in two steps, from the Register of the Total Population. Initially, and to assure a good representation of all parts of the country, 500 individuals were sampled from each of the 21 counties in Sweden. The second part consisted of an enriched selection in ten counties, including a total of 33 405 individuals. All in all, questionnaires were sent to 43 905 Swedish adults in the ages 18-80 years who had lived in Sweden for at least five years. The survey was answered by 25 851 subjects (59.4%) and for these, we obtained additional information on residential address coordinates, country of birth, income and education from registers held by Statistics Sweden.

The study population in Paper IV consisted of a sub-population of the NEHS07, including participants from the three largest cities in Sweden: Stockholm, Gothenburg and Malmö. These cities have been mapped according to the first phase of the END [35] which enabled a detailed noise exposure assessment. In total, 2 570 subjects were included: 1 242 from Stockholm, 1 072 from Gothenburg and 256 from Malmö. In paper V, the total population of the NEHS07 (n=25 851) as well as the sub-population was used.



**Figure 5.** Design of paper IV (Noise exposure and annoyance; application and evaluation of END maps) and V (Traffic Load respectively noise exposure and cardiovascular outcomes).

### 3.2.2 Assessment of exposure

For the purpose of paper IV (and subsequently also for paper V), we assessed the exposure to  $L_{den}$  levels of road traffic and railway noise, respectively, at the residential address of the participants of the sub-population. The assessments were performed both manually and through an automatic procedure, using GIS and digital END maps from Stockholm, Gothenburg and Malmö.

Noise maps and local technical reports were retrieved from the Environment Health Administrations in each city. Additional digital background data, such as city borders, roads, railways and buildings, were obtained from the local Offices of Urban Development. The cities used different consulting firms for the noise mappings (Ingemansson Technology AB, WSP and Acoustic Control AB), and as a result, various software and reference systems had been used. Noise levels were calculated using CadnaA (DataKustik GmbH in Munich, Germany), SoundPlan (SoundPLAN International LLC) or MapNoise (WSP). To harmonize the data, we converted the noise maps and background information to the Swedish national reference system at the time (RT90 2,5 GonV). Data management and exposure assessments were performed in ArcGIS Desktop (9.3.1) and MapInfo Professional (9.0).

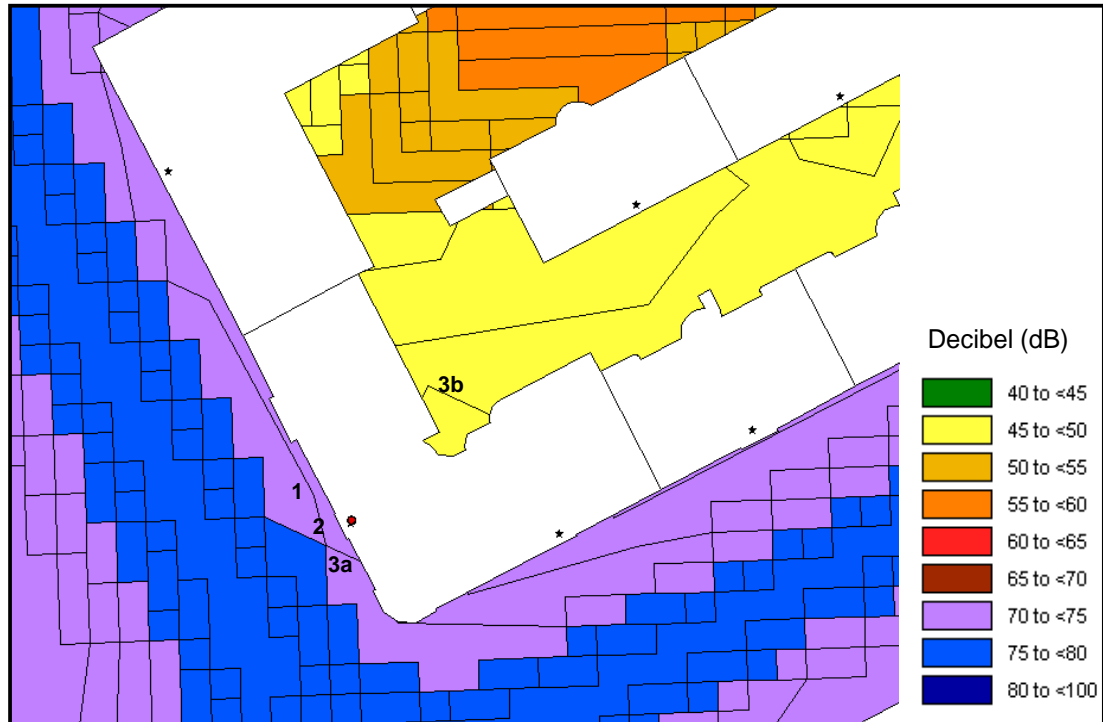
To estimate the residential noise exposure manually, we superimposed address coordinates for the 2 570 participants on the noise maps for road and railway traffic, respectively. The coordinates were then linked to buildings, around which the noise exposure was assessed. Subjects whose address could not be linked to a building were excluded,  $n=74$  (3%), thus resulting in a final population of 2 496 subjects.

For each participant, we assessed the  $L_{den}$  levels of road traffic and railway noise at three different geographical points: 1) at the most exposed façade of the building, 2) at the exact address point, and 3) at the most exposed façade of the dwelling. These are referred to as the “building”, “address” and “dwelling” estimates in the following text (*Figure 6*). The dwelling estimate was based on visual inspection of the noise maps together with survey data on the dwelling’s orientation in relation to the nearby environment. The following survey question was used to locate dwellings within apartment buildings, allowing for more than one answer:

*“Does your residence have a window facing... (a) larger street or traffic route; (b) local street; (c) railway (including subway, trams etcetera); (d) industry or industrial area; (e) inner yard or back yard; (f) garden or park; (g) nature (forest, lake, meadow or open field); (h) other than listed, what?”.*

The automated method was based on scripts, written in MapInfo Professionals programming language MapBasic (version 9.0). This procedure required some adjustments of the noise maps as well as creation of 2m wide buffer zones around buildings and address points. The highest and lowest noise level within the buffer zones were selected and stored in result tables. Only building and address estimates were assessed since we did not develop a procedure for including survey data on dwelling orientation.

For both methods, the  $L_{den}$  levels were recorded in 5-dB categories, ranging from  $<45$  to  $\geq 75$  dB.



**Figure 6.** Example showing geographical points used for assessing noise exposure at an address, indicated by the red dot: 1) Building=70-75 dB; 2) Address =70-75 dB; 3a) Dwelling, windows towards street=70-75 dB; 3b) Dwelling, windows towards inner yard=45-50 dB.

For the total sample in paper V, we also assessed exposure to Traffic Load (TL=traffic flow  $\times$  road length) within a 500 m radius around each participant's residential address. TL was estimated by the Swedish Metrological and Hydrological Institute (SMHI) and is expressed in millions of vehicle kilometers per year (Mvkm/y). Data on traffic flows and length of road segments were available in the Swedish National Road Database which includes information on all major private, municipal and state owned roads. TL was recorded on a continuous scale, ranging from 0 to 69.28 Mvkm/y.

Furthermore, the SMHI also assessed average concentrations of residential air pollution. Receptor based local, urban, regional and total concentrations of nitrogen dioxide (NO<sub>2</sub>) and particulate matter with diameter less than 10 micrometer (PM<sub>10</sub>) were calculated by dispersion modeling using the SIMAIR system [82]. The urban contribution was calculated on a grid with a spatial resolution of 1x1 km<sup>2</sup>, while the local traffic NO<sub>2</sub> and PM<sub>10</sub> contributions were simulated directly at the residence address coordinate as the summed impact from all traffic line sources within a radius of 250 m.

### 3.2.3 Assessment of outcome

The NEHS07 included questions on health and annoyance in relation to various environmental factors, such as noise annoyance evoked by road and railway traffic. In paper IV, we compared the observed and predicted proportions of annoyed and highly annoyed residents as a function of  $L_{den}$  exposure, using data on noise annoyance from the survey questionnaire in conjunction with established exposure-response relationships for transportation noise annoyance [63, 83]. Annoyance was scaled using the 5-point category format proposed by ISO [84] and based on the question

*“Thinking about the last 12 months, in or near your home, how much are you disturbed or annoyed by noise or other sounds from...b) road traffic, c) railway traffic (subway, tram etcetera)”.*

Subsequently, we classified noise annoyance as the proportion *annoyed* or *highly annoyed* individuals, using the cut-off definitions proposed by Miedema and Oudshoorn [85, 86].

The main outcomes of paper V, self-reported hypertension and CVD, were based on two binary questions in the survey:

- 1) *“Have you been diagnosed with hypertension by a physician?”*, and
- 2) *“Do you have, or have you had, any of the following diseases: f... cardiovascular disease?”*

Additionally, we assessed the associations with general health, noise annoyance and sleep disturbances. General health was assessed using a five grade scale, ranging from “very good” to “very bad”. We classified subjects as having a *poor health* if they reported “bad” or “very bad” health. Noise annoyance was based on the same 5-point question as in paper IV; however, subjects were classified as *annoyed* if they reported being “much” or “very much” annoyed by noise. Sleep disturbances were assessed through two four graded questions regarding difficulties of falling asleep and awakenings during the night (every week, year around; every week, parts of the year; seldom; never). Subjects were classified as *sleep disturbed* if they reported either difficulties of falling asleep or awakenings “every week, year around”, or “every week, parts of the year”.

### 3.2.4 Statistical analyses

To evaluate the agreement between the building, address and dwelling estimates in paper IV, we assessed Cohen's kappa coefficient ( $\kappa$ ) and calculated the pairwise differences between the estimates, presented as the number (and proportion) of complete matches in 5 dB categories as well as within  $\pm 5$ , 10 and  $\geq 15$  dB. To compare the observed and predicted proportions of annoyed and highly annoyed residents, as a function of  $L_{den}$  exposure, we calculated the root mean square deviation (rms) between predicted and observed proportions of annoyed residents.

In paper V, differences in the distribution of background characteristics, diseases and complaints according to level of exposure were assessed by the Pearson's Chi-square test for categorical variables and the student's t-test for continuous variables. Furthermore, we applied logistic regression models to assess prevalence Odds Ratios (OR) and 95% CIs for the associations between the exposures and outcomes.

TL was modeled in quintiles and as a binary variable, using the lowest quintile as reference group. In the sub-population, road traffic and railway noise were categorized in five exposure groups,  $L_{den} < 50$ , 50-54, 55-59, 60-64 and  $\geq 65$  dB, however, for railway noise, the two highest noise categories were collapsed since there were few subjects exposed at  $\geq 65$  dB. Furthermore, we also dichotomized the traffic noise variables, with a cutoff at 50 dB.

