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LONG-TERM EXPOSURE TO TRANSPORTATION NOISE IN RELATION TO METABOLIC AND CARDIOVASCULAR OUTCOMES

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Long-term exposure to transportation noise in relation to metabolic and cardiovascular outcomes

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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*The day will come when man will have to fight noise
as inexorably as cholera and the plague*

Robert Koch, Nobel Prize laureate

ABSTRACT

Transportation noise exposure is increasing because of rapid urbanization and transportation growth. Environmental noise exposure affects a large part of the population and gives rise to widespread annoyance and sleep disturbances. However, the evidence on metabolic and cardiovascular effects of long-term exposure to transportation noise from different sources is mostly limited and of low quality, hampering comprehensive risk assessment, although such effects may be of great public health significance. The main aim of this thesis was to study the development of obesity and cardiovascular outcomes in relation to exposure to noise from road traffic, railways and aircraft, and particularly the role of interactions.

The four cohorts under study were based in Stockholm County and included a total of more than 22,000 adults followed for up to 20 years. Three of the papers in the thesis used only one of these cohorts, the SDPP cohort, including close to 8,000 subjects at recruitment. Individual assessment of exposure to noise from road traffic, railways or aircraft was based on a detailed residential history for each study participant as well as a newly developed database containing longitudinal information on determinants of noise levels generated by the three transportation noise sources. Data on air pollution exposure was obtained from dispersion models based on a similar methodology. Information on covariates and health outcomes was based on questionnaires and registers, and the health outcome data were further supplemented with information from clinical investigations.

For obesity markers, the strongest associations were observed in relation to aircraft noise. A 10 dB higher level in exposure was associated with a waist circumference increase and weight gain of 0.16 cm/year (95% CI 0.14–0.17) and 0.03 kg/year (95% CI 0.01–0.04), respectively. Road traffic noise exposure was related to a waist circumference increase of 0.04 cm/year (95% CI 0.02–0.06) per 10 dB L_{den} , while no clear association was observed for railway noise. The incidence rate ratio of central obesity in relation to number of sources of transportation noise exposure increased from 1.22 (95% CI 1.08–1.39) among those exposed to only one source to 2.26 (95% CI 1.55–3.29) among those exposed to all three transportation noise sources. Moreover, aircraft noise exposure was related to incidence of hypertension (hazard ratio: 1.16; 95% CI 1.08–1.24 per 10 dB L_{den}), but no associations appeared for other transportation noise sources. No clear or consistent associations were observed between transportation noise exposure and risk of ischemic heart disease (IHD) or stroke. However, there appeared to be an increased risk of IHD in women related to road traffic noise exposure, while the opposite held true for men. Higher risks appeared of both IHD and stroke incidence in those exposed to all three noise sources, with hazard ratios of 1.57 (95% CI 1.06–2.32) and 1.42 (95% CI 0.87–2.32), respectively.

In conclusion, our findings indicate adverse effects of long-term transportation noise exposure on some metabolic and cardiovascular outcomes, and suggest that combined exposure to different transportation noise sources may be particularly harmful.

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- III. **Pyko, A.**, Lind, T., Mitkovskaya, N., Ögren, M., Östenson, C.-G., Wallas, A., Pershagen, G., Eriksson, C. Transportation noise and incidence of hypertension. Under revision for *Int. J. Hyg. Env. Health*.
- IV. **Pyko, A.**, Andersson, N., Eriksson, C., de Faire, U., Lind, T., Mitkovskaya, N., Ögren, M., Östenson, C.-G., Pedersen, N. L., Rizzuto, D., Wallas, A., Pershagen, G. Long-term transportation noise exposure and incidence of ischemic heart disease and stroke. Manuscript.

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LIST OF ABBREVIATIONS

BC	Black Carbon
BMI	Body-mass index
CEANS	The Cardiovascular Effects of Air pollution and Noise in Stockholm Cohort
CI	Confidence interval
CVD	Cardiovascular diseases
DAG	Directed Acyclic Graph
GIS	Geographical Information Systems
HPA axis	Hypothalamic-Pituitary-Adrenal axis
HR	Hazard ratio
ICD	International Classification of Diseases
IHD	Ischemic heart disease
IRR	Incidence rate ratio
$L_{Aeq,24h}$	The equivalent continuous A-weighted sound pressure level during 24-h
L_{den}	The equivalent continuous A-weighted sound pressure level during 24-h, with penalties for exposure occurring during evening and night
L_{night}	The equivalent continuous A-weighted sound pressure level during night time
MI	Myocardial infarction
NO_x	Nitrogen Oxides
OR	Odds Ratio
RR	Relative risk
SALT	The Screening Across the Lifespan Twin Study
SAM axis	Sympathetic-Adrenal-Medullary axis
SDPP	The Stockholm Diabetes Preventive Program
SIXTY	The cohort study of 60 year old men and women from Stockholm
SNAC-K	The Swedish National Study of Aging and Care in Kungsholmen
WHO	World Health Organization

*

1 INTRODUCTION

Over last decades there has been a shift of the global burden of diseases from communicable to non-communicable, such as metabolic and cardiovascular diseases (CVD). Recent studies indicate that environmental factors may contribute to the development of CVD (Lim et al., 2012). Among these, air pollution and transportation noise may contribute to up to 75% of the burden of disease attributable to environmental factors in Europe (Hänninen et al., 2014).

The number of people exposed to noise is growing because of increasing transportation and urbanisation. Currently, large parts of the population are exposed to increased levels of noise, particularly from traffic. In Europe, 67% of the population living in agglomerations with more than 250,000 inhabitants is exposed to road traffic noise levels exceeding the WHO guideline value of 55 dB L_{den} (EEA, 2009; WHO, 2009). It has been estimated that transportation noise leads to more than 1 million healthy life-years lost each year in Western Europe, attributed mostly to sleep disturbance and annoyance, but cardiovascular diseases also contribute substantially (Mendis et al., 2011).

In Sweden, more than two million people are exposed to traffic noise levels exceeding 55 dB L_{den} outside their residence and almost one million are annoyed by noise in their dwelling. Recent data indicate that both road traffic and railway noise contribute to the burden of disease in Sweden, including nearly 1,000 cases of myocardial infarction yearly (Eriksson et al., 2017). Significant exposure to aircraft noise also occurs in certain areas.

1.1 TRANSPORTATION NOISE

In general, noise can be defined as any sound that is subjectively unpleasant or disturbing and causes unwanted effects. These effects are manifested through direct pathways or indirectly, involving cognitive perception (Babisch, 2002). Sound pressure is measured in decibels (dB) and expressed on a logarithmic scale. In environmental and epidemiological literature the noise indicators most commonly used include:

$L_{Aeq,24h}$	The equivalent continuous A-weighted sound pressure level during 24-h.
L_{den}	The equivalent continuous A-weighted sound pressure level during 24-h, with a 10 dB penalty added to the levels during the night and a 5 dB penalty added to the levels during evening hours to reflect the extra sensitivity to noise during these time periods.
L_{night}	The equivalent continuous A-weighted sound pressure level during night time.

A-weighting is applied to the sound spectrum to represent the sensitivity of the human hearing organ to different frequencies.

In Europe, road traffic is the dominating source of transportation noise, however, both railways and aircraft contribute in certain areas. Various noise sources produce noise with different acoustic characteristics (sound level, frequency spectrum, time course, sound level rise time etc.) and have different diurnal distributions. Therefore, noise levels from different noise sources cannot easily be merged into one indicator and separate exposure-response curves are used for different noise sources (van Kempen and Babisch, 2012). Moreover, exposure to different noise sources can have both independent as well as joint adverse health effects and it is desirable to assess effects of exposure to each of noise sources separately as well as to evaluate the effect of combined exposure to noise from different sources.

1.2 METABOLIC AND CARDIOVASCULAR DISEASES

1.2.1 Obesity

Overweight and obesity is defined by WHO as “abnormal or excessive fat accumulation that may impair health”. It is mainly caused by an imbalance between energy intake and energy use. One can assess *general* obesity using the Body Mass Index (BMI) which is defined as a person's weight in kilograms divided by the square of the height in meters (kg/m^2). BMI is used to classify overweight and obesity ($\text{BMI} \geq 25 \text{ kg/m}^2$ and $\geq 30 \text{ kg/m}^2$, respectively) (WHO, 2000). However, BMI does not distinguish differences in body composition. Therefore, other measures are also used, such as waist circumference or waist-hip ratio, which are measures of *central* (abdominal) obesity. According to WHO, those in the European population with a waist circumference over 102 cm (men) and 88 cm (women) are classified to have a substantially increased risk of metabolic complications (WHO, 2008).