Confounding was investigated using a backward variable selection technique. Tested factors included sex (male; female), age (continuous), education (elementary school; upper secondary school; university), country of birth (Sweden; other), smoking (never; former; current), exposure to air pollution (local, regional, urban and total concentrations of  $NO_2$  and  $PM_{10}$ ) and region (Scania; South East and Gotland; West; Mälardalen; Stockholm; Central; North). Effect modification was assessed through inclusion of interaction terms between the binary exposure variables and the covariates of interest in the multivariate model, including sex, age (18-39; 40-59;  $\geq 60$  years), education, smoking, number of years at residence ( $< 5$ ;  $\geq 5$  years), noise exposure at the bedroom side (yes; no), noise annoyance (yes; no) and air pollution (quartiles of total  $NO_2$  and  $PM_{10}$ ). Furthermore, we also assessed correlations between TL, concentrations of  $NO_2$  and  $PM_{10}$  and road traffic noise by Pearson's correlation coefficient ( $r$ ).

The analyses were conducted using STATA SE version 11.0.

## 4 RESULTS

In the following, results from the articles are summarized for each study separately. In addition, some new analyses were conducted for the long-term effects of aircraft noise, combining outcome data on hypertension, BMI, waist circumference and diabetes. These are presented in section 4.3 below.

### 4.1 AIRCRAFT NOISE AND HYPERTENSION

The results in paper I are based on analyses of 2 020 males who had complete data on confounding factors (age and BMI). Among these, we identified 626 cases of hypertension, corresponding to a cumulative incidence of 31% during the follow-up (*Table 2*). In the group exposed to aircraft noise levels  $\geq 50$  dB(A) FBN, the cumulative incidence was 35%, which in comparison to the cumulative incidence of 30% in the reference group yielded an adjusted RR of 1.19 (95% CI 1.03-1.37). An analysis of the risk increase per 5 dB(A) FBN resulted in an adjusted RR of 1.10 (95% CI 1.01-1.19). Similar results were also found using the maximum noise level; RR 1.10 (95% CI 1.02-1.19).

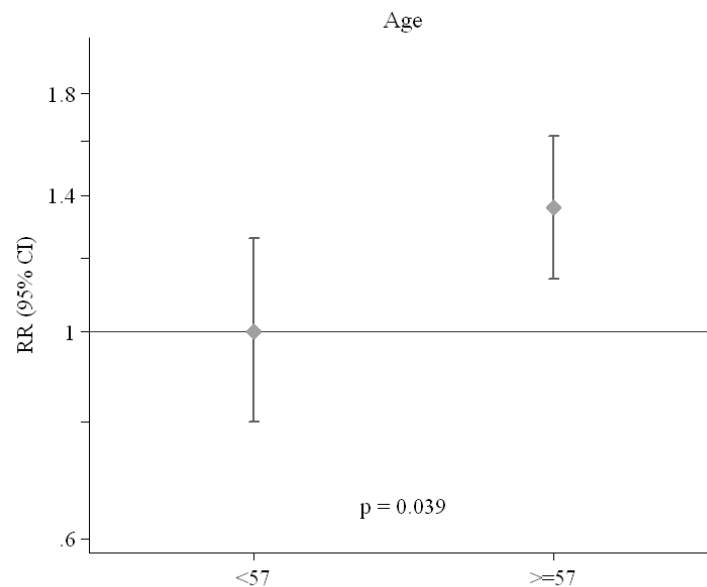
**Table 2.** Association between aircraft noise exposure and cumulative incidence of hypertension among men in the Stockholm Diabetes Prevention Program.<sup>a</sup>

Noise exposure	No.	No. with hypertension	Crude		Adjusted <sup>b</sup>	
			RR <sup>c</sup>	95% CI	RR <sup>c</sup>	95% CI
Energy averaged noise level						
Continuous (per 5 dB(A))			1.11	1.02–1.21	1.10	1.01–1.19
Dichotomous						
<50 dB(A)	1610	478	1.00	-	1.00	-
$\geq 50$ dB(A)	410	148	1.22	1.05–1.41	1.19	1.03–1.37
Maximum noise level						
Continuous (per 3 dB(A))			1.11	1.02–1.21	1.10	1.02–1.19
Dichotomous						
<70 dB(A)	1709	513	1.00	-	1.00	-
$\geq 70$ dB(A)	311	113	1.21	1.03–1.43	1.20	1.03–1.40

<sup>a</sup>Based on subjects with complete data on exposure and confounding variables. <sup>b</sup>Adjusted for age and BMI. <sup>c</sup>RR=Relative Risk.

After exclusion of the participants who had smoked or used snuff prior to or during the clinical examination, the study population comprised 1 582 subjects. Generally, stronger estimates were indicated in this group. For example, the RR among those exposed to aircraft noise levels  $\geq 50$  dB(A) FBN was 1.29 (95% CI 1.11-1.50) and the risk increase per 5 dB was 1.15 (95% CI 1.05-1.25).

The analyses of effect modification did not indicate any interactive effects except for age. Males who were 57 years or older had a significantly higher increased risk of hypertension when exposed to noise levels  $\geq 50$  dB(A) FBN in comparison to younger males: RR 1.36 (95% CI 1.14-1.62) and 1.00 (95% CI 0.80-1.26), respectively (*Figure 7*). There were also tendencies of increased risks among subjects with normal glucose tolerance (RR 1.29; 95% CI 1.10-1.52), never smokers (RR 1.33; 95% CI 1.10-1.62) and those who were not annoyed by noise from other sources (RR 1.27; 95% CI 1.09-1.48), although the interaction terms were not statistically significant ( $p < 0.05$ ) for these factors.



**Figure 7.** Relative risk for hypertension associated with aircraft noise exposure  $\geq 50$  dB(A) FBN among males below and equal to or above the mean age of 57 years (bars indicating 95% CI).

In paper II, the total population for analyses included 4 721 subjects (1 945 men and 2 776 women) after exclusion of those with missing data on the confounding variables (age, SES, BMI and tobacco use). The corresponding number for the subpopulation, excluding those who used tobacco prior to our during the clinical examination, was 3 902 subjects (1 423 men and 2 479 women).

In this study, we did not observe an increased risks for hypertension in relation to aircraft noise when analyzing men and women jointly; the RR being 1.02 (95% CI 0.90-1.15) for those exposed to  $L_{den}$  levels  $\geq 50$  dB(A) in comparison to the reference group (*Table 3*). However, after stratification for sex, there was a tendency towards an increased risk among males but not among females.

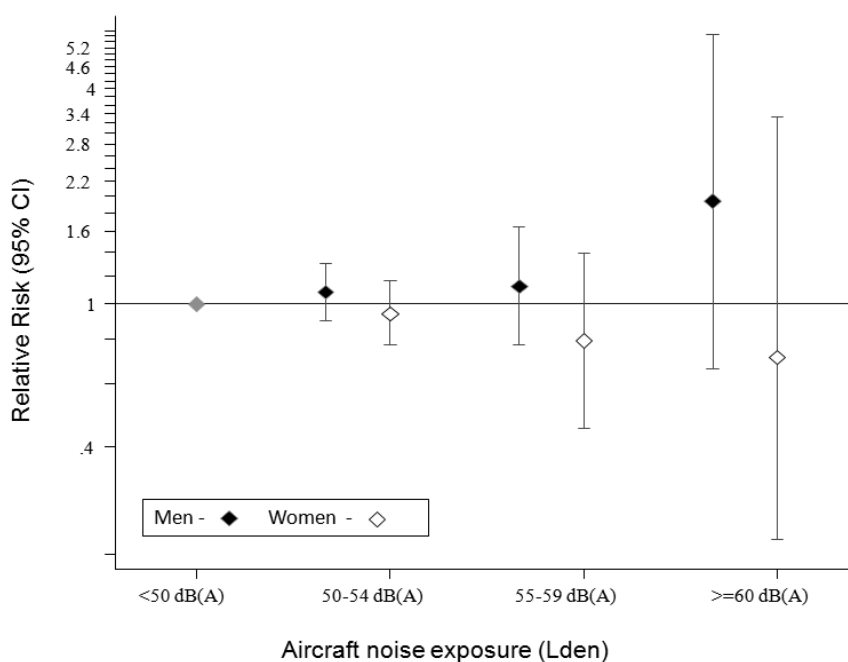
**Table 3.** Aircraft noise exposure and cumulative incidence of hypertension among men and women from five municipalities in Stockholm.

dB(A) <sup>b</sup>	Total (n=4721 <sup>a</sup> )				Men (n=1945 <sup>a</sup> )				Women (n=2776 <sup>a</sup> )			
	No.	No. with hypertension	RR <sup>c</sup>	(95% CI)	No.	No. with hypertension	RR <sup>c</sup>	(95% CI)	No.	No. with hypertension	RR <sup>c</sup>	(95% CI)
Dichotomous												
<50	4128	1169	1.0	-	1653	510	1.0	-	2475	659	1.0	-
≥50	593	177	1.02	(0.90-1.16)	292	99	1.09	(0.92-1.29)	301	78	0.92	(0.76-1.11)
Categorical												
50-54	492	148	1.04	(0.90-1.19)	243	81	1.08	(0.90-1.30)	249	67	0.94	0.77-1.16
55-59	87	25	0.96	(0.70-1.32)	44	16	1.12	(0.77-1.64)	43	9	0.79	(0.45-1.39)
≥60	14	4	0.99	(0.70-2.14)	5	2	1.94	(0.66-5.65)	9	2	0.71	(0.22-3.33)
Continuous (per 5 dB(A))	-	-	1.01	(0.91-1.11)	-	-	1.08	(0.95-1.23)	-	-	0.92	(0.79-1.07)

<sup>a</sup>Excluding subjects with missing data on confounding variables. <sup>b</sup>Aircraft noise levels measured in L<sub>den</sub>; the A-weighted 24-hour equivalent continuous sound pressure level, using the EU standard weights plus 5 dB for evening noise events (19.00-23.00) and plus 10 dB for night time noise events (23.00-07.00). <sup>c</sup> RR=Relative Risk, adjusted for age, socioeconomic index, smoking and body mass index.

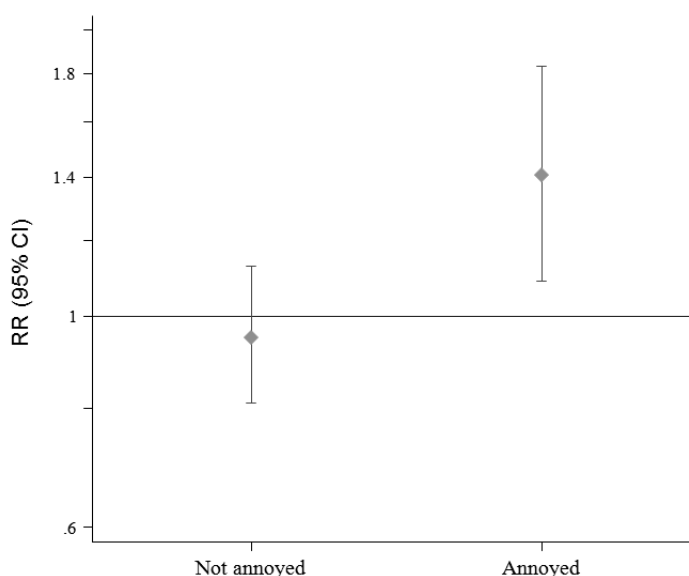


After exclusion of subjects who used tobacco prior to or during the blood pressure measurements, there was a statistically significant risk increase per 5 dB(A)  $L_{den}$  among males: RR 1.21 (95% CI 1.05-1.39). No such exposure-response association was observed for females: RR 0.97 (95% CI 0.83-1.13) (*Figure 8*).