The worldwide prevalence of obesity nearly doubled between 1980 and 2014 (WHO, 2014). Both general and central obesity are risk factors for diabetes, hypertension, coronary heart disease and stroke, certain cancers, obstructive sleep apnoea and reproductive problems as well as overall mortality (WHO, 2014, 2008). WHO has estimated that more than 1.9 billion adults were overweight and over 650 million of these were obese (WHO, 2015). Moreover, at least 3.4 million deaths per year worldwide may be attributed to overweight or obesity (Ng et al., 2014).

1.2.2 Hypertension

Hypertension is a condition in which the blood vessels have persistently raised pressure. During 1975–2015, the number of adults with hypertension increased from 594 million to more than 1.13 billion worldwide, largely in low-income and middle-income countries (Zhou et al., 2017). The increasing prevalence is explained by population growth and ageing, as well as by behavioural risk factors. In 2015, high blood pressure was associated with the highest global burden of disease among all risk factors – more than smoking or obesity (Forouzanfar et al., 2016). Independently or together with other risk factors, hypertension increases the risk of coronary heart disease, stroke and kidney failure. Therefore, of the more than 17 million

deaths a year attributed to CVD, nearly 9.4 million are complications of hypertension (Lim et al., 2012). At least 45% of the deaths due to CVD and 51% of the deaths due to stroke can be attributed to hypertension (WHO, 2013).

1.2.3 Cardiovascular diseases

Cardiovascular diseases are the leading cause of death globally (WHO, 2014), and contribute to more than one-third of the global mortality. In 2015, WHO estimated that 17.7 million people died from CVD, including 7.4 million due to coronary heart disease and 6.7 million due to stroke.

Behavioural risk factors such as tobacco smoking, physical inactivity, unhealthy diet and alcohol overuse are important risk factors for CVD. These factors are also related to metabolic outcomes (diabetic conditions, dyslipidemia, obesity), which can be intermediate steps in the development of CVD. Atherosclerosis is often contributing to CVD development, and is an inflammatory process affecting the blood vessels. The inflammation leads to accumulation of fatty acids and cholesterol, forming fatty deposits (plaque), which makes it harder for blood to flow through the vessel. Moreover, the plaque may rupture and release thrombogenic agents, which can lead to a block of a coronary or cerebral blood vessel. Thus, coronary heart disease (including myocardial infarction) and cerebrovascular disease (stroke) can be caused. Moreover, atherosclerosis is a pathway to develop diseases of the arteries, including hypertension and peripheral vascular disease.

1.3 HEALTH EFFECTS OF TRANSPORTATION NOISE

The evidence on biological effects of transportation noise is provided by laboratory studies, field investigations and epidemiological research. Acute effects such as hearing loss or tinnitus occur if the sound level is high. Effects of long-term exposure to more moderate levels of noise may develop over years of exposure. The pathogenic mechanisms bridging the gap between acute and chronic effects of traffic noise are not fully understood but probably involve consequences of long-term stress and sleep disturbances (Basner et al., 2015; Brink, 2012). This thesis is focused on long-term exposure to transportation noise and its adverse health effects, especially on CVD and metabolic outcomes.

Long-term exposure to noise from road traffic, railways and aircraft has been studied in relation to metabolic diseases and CVD primarily during the last decade. The most recent studies were summarized in a systematic review by van Kempen et al. (2017) performed within the framework of the development of new WHO Environmental Noise Guidelines for the European Region. The evidence from the WHO review and other studies is presented below separately for each of the outcomes under study, to some extent including data published after the thesis work was initiated.

1.3.1 Obesity

The first study on obesity in relation to transportation noise had a longitudinal design and showed an association between aircraft noise exposure and waist circumference with an increment of 1.51 cm and 95% confidence interval (CI) of 1.13–1.89 *per* 5 dB L_{den} , however, no clear associations were reported for other metabolic markers like body mass index or type 2 diabetes (Eriksson et al., 2014).

Recent studies have provided inconsistent results on road traffic noise exposure and obesity markers. A cross-sectional Norwegian study did not find an association between road traffic noise exposure and BMI with estimates of 0.01 (95% CI -0.11–0.13) and -0.04 (95% CI -0.14–0.06) kg/m^2 *per* 10 dB L_{den} in women and men, respectively (Ofteidal et al., 2015). The only statistically significant positive association was seen in highly noise sensitive women. A cross-sectional study from Denmark reported associations between road traffic noise 5 years preceding the enrolment and BMI as well as waist circumference with estimates of 0.19 kg/m^2 (95% CI 0.13–0.24) and 0.30 cm (95% CI 0.16–0.45) *per* 10 dB L_{den} , respectively (Christensen et al., 2016). The findings were confirmed in a longitudinal study of the same cohort with road traffic being associated with a yearly weight gain of 15.4 g (95% CI 2.14–28.7) and a yearly waist circumference increase of 0.22 mm (95% CI 0.02–0.43) *per* 10 dB L_{den} during a mean follow-up time of 5 years (Christensen et al., 2015). For road traffic noise, the WHO systematic review by van Kempen et al. (2017) reported non-significant combined estimates of 0.03 kg/m^2 (95% CI -0.10–0.15) *per* 10 dB L_{den} for BMI and 0.17 cm (95% CI -0.06–0.40) *per* 10 dB L_{den} for waist circumference.

Considering railway noise, a cross-sectional Danish study found statistically significant associations of 0.18 kg/m^2 (95% CI 0.00–0.36) for BMI and 0.62 cm (95% CI 0.14–1.09) for waist circumference in those exposed to rail traffic noise at levels above 60 dB L_{den} (Christensen et al., 2016). A longitudinal study from the same team reported estimates for weight gain and waist circumference change in relation to railway noise of 3.57 g/year (95% CI -6.07–13.2) and of -0.065 mm/year (95% CI -0.22–0.093) *per* 10 dB L_{den} , respectively (Christensen et al., 2015).

Overall, some findings suggest that transportation noise may be associated with obesity markers, however, the WHO-review rated the quality of the evidence as “low” and indicated a need of further research (van Kempen et al., 2018). Moreover, longitudinal data are limited as well as studies on combined exposure to different noise sources.

1.3.2 Hypertension

The majority of available publications on transportation noise and hypertension are of cross-sectional design. The first longitudinal study on hypertension in relation to transportation noise was performed by Eriksson et al. (2007). A subsequent report based on this cohort showed a tendency to a positive association for the incidence of hypertension in relation to aircraft noise for men, with relative risk (RR) of 1.17 (95% CI 0.90–1.51), but not for women (RR 0.85; 95% CI 0.62–1.15) *per* 10 dB L_{den} (Eriksson et al., 2010). Overall, the combined

RR estimated in the WHO-review was 1.00 (95% CI 0.77–1.30) *per* 10 dB L_{den} . Aggregated data from nine cross-sectional studies on aircraft noise tended to show an association with hypertension (RR 1.05; 95% CI 0.95–1.17). A recent cohort study from Greece reported that nighttime aircraft noise was associated with incident hypertension with an OR of 2.63 (95% CI 1.21–5.71) *per* 10 dB L_{night} (Dimakopoulou et al., 2017).

The WHO-review found a statistically significant association between road traffic noise and hypertension prevalence with a RR of 1.05 and 95% CI of 1.02–1.08 *per* 10 dB L_{den} based on a meta-analysis of 26 cross-sectional studies (van Kempen et al., 2018). This was, however, not confirmed in a cohort study from Denmark, reporting an incidence rate ratio (IRR) of 0.97 (95% CI 0.90–1.05) *per* 10 dB L_{den} (Sørensen et al., 2011b). In a recent report from the ESCAPE consortium road traffic noise tended to be weakly associated with the incidence of self-reported hypertension but not with measured hypertension, displaying RRs of 1.03 (95% CI 0.99–1.07) and 0.99 (95% CI 0.94–1.04) *per* 10 dB L_{den} , respectively (Fuks et al., 2017).