**Figure 8.** Relative risk of hypertension associated with different levels of aircraft noise exposure ( $L_{den}$ ) among males and females (bars indicating 95% CI).

Due to limited power, effect modification was only assessed for the population as a whole. Aircraft noise annoyance was the only factor that significantly modified the effect of the exposure ( $p=0.01$ ). The RR for hypertension related to aircraft noise exposure  $\geq 50$  dB(A)  $L_{den}$  among subjects reporting annoyance was 1.42 (95% CI 1.11-1.82), and 0.91 (95% CI 0.77-1.07) among those not reporting annoyance (*Figure 9*).



**Figure 9.** Relative risk for hypertension associated with aircraft noise exposure  $\geq 50$  dB(A)  $L_{den}$  among not annoyed and annoyed males and females (bars indicating 95% CI).

## 4.2 AIRCRAFT NOISE, OBESITY AND TYPE 2 DIABETES

In paper III, the cohort for analyses included 5 156 subjects (2 091 males and 3 065 females) after additional exclusions of subjects with missing data on confounders (sex, age, FHD, SES, physical activity, tobacco use and psychological distress). Additionally, 28 subjects had missing data on BMI and 22 on waist circumference, resulting in populations of 5 128 and 5 134 subjects, respectively.

The mean increase in BMI between baseline and follow-up was 1.10 kg/m<sup>2</sup> (standard deviation 1.99), and for waist circumference it was 4.40 cm (standard deviation 6.45). In total, we identified 434 cases of prediabetes and 172 cases of Type 2 diabetes during the study period, corresponding to cumulative incidences of 8% and 3%, respectively.

Long-term aircraft noise was associated with a 0.03 kg/m<sup>2</sup> increase in BMI between baseline and follow-up per 1 dB rise in L<sub>den</sub> (Table 4). However, there was no clear exposure-response relationship, and after additional adjustments for contextual confounding, no statistically significant associations were found.

Waist circumference was significantly associated with aircraft noise in all models, showing an increase of 3.61 cm (95% CI 3.10 to 4.12) among those exposed ≥50 dB(A) compared to the reference group. The estimate was reduced but remained statistically significant after adjustments for contextual confounding; 1.70 cm (95% CI 0.93 to 2.47). Furthermore, an exposure-response association was present (b<sub>per dB</sub>=0.38, 95% CI 0.25-0.50; b<sub>50-54 dB</sub>=1.63, 0.82-2.44; and b<sub>≥55 dB</sub>=1.94, 0.45-3.43).

**Table 4:** Linear regression coefficients (b) for the association between aircraft noise exposure and body mass index respectively waist circumference among participants in the Stockholm Diabetes Prevention Program, assessed by ordinary linear regression.

Aircraft noise exposure (L <sub>den</sub> <sup>a</sup> )	BMI <sup>b</sup> (n=5 128)	Waist circumference <sup>c</sup> (n=5 134)
	<b>b (95 % CI)</b>	<b>b (95 % CI)</b>
Continuous, per dB(A)	0.03 (0.01 – 0.06)	0.60 (0.52 – 0.70)
Continuous, per dB(A) <sup>d</sup>	0.03 (0.00 – 0.05)	0.62 (0.54 – 0.70)
Categorical, dB(A) <sup>d</sup>		
<50	0.00	0.00
50-54	0.17 (-0.01 – 0.35)	3.64 (3.08 – 4.20)
≥55	0.04 (-0.33 – 0.40)	3.48 (2.34 – 4.62)
Dichotomous, dB(A) <sup>d</sup>		
<50	0.00	0.00
≥50	0.15 (-0.02 – 0.31)	3.61 (3.10 – 4.12)
Dichotomous, dB(A) <sup>e</sup>		
<50	0.00	0.00
≥50	0.05 (-0.15 – 0.25)	1.70 (0.93 – 2.47)

<sup>a</sup>L<sub>den</sub>: the A-weighted 24-hour equivalent continuous sound pressure level, with an addition of 5 dB for evening noise events (In Sweden defined as the period 19.00-23.00 hours) and 10 dB for night time noise events (In Sweden: 23.00-07.00 hours). <sup>b</sup>Difference in Body Mass Index (kg/m<sup>2</sup>) from baseline to follow-up. <sup>c</sup>Difference in waist circumference (cm) from baseline to follow-up. <sup>d</sup>Model adjusted for sex, age, family history of diabetes, socioeconomic status, physical activity, tobacco use and psychological distress. <sup>e</sup>Model additionally adjusted for area level mean income (yearly) and unemployment (%).

The analyses of associations between aircraft noise and cumulative incidence of prediabetes and Type 2 diabetes did not indicate any increased risks in the overall population. The OR for prediabetes and Type 2 diabetes combined was 0.95 (95% CI 0.73 to 1.23) for those exposed at  $\geq 50$  dB(A)  $L_{den}$  in comparison to the reference group when adjusting for the individual-based confounders, and 0.87 (95% CI 0.64 to 1.18) in the fully adjusted model (data not shown).

Stratifying for sex, there was, however, a twofold statistically significant increased risk of Type 2 diabetes among the noise exposed women when adjusting for the individual-based confounders (Table 5). Additionally, there was a tendency towards a positive exposure-response association. No increased risks were seen for men and after additional adjustments for contextual confounding, the estimates for women were reduced and no longer statistically significant.

**Table 5:** Odds Ratio (OR) for the associations between aircraft noise exposure and cumulative incidence of Type 2 diabetes among males and females in the Stockholm Diabetes Prevention Program, assessed by logistic regression.

Aircraft noise exposure ( $L_{den}$ <sup>a</sup> )	Type 2 diabetes <sup>b</sup>	
	Males (n=1 855) OR (95% CI)	Females (n=2 889) OR (95% CI)
Continuous, per dB(A)	0.98 (0.89-1.08)	1.11 (1.01-1.21)
Continuous, per dB(A) <sup>c</sup>	0.97 (0.88-1.07)	1.09 (0.99-1.20)
Categorical, dB(A) <sup>c</sup>		
<50	1.00	1.00
50-54	0.96 (0.52-1.78)	1.82 (0.86-3.85)
$\geq 55$	0.33 (0.05-2.50)	2.85 (0.82-9.92)
Dichotomous, dB(A) <sup>c</sup>		
<50	1.00	1.00
$\geq 50$	0.85 (0.47-1.53)	2.00 (1.03-3.90)
Dichotomous, dB(A) <sup>d</sup>		
<50	1.00	1.00
$\geq 50$	0.72 (0.37-1.40)	1.68 (0.83-3.40)

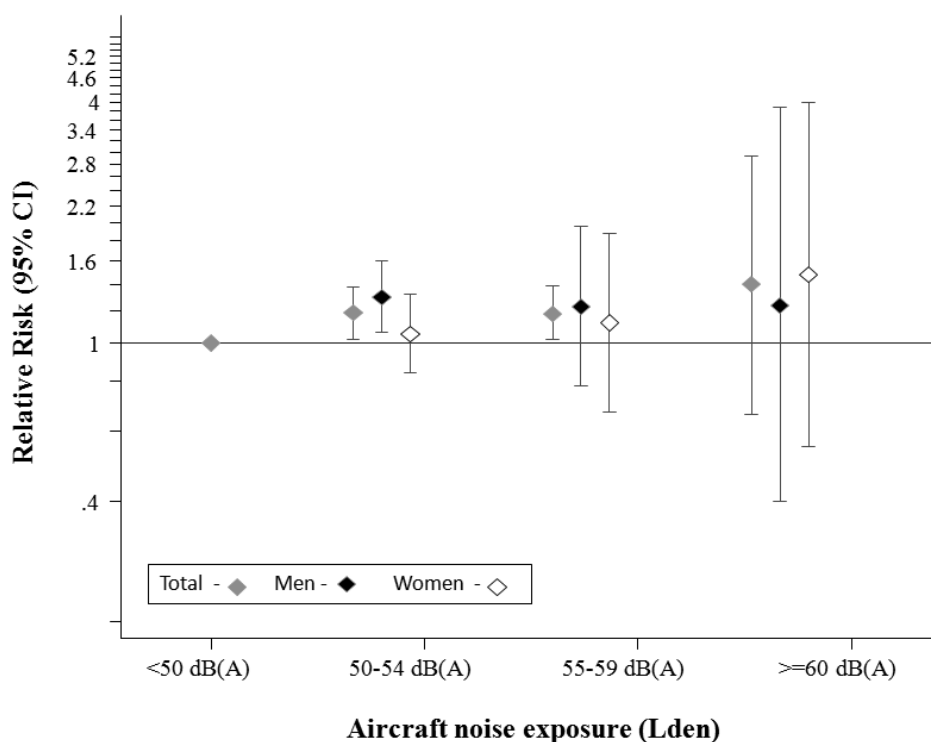
<sup>a</sup>  $L_{den}$ : the A-weighted 24-hour equivalent continuous sound pressure level, with an addition of 5 dB for evening noise events (In Sweden defined as the period 19.00-23.00 hours) and 10 dB for night time noise events (In Sweden: 23.00-07.00 hours). <sup>b</sup> Physician diagnosis during the study period or identified at follow-up. <sup>c</sup> Model adjusted for sex, age, family history of diabetes, socioeconomic status, physical activity, tobacco use and psychological distress. <sup>d</sup> Model additionally adjusted for area level mean income (yearly) and unemployment (%).

The analyses of effect modification showed no statistically significant results. However, for BMI and waist circumference, interaction was suggested between aircraft noise and job strain ( $p=0.093$  and  $0.086$ , respectively). The increase in BMI for subjects exposed at  $\geq 50$  dB(A) was  $0.14 \text{ kg/m}^2$  (95% CI  $-0.04$  to  $0.31$ ) for those with low job strain and  $0.60 \text{ kg/m}^2$  (95% CI  $0.09$  to  $1.10$ ) for those reporting high job strain. Corresponding increases for waist circumference was  $3.50 \text{ cm}$  (95% CI  $2.95$  to  $4.05$ ) and  $4.98 \text{ cm}$  (95% CI  $3.38$  to  $6.58$ ), respectively. As reported above, females seemed to be at higher risk for Type 2 diabetes than males following noise exposure  $\geq 50$  dB(A) ( $p=0.060$ ). Furthermore, physical activity was suggested to modify the effect of aircraft noise exposure on the risk of prediabetes and Type 2 diabetes ( $p=0.051$ ). Subjects exposed to aircraft noise  $\geq 50$  dB(A) with a high physical activity had a significantly reduced risk of prediabetes and Type 2 diabetes, OR= $0.50$  (95% CI  $0.26$  to  $0.94$ ), to be compared with an OR of  $1.43$  (95% CI  $0.76$  to  $2.70$ ) among the sedentary.

Sleep disturbances were not significantly related to any of the outcomes and did not seem to modify the effects of aircraft noise exposure. BMI, on the other hand, was associated with prediabetes as well as Type 2 diabetes, but the risk estimate for aircraft noise did not change significantly after its inclusion in the model.

### 4.3 COMBINED ANALYSES ON AIRCRAFT NOISE

In the combined analyses, the cohort for analyses included 4 012 subjects (1 667 males and 2 345 females) after exclusion of subjects with missing data on confounders (age, FHD, SEI, physical activity and alcohol). In total, 1 566 subjects were classified as cases since they had at least one of the four outcomes hypertension, generalized obesity, abdominal obesity or prediabetes/Type II diabetes. This corresponded to a cumulative incidence of 39%. Of the 1 566 subjects classified as cases, 491 (31%) had at least two outcomes, 136 (9%) had at least three outcomes and 26 (2%) had all outcomes. In the group exposed to aircraft noise levels  $\geq 50$  dB(A)  $L_{den}$ , the cumulative incidence was 46% which in comparison to the cumulative incidence of 38% in the reference group yielded an adjusted RR of 1.19 (95% CI 1.04-1.37). The risk increase per 5 dB(A)  $L_{den}$  of having one of the four outcomes was statistically significant for males (RR 1.19; 95% CI 1.03-1.37) but not for females (RR 1.07; 95% CI 0.92-1.25) (Figure 10). Additional adjustments for contextual confounding (mean income and unemployment clustered on area-level) did not influence the risk estimates.



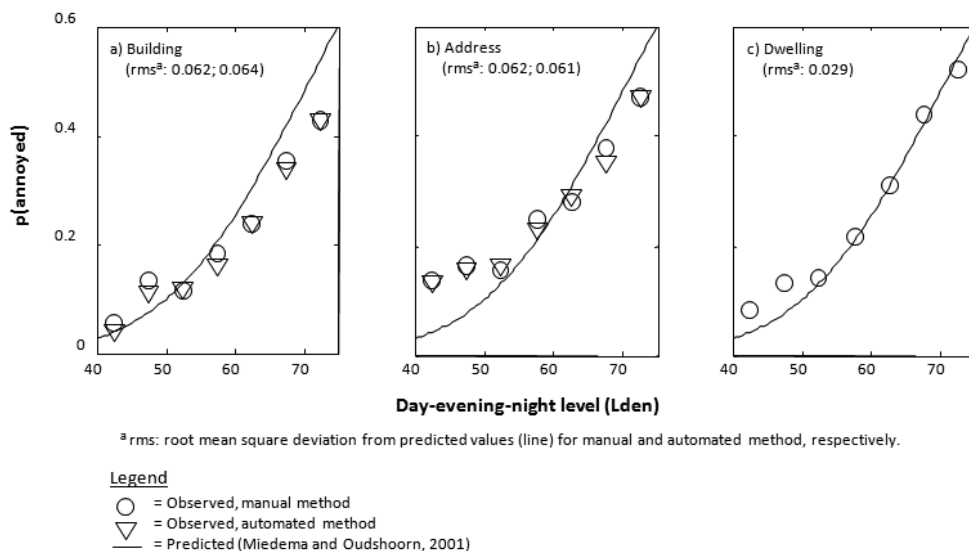
**Figure 10.** Relative risk of having at least one of four outcomes (hypertension, general obesity, abdominal obesity or prediabetes/Type II diabetes) associated with different levels of aircraft noise exposure (bars indicating 95% CI).

#### 4.4 EVALUATION OF THE SWEDISH END MAPS

Among the 2 496 participants included in paper IV, in which we applied and evaluated the Swedish END maps, the average  $L_{den}$  level of road traffic was 58 dB(A) using the building estimate, 53 dB(A) using the address point estimate and 55 dB(A) using the dwelling estimate (see Figure 6 for a description of the noise estimates). Corresponding figures for railway noise were 47, 45 and 46 dB(A), respectively. The difference in mean exposure levels between the manual and automated methods were 1 dB or less.

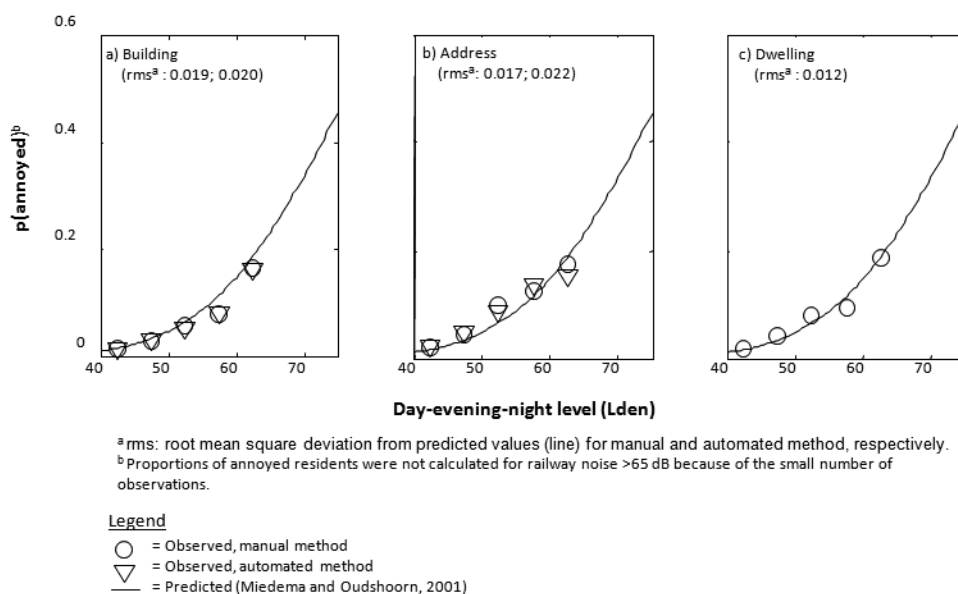
The agreement between the road traffic noise estimates were highest between the address and dwelling estimates ( $\kappa=0.64$ ) and lowest between the building and address estimates ( $\kappa=0.40$ ). The building estimate, which by definition gives the highest values, was at least one dB-category higher in 51% of the cases in comparison to the address estimates and in 39% in comparison to the dwelling estimates. Generally, there was a better agreement between the noise estimates for railway noise, with  $\kappa$  ranging from 0.58 (building-address) to 0.77 (address-dwelling). Here, the building estimates were at least one dB-category higher in 23% of the cases compared to the address estimates and in 16% compared to the dwelling estimates.

The comparison of observed and predicted proportions of annoyed and highly annoyed residents indicated a high agreement for all three estimates of road traffic noise (rms ranging from 0.029 to 0.064) and there were no systematic differences between the manual and automated methods (Figure 11a-c). The best agreement between observed and predicted data was, however, indicated for the manually derived dwelling estimate. Considering the building estimates, fewer residents than predicted reported noise annoyance at higher noise levels. Furthermore, the proportion of annoyed residents was higher than predicted at noise levels below 50 dB for all three estimates, although most prominent for the address estimates. Similar patterns were also apparent for the proportion of highly annoyed residents (Data not shown).



**Figure 11.** Observed (symbols) and predicted (curves) proportions of annoyed residents as a function of road traffic noise exposure, according to method and location of assessment.

For railway noise, all three estimates performed equally well in predicting the prevalence of annoyance, with a rms ranging from 0.004 to 0.022 (*Figure 12a-c*). Again, there were no systematic differences between the automated and the manual methods.



**Figure 12.** Observed (symbols) and predicted (curves) proportions of annoyed residents as a function of railway noise exposure, according to method and location of assessment.

#### 4.5 ROAD TRAFFIC AND RAILWAY NOISE, HYPERTENSION AND CVD

In paper V, the cohort for analyses included 23 845 subjects after exclusion of subjects with missing data on confounders (age, education, country of birth and smoking). In addition, 155 subjects had missing data on hypertension and 722 on cardiovascular disease, resulting in populations of 23 730 and 23 123 subjects, respectively. The time-window analyses including only those who were diagnosed with hypertension between 1997 and 2007 comprised 22 112 subjects. The sub-population included 2 313 subjects after exclusion of those with missing data on confounders; 11 had missing on hypertension and 65 on CVD, resulting in populations of 2 302 and 2 248, respectively. The time-window analysis, including only those with diagnosis of hypertension between 1997 and 2007, comprised 2 187 subjects.

The prevalence of self-reported hypertension was 21% in the total population and 17% in the subpopulation. The corresponding figures for prevalence of CVD were 10% and 7%, respectively (*Table 6*). As expected, both noise annoyance and sleep disturbances showed clear exposure-response associations with TL as well as  $L_{\text{den}}$  levels of road traffic and railway noise, supporting the validity of the exposure assessment methodology. However, no such associations were evident for hypertension, CVD or poor health.

**Table 6:** Prevalence of diseases and complaints according to Traffic Load within 500m and  $L_{den}$  levels of road traffic and railway noise in respondents to the Swedish Environmental Health Survey 2007.

	N	Outcomes, n (%) <sup>a</sup>				
		Hypertension	CVD <sup>b</sup>	Poor health	Noise annoyance	Sleep disturbance
<b>Total population</b>	25 851	5 370 (21)	2 402 (10)	1 381 (6)	1 848 (7)	1 191 (5)
<i>TL within 500m<sup>c</sup></i>						
Quintile 1	5 151	1 097 (21)	447 (9)	239 (5)	104 (2)	121 (2)
Quintile 2	5 141	1 096 (21)	489 (10)	284 (6)	228 (5)	137 (3)
Quintile 3	5 207	1 139 (22)	529 (11)	281 (6)	366 (7)	224 (4)
Quintile 4	5 179	1 112 (22)	496 (10)	293 (6)	476 (9)	298 (6)
Quintile 5	5 173	926 (18)	441 (9)	284 (6)	674 (13)	411 (8)
<b>Sub-population<sup>d</sup></b>	2 498	423 (17)	161 (7)	139 (6)	275 (11)	187 (8)
<i>Road noise, <math>L_{den}</math><sup>e</sup></i>						
<50	755	130 (17)	53 (7)	54 (7)	36 (5)	43 (6)
50-54	650	109 (17)	36 (6)	27 (4)	40 (6)	33 (5)
55-59	457	82 (18)	35 (8)	24 (5)	46 (10)	29 (6)
60-64	320	58 (18)	21 (7)	16 (5)	52 (16)	36 (11)
≥65	316	44 (14)	16 (5)	18 (6)	101 (32)	46 (15)
<i>Railway noise, <math>L_{den}</math><sup>e</sup></i>						
<50	2003	333 (17)	121 (6)	116 (6)	17 (1)	137 (7)
50-54	230	44 (19)	19 (8)	10 (4)	8 (3)	20 (9)
55-59	146	27 (18)	12 (8)	5 (3)	6 (4)	14 (10)
≥60	118	19 (16)	9 (8)	8 (7)	17 (14)	16 (14)

<sup>a</sup> Less than 4% missing for all outcomes. <sup>b</sup> CVD=Cardiovascular disease. <sup>c</sup> TL=Traffic Load within 500m around the address in millions of vehicle kilometers per year. <sup>d</sup> Subjects from the three largest cities in Sweden (Stockholm, Gothenburg and Malmö). <sup>e</sup>  $L_{den}$ : The A-weighted 24-hour equivalent continuous sound pressure level, with an addition of 5 dB for evening noise events (In Sweden defined as the period 19.00-23.00 hours) and 10 dB for night time noise events (In Sweden: 23.00-07.00 hours).