For railway noise, the WHO-review included four cross-sectional investigations together showing a tendency to an association with prevalence of hypertension, RR 1.05 (95% CI 0.88–1.26). Furthermore, a longitudinal study by Sørensen et al. (2011b) suggested a positive association for incidence of hypertension with an IRR of 1.08 (95% CI 0.98–1.19) in those exposed to railway noise of 60 dB L_{den} or more.

Summing up, the WHO-review rated the quality of the evidence on transportation noise and hypertension as “very low” and indicated that any estimate of effect is uncertain (van Kempen et al., 2018). This primarily had to do with the fact that mostly cross-sectional studies were available with well-known limitations regarding possibilities for causal inference.

1.3.3 Ischemic heart disease and stroke

Over the last decades there is growing evidence of adverse cardiovascular effects of transportation noise from different sources based on studies of prevalence, incidence as well as mortality from IHD and stroke. Regarding road traffic noise the WHO-review included results from three cohort and four case-control studies and reported a statistically significant association for incidence of IHD with a RR of 1.08 (95% CI 1.01–1.15) *per* 10 dB L_{den} (van Kempen et al., 2018). Moreover, a visualisation of the shape of the association indicated that the risk of IHD increased continuously from above 50 dB L_{den} . Overall, the quality of the evidence for road traffic noise and incidence of IHD was rated as “high”.

For aircraft noise and incidence of IHD, the review calculated a RR of 1.09 (95% CI 1.04–1.15) *per* 10 dB L_{den} based on two studies with ecological design. Considering railway noise, the review included four cross-sectional studies with a pooled RR of 1.18 (95% CI 0.82–1.68) *per* 10 dB L_{den} for prevalence of hypertension. The quality of the evidence was rated as “very low” (van Kempen et al., 2018).

The WHO-review suggested an association of transportation noise with CVD mortality and reported combined RR estimates for aircraft and road traffic noise of 1.04 (95% CI 0.97–1.12) and 1.05 (95% CI 0.97–1.13) *per* 10 dB L_{den} , respectively. Moreover, a recent nationwide cohort study from Switzerland found statistically significant associations for all three transportation noise sources and myocardial infarction mortality with adjusted hazard ratios (HR) *per* 10 dB L_{den} of 1.038 (95% CI 1.019–1.058), 1.018 (95% CI 1.004–1.031), and 1.026 (95% CI 1.004–1.048) from road traffic, aircraft and railways, respectively (Héritier et al., 2017).

Relatively few studies have investigated the impact of transportation noise on stroke. One cohort study showed a RR for stroke incidence related to road traffic noise exposure of 1.14 (95% CI 1.03–1.25) *per* 10 dB L_{den} (Sorensen et al., 2011). With regard to aircraft noise, the WHO-review included two ecological studies with combined RRs of 1.05 (95% CI 0.96–1.15) *per* 10 dB L_{den} for stroke incidence and 1.07 (95% CI 0.98–1.17) *per* 10 dB L_{den} for stroke mortality (van Kempen et al., 2018). Overall, The WHO systematic review rated the quality of the evidence supporting an association between transportation noise and stroke as “low”.

It may be concluded that, with the exception of road traffic noise and IHD, very few longitudinal studies are available on cardiovascular effects of transportation noise. However, the plausibility of an association calls for further and improved research. Furthermore, little is known about induction periods for cardiovascular effects of noise and the impact of combined exposure to noise from several sources.

1.3.4 Interactions

Transportation noise exposure is one among many environmental stressors that may cause adverse health effects. According to the multiple environmental stressor theory, several stressors may enhance the effect of each other (Stansfeld and Matheson, 2003). Thus, in a case-control study on myocardial infarction in Stockholm County Selander et al. (2013) found that exposure to a combination of traffic noise, occupational noise and job strain is particularly harmful. Participants exposed to one, two, or three of these factors showed increasing risks of myocardial infarction with ORs of 1.16, (95% CI 0.97–1.40), 1.57 (95% CI 1.24–1.98) and 2.27 (95% CI 1.41–3.64), respectively. Moreover, simultaneous exposure to two or three of these factors was common and occurred among about 20% of the controls. In most epidemiological studies on health risks related to noise exposure effects of combined exposure to different noise sources were not investigated. The only evidence on obesity in relation to transportation noise is available from a Danish study suggesting a stronger association between road traffic noise and weight gain as well as waist circumference increase in those simultaneously exposed to railway noise > 55dB L_{den} (Christensen et al., 2015). There is a great need for further investigations of interactions between different environmental stressors including noise for both metabolic outcomes and CVD.

Several epidemiological studies have reported an interaction between transportation noise exposure and age. Studies on hypertension by Bodin et al. (2009) and de Kluizenaar et al. (2007) showed stronger associations for road traffic noise among middle-aged (40-60 years) than at higher ages. However, cohort studies focused on stroke and type 2 diabetes indicated stronger effects in those over 60 and 64 years of age, respectively (Sørensen et al., 2011a, 2014). Available studies on obesity in relation to transportation noise did not report age interactions (Christensen et al., 2015, 2016; Oftedal et al., 2015).

The evidence on gender interaction in noise studies appears inconsistent. For example, Eriksson et al. (2010) reported a significantly increased risk of hypertension in relation to an aircraft noise exposure increase of 5 dB L_{den} in men, but not in women. Babisch et al. (2005) found that road traffic exposure >70 dB $L_{day(6-22)}$ was associated with myocardial infarction only in men. Results of a Danish cohort study on myocardial infarction also suggested stronger effects in men (Sørensen et al., 2012). Huss et al. (2010) reported increased risks of MI mortality related to aircraft noise in men but not in women. However, Selander et al. (2009b) and Beelen et al. (2009) did not find gender differences in cardiovascular incidence and mortality related to road traffic noise. Moreover, Gan et al. (2012) reported no gender differences but found a 7% nonsignificant excess risk of coronary mortality in women after adjustment for traffic-related air pollutants.

There is conclusive evidence that long-term exposure to air pollution such as airborne particles can increase the risk of cardiovascular disease (WHO, 2016). However, it is not common in noise studies to have measures of air pollution or address the issue of co-exposure to noise in air pollution studies, although the two exposure factors may have important common sources, such as road traffic. There is a limited number of studies reporting on interaction effects between noise and air pollution exposure in relation to the risk of cardiovascular or metabolic diseases. Selander et al. (2009b) investigated possible modification of the association between road traffic noise and incidence of myocardial infarction by air pollution but no strong interaction was revealed.

1.4 BIOLOGICAL MECHANISMS OF NOISE EFFECTS

1.4.1 General stress model

According to the general stress model, noise can cause metabolic effects and CVD by activating the nervous and endocrine systems, as well as by affecting the quality of sleep, communication, and activities, with subsequent emotional and cognitive responses, including annoyance (Babisch, 2003).

The auditory system is as an important warning system which remains active also during sleep. Noise-induced effects are generally realized through two different systems, the Sympathetic-Adrenal-Medullary (SAM) axis and the Hypothalamic-Pituitary-Adrenal (HPA) axis (Lundberg, 1999; Spreng, 2000a). The SAM axis describes how the body prepares for “fight-or-flight” with the mobilisation of energy to the muscles, heart and brain, as well as

reduction of blood flow to the internal organs by secretion of adrenaline and noradrenaline from the adrenal medulla. Effects of adrenaline and noradrenaline include increased heart rate, stroke volume and vasoconstriction (resulting in increased blood pressure), mobilisation of glucose and free fatty acids as well as aggregation of thrombocytes (Babisch, 2003).

The HPA axis is responsible for an endocrine response with production of glucocorticoids, including cortisol (Majzoub, 2006). Effects of cortisol include elevation of blood glucose levels, lipolysis, suppression of immune responses and elevation of blood pressure (Babisch, 2003; Spreng, 2000b). Hyperactivity of the HPA axis, commonly seen in chronic stress situations, is characterised by a “defeat-type” of reaction and associated with feelings of distress, anxiety and depression (Björntorp, 1997; Martinac et al., 2014). Imbalance of the stress system may be detrimental to health. Chronically high levels of cortisol may lead to several health effects including alterations in the adipose tissue and visceral fat deposition, hypertension, dyslipidemia and insulin resistance (Björntorp, 1997; Eriksson et al., 2014, 2010; Kyrou and Tsigos, 2007; Rosmond, 2003; Selander et al., 2009a; Spreng, 2000b).