We did not find any statistically significant associations between TL and hypertension or CVD (Table 7). Similarly, in the sub-population, there was no association between road traffic noise and the cardiovascular outcomes. For railway noise we did not find statistically significant ( $p < 0.05$ ) associations with hypertension, however, the risk of CVD in relation to noise exposure equal to or above 50 dB(A) approached statistical significance: OR 1.55 (95% CI 1.00-2.40). None of the air pollutants were associated with hypertension or CVD after adjustments and inclusion of these variables in the regression models did not influence the results with regard to noise.

Of the investigated variables, only education significantly modified the associations between TL and the cardiovascular outcomes, where those with higher education seemed to have a reduced risk ( $p = 0.009$  for hypertension and CVD both). The associations for road traffic and railway noise did not seem to be modified by any of the investigated covariates (data not shown).

The correlation between TL and total concentrations of  $NO_2$  and  $PM_{10}$  were  $r = 0.65$  and  $0.59$ , respectively. For road traffic noise, the corresponding figures were  $r = 0.44$  and  $0.46$ . Generally, the local, traffic related, fraction showed the highest correlation with TL and road traffic noise compared to the regional and urban components. Finally, the correlation between TL and road traffic noise was  $r = 0.39$ .

**Table 7.** Associations between exposure variables (Traffic Load within 500m,  $L_{den}$  levels of road traffic and railway noise), and self-reported hypertension and CVD in respondents to the Swedish Environmental Health Survey 2007.

	Hypertension				CVD <sup>a</sup>	
	Ever		1997-2007		Ever	
	OR <sup>b</sup>	95% CI	OR <sup>b</sup>	95% CI	OR <sup>b</sup>	95% CI
<b>Total population</b>						
<i>TL within 500m<sup>c</sup></i>						
Quintile 1	1.0	-	1.0	-	1.0	-
Quintile 2	0.91	(0.82-1.02)	1.08	(0.74-1.59)	1.05	(0.90-1.22)
Quintile 3	0.96	(0.86-1.07)	1.07	(0.70-1.62)	1.09	(0.93-1.27)
Quintile 4	0.95	(0.85-1.06)	1.25	(0.80-1.96)	1.01	(0.86-1.18)
Quintile 5	0.91	(0.81-1.02)	0.96	(0.59-1.59)	1.01	(0.86-1.19)
<b>Sub-population<sup>d</sup></b>						
<i>Road noise, <math>L_{den}</math><sup>e</sup></i>						
<50	1.0	-	1.0	-	1.0	-
50-54	0.96	(0.69-1.34)	1.08	(0.74-1.59)	0.66	(0.39-1.10)
55-59	1.00	(0.69-1.43)	1.07	(0.70-1.62)	0.89	(0.53-1.50)
60-64	0.99	(0.66-1.49)	1.25	(0.80-1.96)	0.74	(0.40-1.36)
≥65	0.85	(0.55-1.31)	0.96	(0.59-1.59)	0.92	(0.49-1.73)
<i>Railway noise, <math>L_{den}</math><sup>e</sup></i>						
<50	1.0	-	1.0	-	1.0	-
50-54	1.09	(0.71-1.68)	1.00	(0.01-1.64)	1.50	(0.82-2.75)
55-59	1.22	(0.71-2.09)	1.16	(0.62-2.18)	1.56	(0.74-3.31)
≥60	1.05	(0.60-1.83)	0.97	(0.50-1.87)	1.62	(0.76-3.46)

<sup>a</sup> CVD=Cardiovascular disease, <sup>b</sup> OR=Odds Ratio, adjusted for age, birth country, education and smoking.

<sup>c</sup> TL=Traffic Load within 500m around the address in millions of vehicle kilometres per year. <sup>d</sup> Subjects from the three largest cities in Sweden (Stockholm, Gothenburg and Malmö). <sup>e</sup>  $L_{den}$ : The A-weighted 24-hour equivalent continuous sound pressure level, with an addition of 5 dB for evening noise events (In Sweden defined as the period 19.00-23.00 hours) and 10 dB for night time noise events (In Sweden: 23.00-07.00 hours).



## 5 DISCUSSION

The primary objective of this thesis was to explore the long-term effects of traffic noise exposure on cardiovascular and metabolic health outcomes. Furthermore, we aimed to apply and evaluate digital noise maps produced in Sweden according to the END for assessments of residential traffic noise exposure in noise and health research. Below, the main findings for each of the objectives are discussed in relation to previous research findings. Finally, methodological aspects which may have influenced the results are discussed.

### 5.1 CARDIOVASCULAR AND METABOLIC EFFECTS OF TRAFFIC NOISE

#### 5.1.1 Main findings

##### *Aircraft noise and hypertension*

The results from the first two papers in this thesis suggest that long-term aircraft noise exposure may increase the risk for hypertension in men, but not in women. Older males and subjects who were annoyed by the noise seemed to be at particularly high risk. Only a few previous epidemiologic studies have considered the hypertonic effects of aircraft noise exposure and these are all of cross-sectional design [5, 25, 34, 87-89].

Our results on aircraft noise and hypertension are in line with findings from a previous investigation around Stockholm Arlanda Airport by Rosenlund et al. 2001 which, similarly to paper I, used both the FBN and maximum noise level as indicators of noise exposure [89]. In Rosenlund et al., a higher prevalence of hypertension was observed among subjects exposed to aircraft noise  $\geq 55$  dB(A) FBN in comparison to a reference group comprising residents in Stockholm County. Furthermore, there was a tendency of an exposure-response association, however, it was only significant for the maximum noise level (OR per 5 dB 1.8; 95% CI 1.1-3.0). Similar to our findings, older subjects ( $\geq 56$  years) seemed to be at higher risk, but in contrast, there was no difference between men and women. A positive association between aircraft noise and hypertension was also reported from the multi-center HYENA-study (HYpertension and Exposure to Noise near Airports), including 4 861 subjects living near six major European airports [88]. Significant exposure-response relationships were found between night-time aircraft noise exposure ( $L_{\text{night}}$ ) and risk of hypertension (OR per 10 dB 1.14; 95% CI 1.01-1.29), with no differences in risk between men and women. However, the results were not entirely consistent since there was no association using the 16h average aircraft noise level ( $L_{\text{day 16h: 6-22h}}$ ). Furthermore, the same study reported an increased risk of hypertension among men but not in women following long-term exposure to road traffic noise. In 2010, Huss et al., investigated the effects of aircraft noise on mortality from myocardial infarction in the Swiss National Cohort, comprising 4.6 million persons [9]. The results of this study confirmed our findings of elevated risks primarily among male subjects and among those in the highest tertiles of age ( $\geq 82.3$  years). Unfortunately, none of the studies investigated the modifying effects of noise annoyance, which excludes comparisons with the findings in our study.

The diverging results for men and women presented in paper II may have several explanations. On one hand, the epidemiology and progression of cardiovascular disease differ between males and females [90-93]. For example, females tend to develop hypertension 10 years later than males, possibly, a consequence of a protective effect of the female sex hormone estrogen which reduces peripheral vascular resistance [92, 93]. On the other hand, methodological explanations, such as a shorter period of follow-up for females, are also possible.

The increased risk of hypertension among the elderly males in our cohort could be due to the fact that older people may be more sensitive to noise since they are likely to have a higher burden of cardiovascular risk factors than younger subjects [38]. Alternatively, it may be due to a prolonged period of exposure since most of these men had lived more than 10 years at their address. Yet another explanation could be that elderly people who are retired spend more time at home, thus this group would have less bias due to exposure misclassification.

Our finding that the annoyed group were of particularly high risk for noise-induced hypertension needs to be replicated before any definite conclusion can be drawn. However, annoyance can be viewed as a mediator in the relation between noise and somatic health which possibly could amplify the physiological stress response. Another explanation for the increased risk of hypertension among the annoyed could be that this group comprises more subjects with pre-existing disease. In 2003, Babisch et al. found that subjects with pre-existing disease were more often highly annoyed/disturbed by traffic noise than subjects without such health problems [94]. Yet another explanation could be that there is less exposure misclassification among the annoyed.

#### *Aircraft noise and metabolic outcomes*

Our main finding with respect to metabolic effects was an association between aircraft noise and waist circumference. We also observed an increased risk of Type 2 diabetes among noise exposed women; however, since the risk estimates reduced and became non-significant after adjustments for contextual confounding, this finding could be due regional socioeconomic differences. Furthermore, possible interactive effects were suggested between aircraft noise and job strain as well as physical activity.

The findings of paper III provide the first evidence of a link between long-term traffic noise exposure and metabolic effects. Although no previous studies have shown a similar association, a substantial amount of evidence from experimental and field studies link noise exposure to a stress response [49-51, 56, 61, 65, 95], and moreover, link stress to impaired metabolic functions [54, 55, 57-60, 96, 97]. In addition, noise exposure is commonly associated with sleep disturbances [7], which are known to have metabolic complications [66-69, 81]. Although, since the estimates for waist circumference and Type 2 diabetes (among females) were not modified by sleep disturbances, the increased risks among those exposed to long-term aircraft noise is not likely to be mediated by sleep loss. An effect of sleep on metabolic outcomes should, nevertheless, not be excluded since our assessment of sleep disturbances was rather crude (see section 3.1.4).

The twofold risk increase for diabetes seen in females exposed to aircraft noise  $\geq 50$  dB(A)  $L_{den}$  may, as stated above, be a consequence of contextual confounding. However, results from a sub-study of the cross-sectional HYENA-study lend some support of a more pronounced stress response, and thereby possibly an increased diabetes risk, in females than in males [61]. The sub-study examined the effects of aircraft noise on saliva cortisol in 439 men and women living near the six European airports included in HYENA. Women who were exposed to noise levels  $\geq 60$  dB  $L_{Aeq, 24h}$  were found to have a significantly higher morning saliva cortisol concentration than women exposed to levels  $< 50$  dB ( $b = 6.07$  mmol/l; 95% CI 2.32-9.81), whereas no such association was indicated for men. Nonetheless, this possible gender difference clearly needs further investigation.