1.4.2 Sleep disturbances

Transportation noise effects on cardiovascular or metabolic functions may also be mediated through sleep disturbances. Normally sleep has a restorative effect with reduced heart rate and blood pressure, as well as decreased brain glucose metabolism. This effect is achieved by inhibited activity of the HPA axis and the sympathetic nervous system as well as a release of anabolic growth hormones (Van Cauter et al., 2008). Short-term effects of transportation noise on sleep can be divided into *immediate primary* (cortical arousals and awakenings, sleep stage change and autonomic cardiovascular arousal) and “*next-day*” *secondary* effects (fatigue, drowsiness and reduced performance). If transportation noise exposure persists over an extended period of time a chronic noise-induced sleep disturbance may arise (Muzet, 2007; Pirrera et al., 2010). Sleep disturbance together with non-habituating autonomic reactions are believed to cause chronic health effects of noise. Thus, long-term evening and night-noise exposure may be of greater importance than daytime exposure. Furthermore, Miedema and Vos (2007) showed clear exposure-response associations between night-time noise and self-reported sleep disturbance. Aircraft noise is associated with more sleep disturbances than road traffic, followed by railway noise at comparable noise levels. However, road traffic as the most common source of transportation noise contributes to more sleep disturbances in the general population than aircraft and railway noise.

Sleep-deprivation may be of importance for development of metabolic changes by effects on carbohydrate metabolism and appetite regulation. Studies have shown associations between sleep-restriction and impaired glucose tolerance, decreased insulin sensitivity as well as an increased risk of type 2 diabetes (Spiegel et al., 1999; Cappuccio et al., 2010). The two hormones ghrelin and leptin are regulators of food intake and exert opposing functions on appetite and energy expenditure. Disturbance of sleep may affect the balance of these hormones by reducing leptin and increasing ghrelin, subsequently leading to increased adiposity and body mass index (Chaput et al., 2007; Taheri et al., 2004).

2 AIMS

The main aim of this thesis was to study development of obesity and cardiovascular outcomes in relation to exposure to noise from road traffic, railways and aircraft, particularly the role of interactions.

The specific aims were to:

- Assess the association between exposure to different transportation noise sources and markers of obesity, particularly waist circumference and weight.
- Investigate the association between exposure to different transportation noise sources and cardiovascular outcomes, primarily hypertension, ischemic heart disease and stroke.
- Study the role of combined exposure to multiple sources of transportation noise for development of obesity and cardiovascular outcomes.
- Assess the importance of interactions between exposure to transportation noise and air pollution as well as other risk factors in relation to obesity and cardiovascular diseases.

3 MATERIAL AND METHODS

3.1 STUDY POPULATIONS

This thesis is based on four cohorts from Stockholm County, Sweden. These include the Stockholm Diabetes Preventive Program (SDPP), the cohort study of 60-year-old men and women from Stockholm (SIXTY), the Screening Across the Lifespan Twin Study (SALT) and the Swedish National Study of Aging and Care in Kungsholmen (SNAC-K). Taken together the four cohorts comprise the CEANS cohort (Cardiovascular Effects of Air pollution and Noise in Stockholm). The SDPP cohort constituted the study population for papers I, II and III of the thesis, while paper IV was based on the CEANS cohort. A few individuals were recruited into more than one of the CEANS cohorts, however, these were only included in the cohort where they were first recruited.

3.1.1 The Stockholm Diabetes Preventive Program

This program was conducted 1992–2006 in Stockholm County to study risk factors for type 2 diabetes as well as to implement and evaluate methods for prevention. It constitutes a population-based cohort study of 3,128 men and 4,821 women aged 35–54 years at recruitment (Figure 1).

The recruitment of men was done in 1992–1994 and of women in 1996–1998 in five municipalities of Stockholm County (Värmdö, Upplands-Bro, Upplands Väsby, Tyresö and Sigtuna). By design no participants had previously been diagnosed with diabetes and approximately half (53%) had a family history of diabetes in at least one first-degree relative (mother, father, sister or brother), or in at least two second-degree relatives (grandparent, uncle or aunt). The other half of the cohort was matched on age and sex but without a family history of diabetes (Eriksson et al., 2008).

The baseline investigation at recruitment included a questionnaire which covered health status as well as lifestyle habits and potential risk factors such as smoking, alcohol intake, physical activity during leisure time, dietary habits, psychological distress, shift work, insomnia and job strain. Furthermore, trained nurses performed a medical examination including measurements of blood pressure, weight, height and waist circumference.

A follow-up investigation was conducted 2002–2004 for men and 2004–2006 for women focusing on all 7,111 participants from the original study who did not die or move out of Stockholm County (Figure 1). In total, 2,383 men and 3,329 women participated (72% of those in the original sample). The follow-up protocol repeated the baseline investigation but the questionnaire was extended with a section on noise annoyance and noise sensitivity. Subjects participating in both baseline and follow-up investigations without obesity or hypertension at baseline constituted the study base for papers II and III, respectively. The 5,712 subjects from the follow-up investigation formed the basis for the cross-sectional analysis in paper I. Furthermore, this cohort was a part of the study base for paper IV.

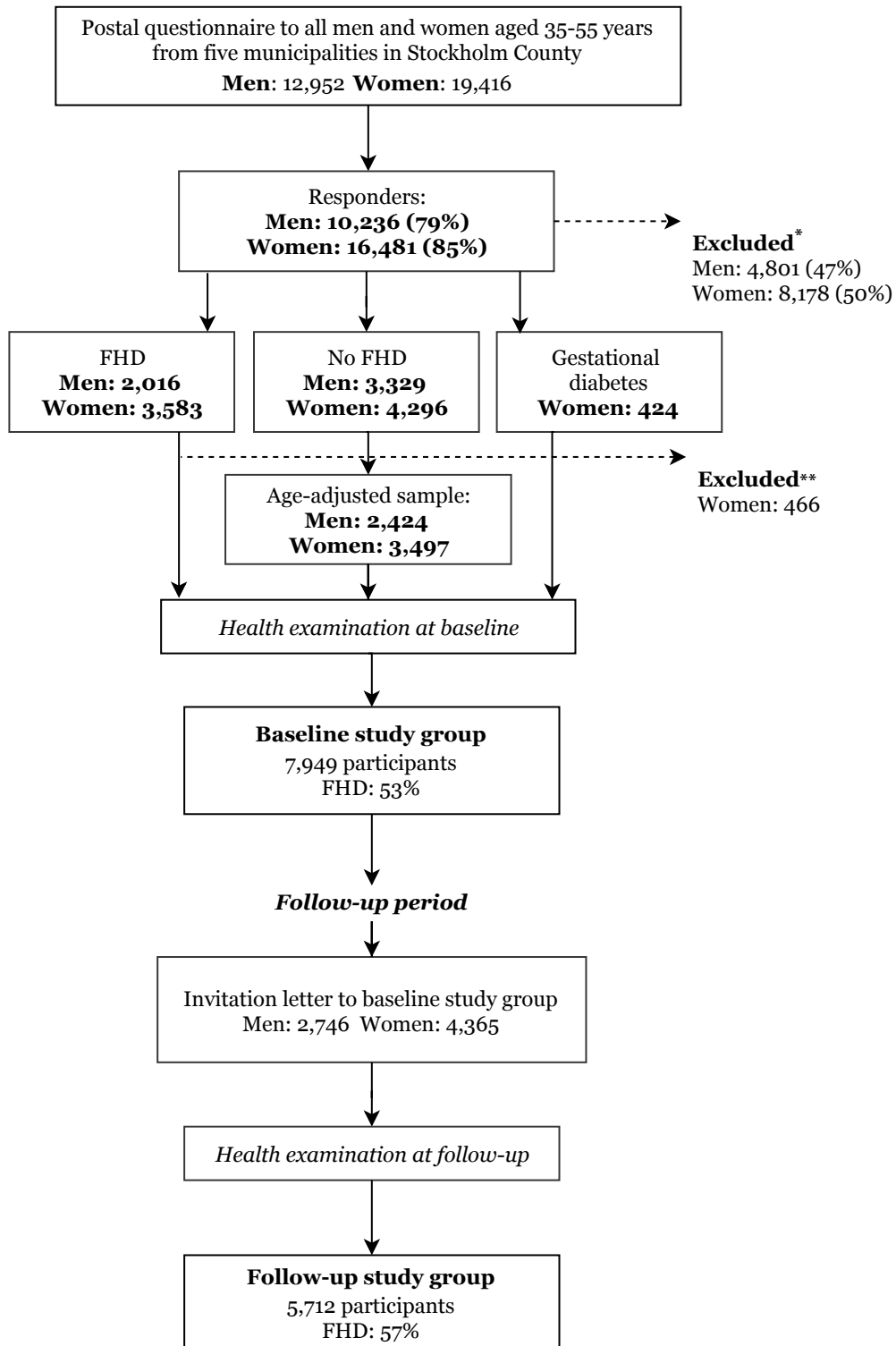


Figure 1. Baseline and follow-up study of men and women in the Stockholm Diabetes Prevention Program.