In addition to the suggested modifying effect of sex on the risk of Type 2 diabetes, interactive effects with aircraft noise were also indicated for job strain and physical activity, although not statistically significant. Job strain, which has previously been suggested to modify the effect of road traffic noise on myocardial infarction [98], was associated with a greater increase in both BMI and waist circumference among subjects exposed to aircraft noise levels  $\geq 50$  dB(A)  $L_{den}$  compared to those exposed below this level. Thus, it seems possible that multiple stressors add to the individuals stress load in a negative way. The inverse scenario was observed for physical activity and Type 2 diabetes, suggesting a buffering effect on the stress load.

#### *Combined analyses on aircraft noise*

In the analyses combining hypertension, generalized obesity, abdominal obesity and prediabetes/Type 2 diabetes, 46% of the subjects exposed to aircraft noise levels  $\geq 50$  dB(A)  $L_{den}$  had at least one of the four outcomes, indicating a risk increase of almost 20% in comparison to the reference group. Furthermore, approximately one third of those classified as cases had two or more outcomes, suggesting the presence of a more complex disease syndrome. According to the definition of the International Diabetes Federation, a person is defined as having a metabolic syndrome if he or she has central obesity plus any of the following four factors: raised triglycerides, reduced high density lipoprotein, raised blood pressure or raised fasting plasma glucose; alternatively specific treatments for lipid abnormalities or hypertension, and previously diagnosed Type 2 diabetes [99]. Since the SDPP cohort did not include measurements of triglycerides or high density lipoprotein for all subjects, we were not able to assess the metabolic syndrome per se, merely some of its components. However, the results from the combined analyses indicate that further investigation of the association between aircraft noise and the metabolic syndrome is desirable.

#### *Traffic Load, road traffic and railway noise and cardiovascular outcomes*

The results from paper V indicated no association between neighborhood TL and self-reported hypertension or CVD in the total population. Similarly, in the sub-population, there was no association between  $L_{den}$  levels of road traffic noise and cardiovascular outcomes, however, we did observe an association between railway noise and self-reported CVD. Our estimates remained unchanged after adjustments for air pollution ( $NO_2$  and  $PM_{10}$ ).

Since detailed noise exposure data was only available for a sub-population, neighborhood TL was used as an indicator of road traffic noise exposure for the total population. Residence close to high traffic roads, for example measured as distance to or traffic density on nearby roads, has been reported to increase the risk of cardiovascular disease [9, 26, 100-102]. Predominantly, these variables have then been used as proxies for traffic related air pollution. Few other studies have used traffic related variables to assess health effects of noise exposure, or to consider the joint effects of noise and air pollution. However, a Dutch cohort study, investigating the joint association of air pollution and noise from road traffic on cardiovascular mortality, found an association between traffic intensity on the nearest road and an increased risk of ischemic heart disease (IHD), RR 1.11; 95% CI 1.03-1.20 [26]. Black smoke, which was used as an indicator of traffic-related particles, was associated with cerebrovascular as well as heart failure mortality. Furthermore, noise exposure >65 dB(A) was related to an increased risk of IHD, but this association approached unity after adjustment for black smoke and traffic intensity. Contrary to these findings, we did not observe an association between neighborhood TL and cardiovascular disease, although the power to detect a statistically significant effect of TL on hypertension and CVD was high (>0.99 and 0.97, respectively, assuming OR=1.2 and two-tailed alpha = 0.05).

The association between road traffic noise and hypertension has been assessed in several epidemiological studies [17, 19, 24, 27, 28, 88, 103] and quantitative exposure-response-associations have been derived in the meta-analysis by van Kempen 2012 [15]. This analysis found a positive association between road traffic noise and hypertension and also concluded that studies differentiating between different age groups did not indicate increased risks among older people ( $\geq 60$  years), and that studies on males reported higher OR per 5 dB(A) than studies investigating women or men and women. Additionally, they found that studies using self-reporting as a method of ascertaining hypertension reported higher OR per 5 dB(A) than those where the diagnosis was ascertained clinically. In respect to these conclusions, our findings on road traffic and hypertension appear contradictory, showing no associations – regardless of age, sex or self-reporting.

Fewer studies have considered other cardiovascular end-points, such as MI, in relation to road traffic noise [22, 26, 98, 104] but in the meta-analysis by Babisch 2008, it was concluded that there is evidence of a relationship between road traffic noise over 60 dB(A) and risk of MI [16]. The lack of association between road traffic noise and self-reported CVD in our study may thus be due to the fact that there are relatively few highly exposed subjects. In addition, the null-results for neighborhood TL as well as road traffic noise and the cardiovascular outcomes could be a consequence of the methodological limitations of our study; these are further discussed in section 5.1.2 below.

Although exposure to short-term railway noise has been shown to impact several cardiovascular functions [105], few studies have investigated the long-term effects of railway noise on cardiovascular outcomes. In the study by Barregård et al. 2009, the risk of hypertension was assessed in relation to traffic noise exposure among a population-based sample from the south-west of Sweden [17]. Neither self-reported hypertension nor the use of anti-hypertensive medication was in this study related to the

24h average railway noise level. In 2011, Sørensen et al., found an 8% increased risk of self-reported hypertension in relation to railway noise above 60 dB(A)  $L_{Aeq,24h}$  among participants in the Danish Diet, Cancer and Health cohort [18]. However, the estimate was statistically insignificant and there were no associations between railway noise and blood pressure. Contrary to these findings, a recent study by Dratva et al. 2012, found significant effects of railway noise on blood pressure, which remained after adjustments for air pollution [8]. The lack of association between railway noise and self-reported hypertension in our study are more in line with the findings by Barregård et al. and Sørensen et al. No previous study seems to exist on railway noise and other cardiovascular end-points, such as IHD, and our results are in this respect unique. Although it could be a chance finding, the suggested association between railway noise  $\geq 50$  dB(A)  $L_{den}$  and self-reported CVD supports an adverse effect of railway noise on the cardiovascular system. This finding, and the significant associations of railway noise and BP by Dratva et al., call for more studies on cardiovascular effects by railway noise.

#### *The role of air pollution*

Both noise and air pollution may contribute to an increased risk of CVD. In our data, the observed correlation between  $L_{den}$  levels of road traffic noise and  $NO_2$  ( $r=0.44$ ) was lower than reported by for example Selander et al. 2009 ( $r=0.60$ ), Davies et al. 2009 ( $r=0.53$ ) and Foraster et al. 2011 ( $r=0.62$ ), but higher than in the study by Gan et al. 2012 ( $r=0.33$ ). The correlation for  $PM_{10}$  ( $r=0.46$ ) also differed from what has previously been reported, for example by Beelen et al. ( $r=0.24$ ) and de Kloizenaar et al. ( $r=0.72$ ). Road traffic noise and air pollution were in our study modeled using different sources of input traffic data, possibly contributing to the relatively low correlation. It was therefore judged that both factors could be included in the models jointly in order to separate their effects. Previous studies of noise and CVD have been inconclusive with regard to the confounding and interactive effects by air pollution. In 2009, Beelen et al. observed a reduction of the noise effect on the risk of IHD mortality after adjustment for black smoke (i.e. traffic related particles), although, this estimate was also adjusted for traffic intensity which may have diluted the effect of noise. Others have reported the reverse, i.e. an increase in the noise estimate after adjustments for air pollution, or no influences at all [8-10]. In the study by Gan et al., traffic noise and black carbon were independently associated with death from coronary heart disease, however, there was no interaction between the two. In our study, inclusion of  $NO_2$  and  $PM_{10}$  in the analyses did not alter the risk estimates for noise and there were no interactive effects. However, some methodological problems may have concealed potentially important effects. In general, it is recommendable that future studies on noise and CVD include data on traffic related air pollution. Improved exposure assessments of both exposures as well as continuous monitoring of their correlations are desirable to identify settings of low correlation (e.g. rural areas, street canyons or shielding of buildings). Possibly, future studies could then be designed to include participants with differing levels of the exposures.

## 5.1.2 Methodological considerations

### *Paper I-III*

The SDPP cohort provided a unique opportunity to study the long-term health effect of aircraft noise because of its longitudinal design and its inclusion of residents close to Stockholm Arlanda airport. Furthermore, digital noise maps and data from clinical examinations enabled objective assessments of both the exposure and the outcomes. However, there are some methodological problems which need to be considered.

Firstly, the SDPP cohort was designed to study risk factors for Type 2 diabetes in relation to heredity and therefore oversampled subjects with a family history of diabetes. Approximately 50% of the participants in the SDPP cohort had a positive family history of diabetes, in comparison to 20-25% in the general population of the corresponding age group (Östenson, personal communication). In theory, subjects with a family history of diabetes could be more vulnerable to long-term aircraft noise since they may be at higher risk of cardiovascular disease. If so, our results may not be generalized to the overall population. In all three papers, we therefore assessed if and how the oversampling affected the association between aircraft noise and the outcomes by including FHD as a potential effect modifier. In neither of the studies, however, did we detect a statistically significant interaction between noise and FHD, suggesting that the effect of noise exposure is similar in the two groups. Thus, the results of our analyses may be generalized to the whole population.

Secondly, one of the main aims of the SDPP was to implement actions to prevent Type 2 diabetes through community based interventions which were performed in three of the municipalities (Sigtuna, Upplands Väsby and Värmdö). A strong effect of the interventions on population health could possibly interfere with the effects of aircraft noise and thereby distort the association. However, the effects of the interventions on measures of blood pressure, body weight and glucose tolerance were found to be small and are not believed to have influenced our results (Östenson, personal communication). If anything, the effect of the noise exposure may have been attenuated because two of the most aircraft noise exposed municipalities (Sigtuna and Upplands Väsby) were intervention municipalities, thereby possibly affecting the participants' life-style, and the outcomes under study, in a positive way.

Another potential source of bias in the studies based on the SDPP cohort is exposure misclassification. Aircraft noise could unfortunately not be assessed at baseline. Instead, we used data from midpoints of the study period, which were intended to be representative for the total period of follow-up. For the second paper, we estimated the average  $L_{den}$  level of aircraft for the time-period 1997 to 2002 in order to account for the gradual decline in noise propagation occurring around Arlanda during the latter part of the study period. However, a comparison of the number of men exposed to noise levels  $\geq 50$  dB(A) in paper I and II, which dropped from 410 to 292, shows that this was probably an underestimation of the true exposure for males since these were followed already from 1992/94 and onwards. For females, the 1997/02 average  $L_{den}$  level is more likely to be closer to the true exposure since these were followed from a later point in time (1996/98). Furthermore, the lack of objective data on exposure to noise from other sources, including road traffic, railway and occupational noise, resulted in imprecision

in the noise estimates. We did, however, adjust for noise annoyance due to these sources which did not alter the risk estimate for aircraft noise significantly. Additionally, although some misclassification of the exposure has occurred, it is not believed to be dependent on outcome status and therefore most likely diluted the associations.