*Persons were excluded as a result of diabetes, foreign origin, unclear family history of diabetes or insufficient information about family history of diabetes. Females aged 35 to 44 years born in the last third of each month were excluded for financial reasons.

** Excluded during the matching procedure.

3.1.2 The cohort study of 60-year-old men and women from Stockholm

This cohort was established to study biological and socio-economic risk factors as well as predictors for cardiovascular diseases (Wändell et al., 2007). It was formed from a random population sample of one-third of all men and women living in Stockholm County who turned 60 years of age between August 1997 and March 1999 (N=5,460). Finally, the cohort included 4,232 subjects (77% of those invited) who filled in a questionnaire covering health status as well as lifestyle habits and potential risk factors for cardiovascular disease. These subjects were included in the study base for paper IV.

3.1.3 The Screening Across the Lifespan Twin Study

The Screening Across the Lifespan Twin Study was used as a sampling frame to select individuals from the Swedish Twin Register who lived in Stockholm County and were investigated in 1998-2002 (Lichtenstein et al., 2006). For all recruited participants a computer-assisted telephone interview was conducted, including information on lifestyle and risk factors for cardiovascular disease. A total of 7,043 participants constituted part of the study base for paper IV.

3.1.4 The Swedish National Study of Aging and Care in Kungsholmen

This study had the main aim to improve the understanding of the ageing process and to identify possible preventive strategies to improve health and care in the elderly. It included 3,363 randomly sampled individuals ≥ 60 years of age between March 2001 and June 2004 from Kungsholmen, a central area in Stockholm city (Lagergren et al., 2004). The study participants were stratified for age and year of assessment. Information on potential confounders was collected through interviews, clinical examinations and cognitive tests. In total, 3,363 subjects from this cohort were included in paper IV.

3.2 ENVIRONMENTAL EXPOSURES

A detailed residential history from 1990 and onwards was collected for all study subjects (Figure 2). This is based on computerized address data from the Swedish Tax Agency. The addresses were transformed to geographical coordinates using a property register managed by the Swedish Mapping, Cadastral and Land Registration Authority. The total number of addresses of the study subjects in all four cohorts was 52,225. Automatic geocoding was successful for more than 98%, and following supplementation with manual geocoding about 99% of the addresses could be geocoded. The residential history data were used for the transportation noise and air pollution exposure assessment.

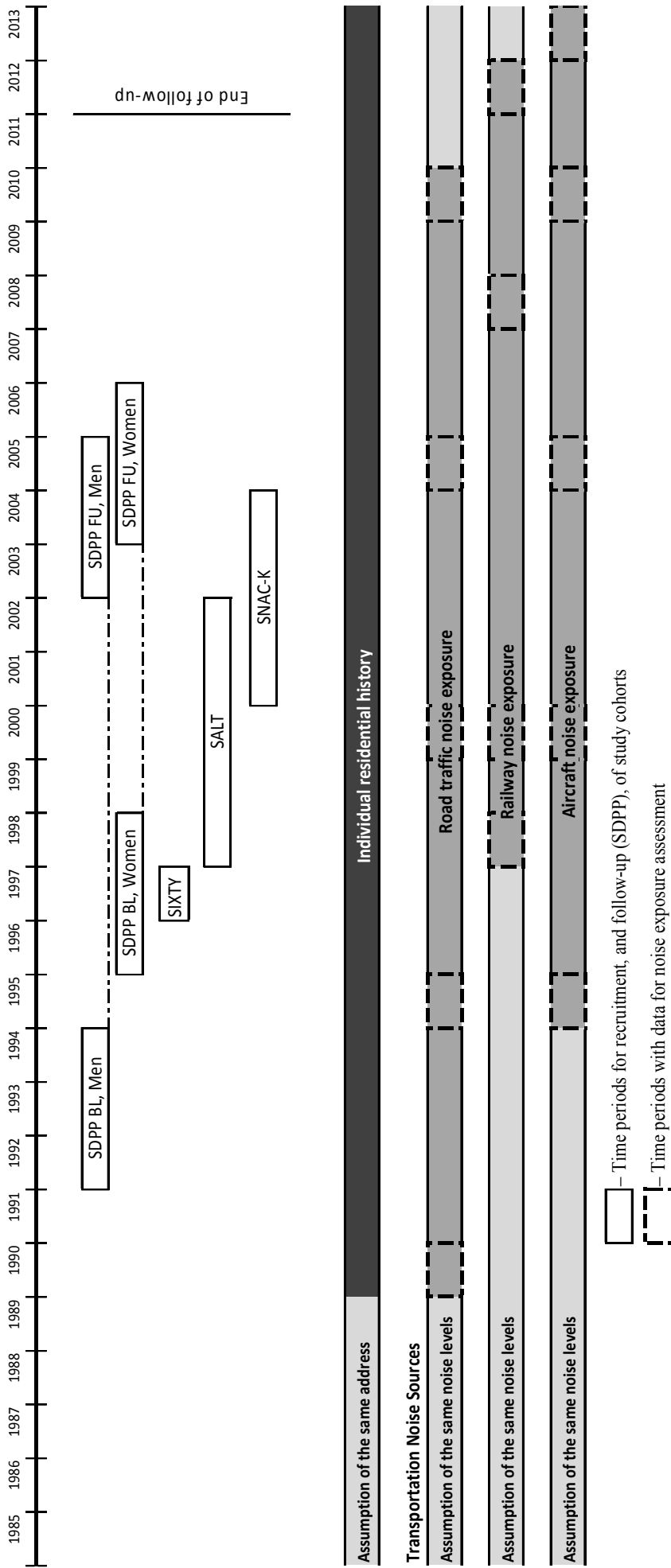


Figure 2. Timeline for enrolment of study participants and collection of information for transportation noise exposure assessment in Stockholm County. SDPP –the Stockholm Diabetes Preventive Program; BL – baseline investigation; FU – follow-up investigation; SIXTY –the cohort study of 60 year old men and women from Stockholm; SAL T – the Screening Across the Lifespan Twin Study; SNAC-K – the Swedish National Study of Aging and Care in Kungsholmen.

3.2.1 Transportation noise

To estimate long-term exposure to road traffic, railway and aircraft noise, we developed a database for calculation of noise levels at residences in Stockholm County as well as a methodology to assess individual noise exposure based on geocoded addresses. The database contains essential information for the noise exposure assessment which was provided by different authorities and agencies (Figure 3). Most of this information was used for the exposure assessment in the thesis:

- 3-dimensional shape of the terrain surface
- road traffic flows on different roads segments for the years 1990, 1995, 2000, 2005 and 2010
- speed limits on the roads
- percentage of heavy vehicles on the roads
- number of light and heavy trains of different types on each railway segment and their speed limits in 2008 and 2012
- train schedules and types of trains 1995-2010
- GIS maps of aircraft noise levels around the two main airports for the years 1995, 2000, 2005, 2010 and 2013
- GIS shapes of all buildings
- shapes of noise barriers
- information about noise insulation measures in Stockholm municipality because of road and railway noise as well as around the Arlanda and Bromma airports.

For papers II, III and IV road traffic and railway noise exposure data were estimated using the noise database. We modelled the 24-h A-weighted continuous sound pressure level at relevant residential addresses based on the information in the database and a simplified version of the Nordic prediction method. The methodology has been validated against the full Nordic prediction method with satisfactory results (Ögren and Barregard, 2016). We converted the L_{Aeq24h} values to L_{den} using penalties of 5 and 10 dB for the evening (19–23) and night (23–07) periods, respectively, and assuming a 24h traffic flow distribution of 75/20/5% during day, evening and night, respectively, for road traffic and the exact 24h distribution for separate segments of the railway lines.

Information on aircraft noise exposure was obtained as noise contours around the Arlanda and Bromma airports for the years 1995, 2000, 2005, 2010 and 2013. For the year 1990, we assumed the same noise level as for 1995 since there were no major structural changes at either of the two airports during this time period. The noise contour data ranged from 45 to 70 dB L_{den} around Arlanda and from 40 to 70 dB L_{den} around Bromma. By superimposing the noise contour data on a layer of buildings where the study participants had lived, each address could be assigned a corresponding noise level.

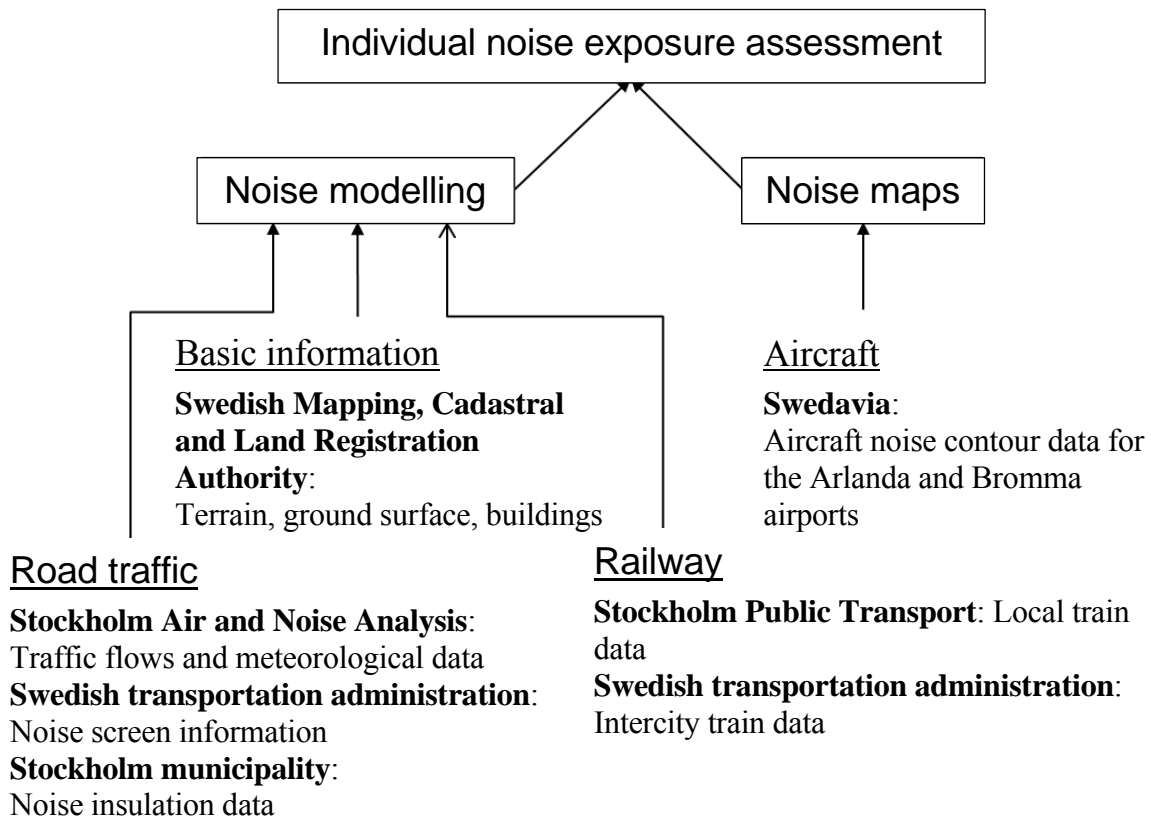


Figure 3. Data sources and providers used for transportation noise exposure assessment 1990-2010 in Stockholm County.

For paper I, we used digitalised maps, primarily from municipalities, of road and railway traffic noise exposure. Levels were expressed in $L_{Aeq,24h}$ with a 5 dB resolution, modelled using the Nordic Prediction Method, and developed according to the European Environmental Noise Directive (EC, 2002). The $L_{Aeq,24h}$ values were recalculated to L_{den} in the same way as described above. Aircraft noise around Arlanda airport was assessed using digital noise maps with 1 dB resolution (range 50 to 65 dB L_{den}) reflecting the period 1997–2002. The aircraft noise data were provided by Swedavia. Geocoded residential addresses where SDPP participants lived at the follow-up investigation were used to obtain individual noise exposure from all three transportation sources.

3.2.2 Air pollution

For paper I–III exposure to air pollution from local road traffic was assessed by dispersion modelling based on a methodology developed to assess long-term source-specific exposure in Stockholm County (Bellander et al., 2001; Gruzieva et al., 2012). The annual mean concentrations of NO_x from local road traffic were calculated using a Gaussian air-quality dispersion model and a wind model, both of which are part of the Airviro Air Quality Management system (<http://airviro.smhi.se>). For paper IV we used an updated methodology

based on dispersion modelling developed to assess long-term source-specific exposure to PM₁₀, PM_{2.5} and Black Carbon (BC) (Segersson et al., 2017). We used annual levels at residential addresses of the study subjects at the follow-up investigation in study I, or estimated time-weighted exposure during relevant time periods based on the residential history for papers II–IV.

3.3 OTHER COVARIATES

For papers I–III we obtained information on potential confounders from the SDPP questionnaires. Thus, for paper I we used data from the follow-up investigation; while for papers II and III we used data from the baseline investigation combined with a section about noise annoyance and noise sensitivity from the follow-up questionnaire. For both papers I and II we evaluated covariates as confounders based on a literature search and development of a relevant directed acyclic graph (DAG) (Textor et al., 2011, 2016). The DAG was used to select a set of confounders for the main models to evaluate associations between transportation noise and obesity. In paper III we included covariates that were significantly associated with the outcome in the final model. In paper IV we homogenized and pooled questionnaire data from the four cohorts and adjusted our models for *a priori* variables identified from the literature as risk factors for ischemic heart disease and/or stroke. Furthermore, for all papers information on household mean income in small geographical areas with an average population of 1,000–2,000 subjects was obtained from registers held by Statistics Sweden to adjust for potential contextual confounding.

3.4 HEALTH OUTCOMES

For papers I and II the assessment of obesity-related outcomes used data from the medical examinations at baseline and/or follow-up. Trained nurses performed measurements of weight and height as well as of waist circumference according to a standard protocol. Height and weight were measured standing without shoes and rounded to the nearest half centimetre or 100 g, respectively. Waist circumference was measured in lying position, midway between the lower costal margin and the iliac crest. Anthropometric markers of obesity were defined according to the WHO criteria for the European population. Body mass index (BMI) was calculated as the weight divided by the squared height (kg/m²) with cut-off values at ≥ 25 and ≥ 30 to define overweight and obesity, respectively (WHO, 2000). Central obesity was defined as a waist circumference ≥ 88 cm for women and ≥ 102 cm for men (WHO, 2008).

In paper II we took into account differences in follow-up time for men and women (means of 10.2 and 8.0 years, respectively) by dividing the change in weight or waist circumference by the individual follow-up time in years (kg/year or cm/year, respectively).

In paper III the hypertension definition was based on a combination of data from the follow-up investigation of SDPP (questionnaire information and blood pressure measurements) as

well as on data from the National Patient Register, held by the National Board of Health and Welfare. Blood pressure at the clinical examination was measured once, in a sitting position after about 5 min rest, with a triple cuff hand aneroid sphygmomanometer. The cut-off for measured blood pressure was set in accordance with the WHO definition of hypertension grade I, i.e. 140/90 mmHg or higher (WHO, 1999). Subjects were identified as cases if they reported usage of antihypertensive treatment or doctors' diagnosis of hypertension during the last 10 years in the follow-up questionnaire, had a systolic blood pressure ≥ 140 mmHg and a diastolic blood pressure ≥ 90 mmHg at the follow-up investigation or had a diagnosis of hypertension (ICD-9 codes 401X before 1998 and ICD-10 codes I10X from 1998) in the National Patient Register.