The issue of contextual confounding was only addressed in paper III and, additionally, in the combined analyses on aircraft noise produced for the summary of this thesis. In paper III, inclusion of area-based mean income and proportion of unemployed resulted in a reduction of the risk estimates for BMI and waist circumference, however, no such effect was seen in the combined analyses. To our knowledge, only one previous study on aircraft noise and cardiovascular outcomes has taken area-based socioeconomic factors into account, showing no effect of these factors on the strength of association for noise [9]. The presence of some residual confounding after the adjustments for individual characteristics in paper III do, however, indicate that future studies on noise should take area-based socioeconomic factors into account.

Since the SDPP cohort was not initially designed to study the cardiovascular effects of noise, some information that may have been of importance for the associations under study was lacking or insufficient. We did for example not adjust for heredity for cardiovascular disease or diet. Furthermore, the low number of exposed cases resulted in imprecision in the effect estimates. Especially in the higher noise categories, the estimates should be interpreted with caution.

#### *Paper IV*

The National Environmental Health Survey 2007 enabled us to investigate the association between living near noisy roads and railways and cardiovascular outcomes in a large population based sample of adult Swedish men and women of a broad age range (18-80 years). Furthermore, by use of residential address coordinates, we were able to perform independent exposure characterizations; for TL, road traffic and railway noise as well as air pollution. However, several methodological problems may have contributed to conceal potentially important associations. The primary limitations of the study include its cross-sectional design, self-reporting of outcomes and exposure misclassification.

Like most epidemiological studies published so far on health effects of noise, our study was of cross-sectional design, which limits the possibilities to infer causality [106]. For example, it was evident that subject with a high TL had lived fewer years at their address, possibly indicating a tendency of people moving out of noise polluted areas. This selection bias may have led to a dilution of the associations in the total population; although, no such tendency was seen in the subpopulation. Furthermore, the cross-sectional design makes it difficult to assure that the exposure preceded the outcome, because they are measured at the same point in time. In an attempt to reduce this problem, we performed a time-window analysis and stratification on duration of residence. However, no increased risks were seen among those diagnosed with hypertension most recently (1997-2007) or among those with a residence time  $\geq 5$  year.

The reliance on self-reported data is likely to have underestimated the prevalence of disease, in particular hypertension which is often asymptomatic and therefore may remain undetected. Studies investigating the quality of self-reporting of hypertension compared to biometrical data have reported varying sensitivity. A Dutch study, comparing data from the Utrecht Health Project, showed a sensitivity of only 34.5% [107]. Other studies have reported somewhat higher quality of self-reported data, for example Oksanen et al. found a sensitivity of 86% for self-reported hypertension when compared to data from registers [108]. In our study, the prevalence of hypertension was 21%. This is slightly lower than what has been estimated for the general population (27%) which indicates some underreporting [43]. Self-reported CVD has in general relatively high sensitivity and underreporting is therefore less of a problem. The misclassification of outcomes is not believed to be dependent on exposure status and may therefore have led to a dilution of the associations.

Neighborhood TL is a crude surrogate for noise exposure, primarily because it does not take shielding from buildings or noise barriers into account. Additionally, it may be a marker also for traffic related air pollution. In our data, the correlation between TL and the  $L_{den}$  level of road traffic noise was fairly low ( $r=0.39$ ) while the correlation with air pollution was higher ( $r=0.65$  and  $0.59$  for  $NO_2$  and  $PM_{10}$ , respectively). In order to avoid confounding by air pollution we therefore included  $NO_2$  as well as  $PM_{10}$  in our analyses, however, this did not alter the risk estimates. Furthermore, the results for the total population, in which we used TL as the exposure indicator, did not differ from the subpopulation, where a more detailed exposure characterization was made using the Swedish END maps. The  $L_{den}$  measure used in the subpopulation is a good indicator of individual noise exposure since it accounts for apartment orientation within buildings. Also, the Swedish END maps are of higher quality than required by the EU directive on noise [35]. For example, because they include noise exposure assessments on the complete road net and use a threshold of 35 dB (Stockholm and Gothenburg) or 45 dB (Malmö), versus 55 dB required by the directive. Still, however, a certain degree of misclassification of exposure is likely to have occurred since we were not able to take several important exposure modifiers into account, including floor height and window insulation. Furthermore, we did not have data on occupational noise exposure. Thus, also exposure misclassification may have contributed to attenuation of the associations.

Other limitations of this study include the relatively low number of exposed cases in the subpopulation, particularly for railway noise and CVD. The increased risk of CVD associated with a railway noise exposure  $\geq 50$  dB(A) could therefore be a chance finding. Furthermore, the study may also suffer from residual confounding, because information on several important risk factors was missing. For example, we were not able to adjust for dietary factors, BMI, physical activity or heredity for cardiovascular disease.



## 5.2 APPLICATION OF END MAPS IN NOISE AND HEALTH RESEARCH

The main finding from our evaluation of the digital END maps which have been produced in Sweden is that they generate valid estimates of residential traffic noise exposure and therefore can be used in noise and health research. The best agreement between observed and predicted proportions of annoyed residents, as a function of the  $L_{den}$  exposure, was found when adjusting for dwelling location within apartment buildings. Another important finding was that the low noise estimates were found to be less valid than high. Furthermore, there were fairly large differences in the methods of the mappings between, and even within, the cities, which calls upon improved standardization and harmonization of future mappings.

No previous study has evaluated the END maps for assessments of residential traffic noise exposure in epidemiologic research and our results therefore remain to be compared with future investigations. The finding that the dwelling estimate showed the highest agreement for the observed and predicted number of annoyed subjects indicates that the precision of the noise estimates can be improved by adding information on dwelling location within apartment buildings. Most previous studies have used the most exposed façade of the building to characterize noise exposure [10, 11, 28, 88], however, in our data, this estimate turned out to differ up to 30 dB(A) in comparison to the dwelling estimate. Furthermore, the observed number of annoyed subjects was lower than predicted when using the most exposed building façade as an indicator of exposure. A misclassification of exposure, by not taking into account that some dwellings face a quieter side, may have contributed to these results. We also observed a higher proportion of annoyance than predicted for all estimates at noise levels  $\leq 50$  dB. The modeled low noise levels thus appeared to be less valid than the moderate or high levels. This may be related to the calculation model, which has a lower precision at large distances from the source (and thereby at low noise levels), or because traffic from small local roads had not been included in the model.

Generally, our findings encourage continuous use of the END maps for exposure assessment purposes. However, since the Swedish END maps exceed the minimum requirements of the first phase of the Directive [36], our results may not apply to maps of less detail. Another issue of importance for the interpretation of the results is that the methodology of the mappings in Stockholm, Gothenburg and Malmö differed in some respects (see table S1 in paper IV). This finding is in line with previous experiences from the implementation of the END maps, indicating that there is a need to increase the standardization even further [109-111]. The Swedish cities were mapped by different consulting firms, using varying software and reference systems. Other differences include input traffic data (which in some areas were based on actual measurements whereas others used default values based on road class), ground surface elevation (1m in Stockholm, 2m in Gothenburg and 10 in Malmö) and grid spacing (2-3m, 10m and 5m, in each city respectively). However, all three cities used the Nordic Prediction Methods for road traffic and railway noise to calculate the exposure [112-114]. Furthermore, we did not detect any substantial differences between the cities with regard to the reporting of annoyance in relation to noise exposure extracted from the maps. To some extent, our findings also depend on study area characteristics. Stockholm, Gothenburg and Malmö are the three largest cities in Sweden and they are

representative for many European cities in their clear urban structure and building types. A majority of our participants (77%) lived in apartment buildings with large differences between the most and least exposed façade. In areas with more detached or semi-detached houses, the exposure difference between the facades may be smaller and the results may thus not be generalizable to areas with other features.

A limitation of this study is the lack of information on additional exposure modifiers, especially floor level and façade and window insulation. It is likely that a more accurate assessment would have been possible if data on these factors could have been taken into account. For example, the present Swedish END maps are in 2D, but preferably future strategic mappings should adopt the 3D technique in order to improve the assessments with regard to floor height [115].

## 6 CONCLUSIONS

Long-term exposure to aircraft noise was associated with an increased cumulative incidence of hypertension among men. Stronger associations were found among older males ( $\geq 57$  years), indicating that age may modify the effect of aircraft noise.

In contrast to males, there was no association between long-term aircraft noise exposure and cumulative incidence of hypertension among females. Thus, the effect of aircraft noise may be gender specific. In both sexes taken together, increased risks of hypertension were found among those who were annoyed by the noise, suggesting that the effect is modified by annoyance.

With regard to metabolic outcomes, long-term aircraft noise exposure was associated with an increased waist circumference among both men and women and, possibly, Type 2 diabetes among women. Sleep disturbances did not modify the effect of noise.

Digital noise maps produced in Sweden according to the European END appear to be useful for assessments of residential traffic noise exposure and future research on noise and health. However, exposure moderating factors, such as dwelling location within apartment buildings, should be taken into account.

Living near noisy roads was not related to an increased prevalence of self-reported hypertension or cardiovascular disease. However, exposure to railway noise appeared to be associated with an increased prevalence of self-reported cardiovascular disease. Methodological limitations make these results difficult to interpret.

Overall, the findings of this thesis provide further evidence of adverse effects of long-term traffic noise exposure on the cardiovascular system. They also indicate a possible link to metabolic effects, in particular abdominal obesity. Clearly, long-term traffic noise exposure may have serious public health effects and research in this area should be prioritized. In particular, efforts need to be focused on enhanced exposure assessments, establishment of outcome specific exposure-response relationships and on disentangling the effects by noise and air pollution.

## 7 SAMMANFATTNING PÅ SVENSKA

En stor andel av befolkningen i Europa utsätts för trafikbuller och exponeringen ökar. Hörselsinnet har direkta förbindelser med det sympatiska nervsystemet och det endokrina systemet vilket medför att höga ljud kan utlösa en stressrespons och därigenom inverka på en rad fysiologiska, metabola och immunologiska processer. Tidigare epidemiologiska studier talar för att trafikbuller har negativa effekter på det kardiovaskulära systemet, men den övergripande bilden är oklar. Det primära syftet med denna avhandling var att undersöka långtidseffekterna av trafikbullerexponering på kardiovaskulära och metabola utfall. Ett sekundärt syfte var att tillämpa och utvärdera de digitala bullerkartor som producerats i Sverige i enlighet med det Europeiska bullerdirektivet (END) för exponeringsbedömningar av trafikbuller.