In [paper IV](#) the outcome definitions were based on a combination of data from the National Patient and the National Cause of Death Registers. Each event was defined based on the International Classification of Diseases: hospitalisation or death with a principal diagnosis of ischemic heart disease (IHD) (ICD9: 410–414; ICD10: I20–I25), or stroke (ICD9: 430–436; ICD10: I60–I65). Subjects with IHD or stroke diagnoses before recruitment were excluded from the analyses. All first events during follow-up were classified as incident, whereas National Cause of Death Register records of IHD or stroke, as well as non-traumatic death within 28 days after an IHD or stroke hospitalisation, were classified as fatal cases.

3.5 STATISTICAL ANALYSIS

In all papers, transportation noise levels were expressed in dB, L_{den} . In [paper I](#) the effect estimates were expressed using an increment of 5 dB L_{den} . In [papers II, III and IV](#) the effect estimates used an increment of 10 dB L_{den} . To test the assumption of linearity between transportation noise and outcomes, we performed analyses with a categorical exposure variable (<45, 45–49, 50–54, and ≥ 55 dB L_{den}) by inserting it in the linear model. Additionally, we performed restricted cubic splines analyses with 3 knots placed at the 10th, 50th, and 90th percentiles (Harrell, 2001).

In [paper I](#) we used a cross-sectional design and linear regression models to analyse the association between transportation noise and continuous outcomes (waist circumference and waist-hip ratio) as well as logistic regression models to analyse the association between transportation noise and prevalence of overweight and central obesity. In addition, we assessed the effect of combined exposure to multiple transportation noise sources at 45 dB L_{den} and above using a dummy variable, indicating participants being exposed to none, one, two or three transportation noise sources (road traffic, trains and/or aircraft).

For the remaining papers, we assessed the time-weighted average transportation noise exposure during relevant time periods for each study participant taking into account the residential history. In [paper II](#) the period of interest was the whole follow-up period. We used linear regression models to analyse associations between transportation noise exposure and

changes in obesity markers as well as Poisson regression models for analyses of associations between transportation noise exposure and incidence of central obesity or overweight.

In [paper III](#) the impact of exposure to transportation noise 1, 5 or 10 years preceding the diagnosis on the development of hypertension was evaluated. Associations between exposure to transportation noise (road, railway and aircraft) and incidence of hypertension were analysed using Cox proportional hazards regression models to compute Hazard Ratios and 95% confidence intervals with age as the underlying time scale. Person-time at risk was calculated from the date of the baseline investigation until diagnosis of hypertension, a competing disease diagnosis (myocardial infarction or cardiac arrhythmia), end of follow-up or death, whichever occurred first.

In [paper IV](#) we also tested different induction periods (the year of the event, as well as 1 to 5 years and 6 to 10 years prior to diagnosis). To analyse associations between exposure to transportation noise (road, railway and aircraft) and incidence of IHD or stroke, we used Cox proportional hazards regression models to compute Hazard Ratios and 95% confidence intervals. Person-time at risk was calculated from enrolment into the study until IHD or stroke diagnosis, death, migration out of Stockholm County or end of follow-up (31 Dec 2011), whichever event occurred first. In order to evaluate potential heterogeneity of the results between the cohorts, we estimated the Higgin's I^2 statistics from a random effect meta-analysis of separate results from each of the cohorts (DerSimonian and Laird, 1986; Higgins and Thompson, 2002).

In all papers, the measures of association were adjusted for potential individual and contextual confounders. To describe relationships between different transportation noise sources as well as with road traffic-related air pollution we used Pearson correlations.

We also explored potential effect modification of the association between transportation noise and outcomes by including interaction terms between the exposure and the covariate of interest in the main models using F -test statistics. The investigated covariates included sex, age, smoking status and traffic-related air pollution (NO_x in [papers I–III](#) and BC in [paper IV](#)), among others.

In [paper I](#), [II](#) and [IV](#) we evaluated effects of combined exposure to several transportation noise sources comparing those exposed to one, two or three of the noise sources at ≥ 45 dB L_{den} to those not exposed. In [paper III](#) we also evaluated effects of exposure to noise from multiple sources by assessing the risk of hypertension in groups exposed to different combinations of transportation noise. For these analyses, we used binary exposure variables (<45 vs ≥ 45 dB L_{den}) and those exposed to noise levels <45 dB L_{den} for all three noise sources constituted the reference group.

In all papers we used hypothesis testing based on two-tailed rejection regions and p -values less than 5% were considered as statistically significant, except for the interaction terms, where we used 10% as significance level.

All statistical analyses were performed using Stata/SE (version 13.1; StataCorp, College Station, TX). Exposure assessment and spatial manipulation of data performed in QGIS (version 2.10.1; QGIS Development Team).

3.6 ETHICAL CONSIDERATIONS

The use of individual data from all of the four cohorts in combination with information from medical registers in order to assess effects of long-term effects of transportation noise on the cardiovascular and metabolic system was approved by the Ethics Committee of Karolinska Institutet, Stockholm, Sweden (CEANS Dnr: 2009/2166-31/5, 2010-02-23).

4 RESULTS

4.1 TRANSPORTATION NOISE LEVELS IN STOCKHOLM COUNTY

Exposure assessment was successfully performed for 22,038 (98.7%) participants in the CEANS cohort. Road traffic was the dominant source of transportation noise exposure (Figure 4). The proportion of participants exposed to railway or aircraft noise sources was almost similar. In total, 37% of the CEANS participants were not exposed noise levels ≥ 45 dB L_{den} from any transportation noise source at recruitment, 38% were exposed to one of three transportation noise sources at this level or higher, 25% to two sources of transportation noise and 1% were exposed to all three sources ≥ 45 dB L_{den} .

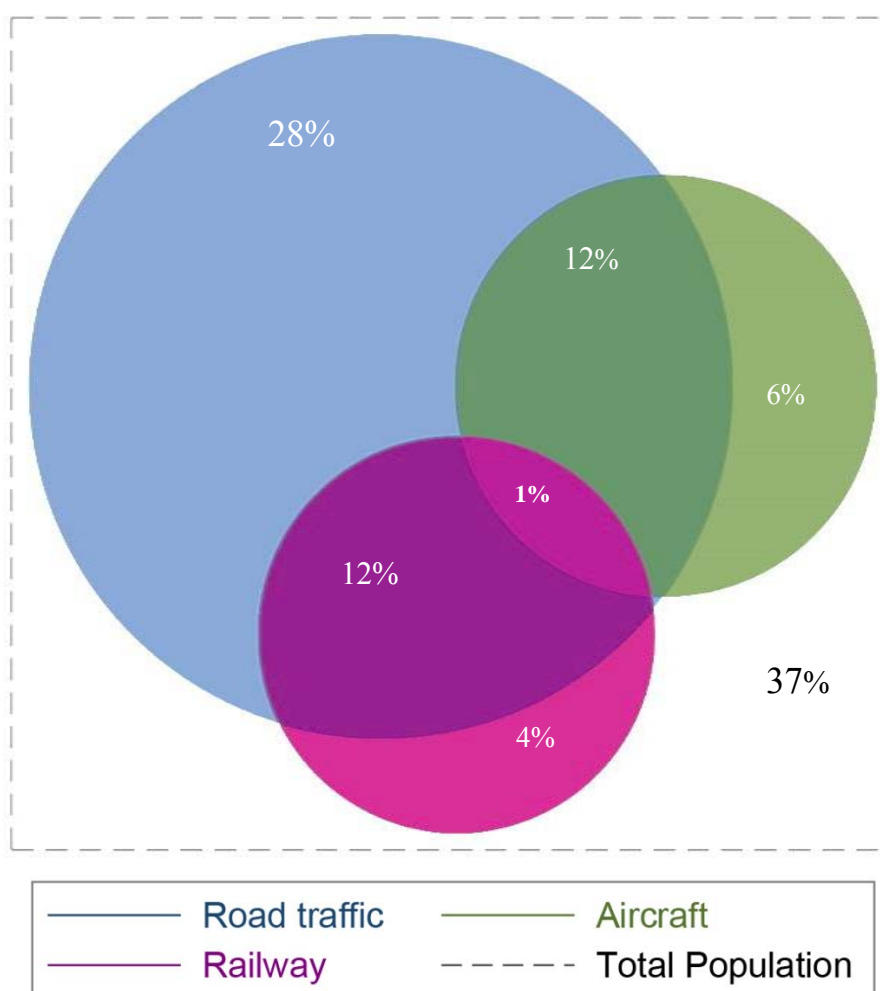


Figure 4. Exposure to noise ≥ 45 dB L_{den} from different transportation sources in the CEANS cohort at recruitment.