Sambanden mellan långtidsexponering för flygbuller och högt blodtryck, övervikt och Typ 2 diabetes undersöktes med hjälp av frågeformulär och kliniska data från en kohort inom Stockholms Diabetespreventiva Program. Exponeringsbedömningen gjordes med hjälp av Geografiska Informationssystem och baserades på deltagarnas boendehistorik. Efter exkludering av personer som använt tobak före de kliniska undersökningarna var risken för hypertoni relaterad till flygbullerexponering förhöjd hos män (RR per 5 dB(A)  $L_{den}$  1,21; 95% KI 1,05-1,39) men inte hos kvinnor (RR 0,97; 0,83-1,13). Starkare samband sågs hos bullerstörda (RR 1,42; 1,11-1,82). Flygbullerexponering var även relaterad till bukomsfång: 0,62 cm (0,54-0,70) per 1 dB(A)  $L_{den}$ . Kvinnor som exponerats för flygbuller  $\geq 50$  dB(A)  $L_{den}$  hade en fördubblad risk för Typ 2 diabetes, även om justering för områdesrelaterade socioekonomiska förhållanden försvagade sambandet.

Ett urval från den Nationella Miljöhälsoenkäten 2007 (NMHE07) användes för att utvärdera de svenska END-kartorna för vägtrafik- och spårbuller. Andel störda vid olika bullerexponeringar jämfördes med redan etablerade exponeringsrespons samband. Överrensstämelsen mellan observerad och predicerad andel störda var generellt god, vilket tyder på att bullerkartorna kan användas för att bedöma exponering för trafikbuller i boendemiljö. Den bästa överrensstämelsen uppnåddes när bullerestimatet från kartorna korrigerades för lägenheternas lokalisering inom byggnaderna.

Tvärnittsanalyser baserade på NMHE07 genomfördes för att studera sambanden mellan trafikarbete, vägtrafik- respektive spårbuller och förekomsten av självrapporterade kardiovaskulära sjukdomar. Varken trafikarbete eller vägtrafikbuller var associerat med de kardiovaskulära utfallen, men det förelåg ett samband mellan spårbuller och kardiovaskulär sjukdom. Resultaten i denna studie är svårtolkade beroende på metodologiska begränsningar.

Sammantaget tyder våra resultat på att långtidsexponering för trafikbuller har en negativ inverkan på kardiovaskulära och metabola utfall. Trafikbuller kan således ha skadliga folkhälsoeffekter och forskning inom detta område bör prioriteras.

## 8 ACKNOWLEDGEMENTS

One of my favorite sayings goes “*The problem with good ideas is that they soon transpire into hard work...*”. The idea of writing a PhD-thesis was certainly great, but it did give me some heavy labor which I couldn’t have managed without help and support from all of you intelligent colleagues, loved family members and brilliant friends. I would especially like to thank:

**My main supervisor**, Professor *Göran Pershagen*; Thank you for believing in me and for taking me on as a PhD-student in your research group, it has been a true privilege to work in this creative, generous and friendly environment! Thanks also for being a good role model, in the field of environmental epidemiology as well as a group leader. I have learnt a lot from you that I will bring with me in the future.

**My co-supervisor**, Professor *Claes-Göran Östenson*; Thank you for excellent guidance and advices in scientific matters, especially endocrinology, and for your continuous support and encouragement throughout my thesis work!

**My co-supervisor**, Associate Professor *Mats Nilsson*; for sharing your expertise in acoustics and statistics with me and for all advices on the day-to-day scientific work – it has been invaluable! Thanks also for excellent collaboration in all other projects outside my thesis work.

**My mentor**, Associate Professor *Gösta Bluhm* – I owe you my career! If you hadn’t been so persistent with me becoming a PhD-student, I doubt I would have been where I am today. Thank you for advices in cardiovascular matters, for always taking an interest in my work and for caring; I am truly grateful.

### **The co-authors of my papers:**

*Mats Rosenlund*, for taking over as a corresponding author on my first paper when I left the IMM to work as a health promoter... *Agneta Hilding*; you have been there for me since day one! Thank you for checking the numbers in all my tables and for posing those tricky questions which I know I should know the answers to but didn’t bother to check (“..yet”). Thanks also for being so supportive and for providing a female perspective on things... *Dag Stenkvist*; I have a post-it patch on my note-board saying “Dag-akuten”, including your mobile phone number – that pretty much sums it up! You have been a tremendous support in my struggles with the management of the END maps and you have taught me everything I needed to know about GIS. Thanks a lot for all your help! *Lars Gidhagen*, for excellent collaboration in the Roadside-study and for all your hard work with the assessments of air pollution and traffic variables! *Tom Bellander*, for always thinking “outside the box” and making me re-evaluate my findings. Your ways of twisting and turning scientific matters makes the research move forward. Thanks also for your support! *Saskia Willers*, boy, did we struggle..;=) Not only at work but all around Sweden; skiing, swimming, biking and running! I am so grateful for our friendship and I hope we can keep in touch (I’ll keep your skis as hostage until you come and visit!). *Andrei Pyko*, a professor to be! I admire your

courage to come to Sweden to study; I know it is not always easy but I am sure you will make it! Thanks for sharing funny stories and everyday life at the IMM.

**All my colleagues, former and current, which I have had the privilege to work with at the unit of Environmental Epidemiology:**

Especially thanks to *Jenny Selander*, my “older-sister” in noise research, for being my speaking-partner in the “noisy-business”, for support in difficult times and for great cooperation in organizing the best IMM-spring party ever! *Birgitta Ohlander*, for excellent help with the manual geocoding of the SDPP addresses in Sigtuna, for friendship and continuous support. ..And for making me go to Friskis & Svettsis on a regular basis! *Eva Undsén*; Thank you for all the help with the administrative stuff, your knowledge and experience of the KI-organization has saved me many times. I’m also grateful for all of our inspiring chats during “fika”! *Anna Bergström*, Thank you for being an excellent female role model in the research world. Your struggle to combine motherhood with an active research career is inspiring, especially since you always do it with a smile! Thanks for all your support. *Anna Sidorchuk*, my dearest, I am so grateful for your friendship and all our talks about life in general and science in particular. Thanks for sharing your life-wisdom with me and for all your great stories. You always make me smile! Many thanks also to the great *Olena Gruzieva*, *Sviatlana Panasevich*, *Michal the-LUR-modeling-man Korek*, always caring *Annika Sääf*, *Anna Gref*, *Jessica Magnusson*, *Johanna Penell*, *Erica Schultz*, *Erik Melén*, *Helen Rosenlund*, *Niclas Håkansson*, *Maria-Pia Hergens*, and *Anna Bessö* for making me feel “at home” at work, for all “fikas” and lunches, IMM-parties, conference travels and workshops, ice-skating evenings, mini-golf tournaments, and much more...

**My colleagues from other units at the IMM and SLL:**

*Jinjin Zheng*, for sharing my nerdy interest in classical music and for all the great tennis matches, *Agneta Åkesson*, for making me reconsider my decision to give up on research, *Emilie Friberg*, *Susanna Larsson*, *Nicola Orsini*, *Camilla Olofsson* and *Charlotte Bergkvist* for being inspiring colleagues, *Annette Engström*, for giving me the opportunity to try out glide flying and for struggling through biostat III with me, *Tomas Lind*, for all the statistical advice, *Sara Nilsson*, for your efforts of gathering information on the noise mappings in Stockholm, *Anne-Sophie Meritt*, *Antonis Georgellis*, *Getahun Bero Bedada*, *André Lauber*, *Niklas Andersson*, *My Svensdotter*, *Auriba Raza* and *Anders Lundin* for all talks during “fikas” and lunches!

**The members of my Journal Club and Work-in-Progress-Group:**

*Lisa Olsson*, for sharing these last struggling months preparing for the disputation with me and for organizing the best-ever IMM-spring party! *Ann Burgaz*, *Bettina Julin* and *Susanne Rautiainen*, the three marvelous Nutritional Musketeers, for sharing IMM-life and for many fun times, *Annmarie Wesley*, for being my private chauffeur to all doctoral parties..., *Tony Bohman*, *Anna Undeman Asarnoj*, *Åsa Neuman*, *Anders Berglund* and *Anette Lannersjö* for sharing your knowledge with me during JCs and WPG sessions. Our discussions have been extremely valuable to me!

### **My brilliant friends:**

Especially thanks to *Lovisa Näslund*, for long-lasting friendship, for sharing my interest in horses and riding and for all motivating and exciting discussions! *Jessica Bergfoth* and *Karin Videfors*, my two health-pedagogue classmates, thank you for your encouragement and for all the fun times we've had together, *Helena Mannerstedt*, for always being my left-side ear during choir rehearsals, concerts and travels, thanks also for sharing your life with me in small and big adventures... *Karoline Ekström*, *Karin Rydin* and *Lina Eriksson*, I cherish our friendship greatly and thank you for all the great experiences we had, and will have, together! *Emma Moreau*, I still call you my neighbor :=) Thanks for caring and for listening, and thanks for letting me rehearse my presentation to Läkarsämman in 2007 for you! *Malin Ljungdahl*, I am so glad we took that French course in Nice together, not that we learnt any French, but because I got to know you better! I hope you will stick by my side for a long time. Thanks also to *Susanne Zetterquist* and *Maria Eriksson*, for inspiring book-club discussions, and to my faraway friends *Jule Adam* and *Ghazala Bashir*, for letting me come and visit you whenever I feel Sweden is just a little too small...

### **Members of Nacka Chamber choir:**

Especially thanks to *Per Rönnblom*, for letting me be a part of this excellent choir! Your never failing sense for great music and high-flying ambitions have given me the opportunity to sing pieces I could only dream about! Thanks also for your kindness and for taking an interest in my PhD-struggles. *Roland 'Rolle' Hallstener*, our (out-) standing chairman, thanks for all laughter's and for your generosity. And to all of you other choir colleagues that has supported me, *Lotta L*, *Anna*, *Pilo*, *Ulrica*, *Catarina*, *Eva*, *Cecilia*, *Anders*, *Kjell*, *Hasse*, *Martin*, *Lasse*..... Ab imo pectore – Gratias!

### **My family:**

*Birgit Eriksson*, I could not have wished for a better mother! You are my role-model in everything I do. I admire your strength and courage to tackle life, your kindness and generosity to all of us around you, and your ability of always seeing the positive side of things. Thank you for being there for me! *Lars Eriksson*, my favorite father! Thank you for giving me the best upbringing one can possibly imagine. Thanks also for your kindness and care, and for supporting all my choices in life, it means the world to me. My sister *Helena*, I'm sorry for biting your belly...:=) Thanks for being at my side throughout life; I know I can always count on you! *Kerstin*, my aunt and spare-mom, thanks for providing me with non-academic books to read! Thanks also for all your care and support; it means a lot. *Kim* and *Göran*, thanks for all the nice birthday-, Christmas-, Easter- and midsummer celebrations, and for your support! Last but not least, *Niclas*, although living less than a kilometer from you during the summers, it took me thirty three years to find you... But I'm so glad I finally did! Thank you for all your love and support, and for giving my life outside of academia a purpose. Puss&kram /L

### **Participants of the SDPP and NEHS07**

As a final note, I would like to acknowledge the efforts made by all *participants of the Stockholm Diabetes Prevention Program* and *the National Environmental Health Survey 2007*. Without your contribution, this research would not have been possible – Thank you!

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