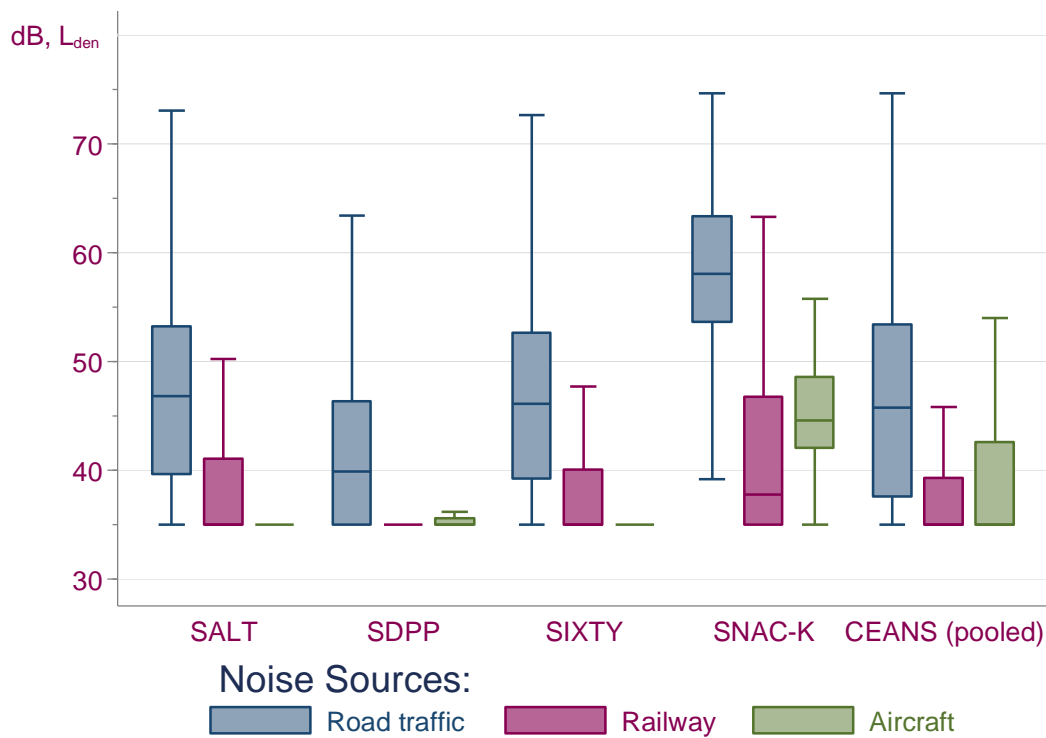


Figure 5. Noise exposure levels (dB L_{den}) from different transportation sources in the CEANS cohorts at recruitment.

Notes: Box plots are defined by the median (middle line) and the lower and upper quartiles (box edges) defining the interquartile range (IQR). The vertical lines (whiskers) indicate the minimum and maximum range (1.5 IQR) excluding outliers.

Source-specific noise exposure levels at recruitment addresses varied across the four cohorts (Figure 5). The highest exposure levels were observed in the SNAC-K cohort, which was recruited from an area in Stockholm city, while the lowest levels were found in the SDPP cohort, with participants from rural and semirural municipalities. Exposure levels in the SALT and SIXTY cohorts were similar, both with participants recruited across the whole Stockholm County. Furthermore, estimated noise levels from different sources in the pooled material did not correlate strongly between each other (Pearson correlation coefficients -0.35 to 0.2)

4.2 TRANSPORTATION NOISE EXPOSURE AND OBESITY

Both in [papers I](#) and [II](#) we looked at transportation noise exposure from different sources and adiposity markers as well as overweight and central obesity. [Paper I](#) had a cross-sectional design and focused on the prevalence of adiposity markers and central obesity. On the other hand, [paper II](#) had a longitudinal design with more detailed exposure data and focused on incidence of overweight and central obesity as well as weight gain and increase of waist circumference. In both papers, we excluded those without exposure data or missing data on outcomes or covariates. Following these exclusions, a study population of 5,075 for [paper I](#)

Table 1. Noise exposure from different transportation noise sources during follow-up for the study cohort from Stockholm County in relation to waist circumference increase and weight gain.

Exposure ^a	No. of subjects	Waist circumference increase (cm/year) ^b		Weight gain (kg/year) ^b	
		β	(95% CI)	β	(95% CI)
Road traffic noise					
Categorical, dB L _{den}					
<45	3,457	0.00	(ref.)	0.00	(ref.)
45–49	958	-0.05	(-0.10–0.003)	-0.02	(-0.07–0.02)
50–54	565	0.12	(0.06–0.18)	0.03	(-0.03–0.09)
≥55	204	0.14	(0.04–0.25)	0.03	(-0.07–0.12)
Continuous					
per 10 dB L _{den}		0.04	(0.02–0.06)	0.01	(-0.009–0.03)
Railway noise					
Categorical, dB L _{den}					
<45	4,788	0.00	(ref.)	0.00	(ref.)
45–49	161	0.01	(-0.10–0.13)	-0.01	(-0.11–0.09)
50–54	125	0.07	(-0.06–0.20)	0.09	(-0.03–0.20)
≥55	110	-0.05	(-0.19–0.09)	-0.02	(-0.14–0.11)
Continuous					
per 10 dB L _{den}		0.01	(-0.01–0.03)	0.01	(-0.005–0.04)
Aircraft noise					
Categorical, dB L _{den}					
<45	4,261	0.00	(ref.)	0.00	(ref.)
45–49	126	0.31	(0.18–0.44)	0.11	(-0.008–0.22)
50–54	590	0.44	(0.38–0.50)	0.06	(0.006–0.12)
≥55	207	0.48	(0.39–0.58)	0.09	(-0.005–0.18)
Continuous					
per 10 dB L _{den}		0.16	(0.14–0.17)	0.03	(0.01–0.04)

^a Time-weighted noise exposures expressed as L_{den} taking into account where the subject had lived during the follow-up period.

^b Results of linear regression model adjusted for sex, age, dietary habits, alcohol consumption, education level, physical activity, smoking status, psychological distress, job strain and shift work.

and 5,184 for [paper II](#) individuals remained with complete information. All results were adjusted for potential confounders.

4.2.1 Waist circumference, waist-hip ratio and prevalence of central obesity

In [paper I](#) we observed an association between exposure to transportation noise from road traffic, railways or aircraft and waist circumference as well as waist-hip ratio. For waist circumference and waist-hip ratio, there were statistically significant increases in risk for road traffic and aircraft noise; for waist circumference this held true for railway noise. The associations appeared particularly strong for aircraft noise. With regard to BMI we did not see any statistically significant associations for any of the transportation noise sources.

Similar results were observed for binary outcomes. The ORs of central obesity defined by waist circumference or waist-hip ratio were 1.18 (95% CI 1.03–1.34) and 1.29 (95% CI 1.14–1.45), respectively, comparing those exposed and unexposed to road traffic noise ≥45 dB L_{den}. The OR for BMI defined obesity was 0.89 (95% CI 0.76–1.04). The OR of central obesity estimates did not change after additional adjustment for area-based mean income or traffic-related NO_x, or after restricting the population to those exposed only to road traffic noise or who did not change their address during 10 years or more.

4.2.2 Waist circumference increase, weight gain and incidence of central obesity

In [paper II](#) we observed associations between transportation noise exposure from different sources and waist circumference increase (Table 1). The association appeared strongest for aircraft noise with a waist circumference increase of 0.16 cm/year (95% CI 0.14–0.17) *per* 10dB L_{den} , while for road traffic noise and the increase was 0.04 cm/year (95% CI 0.02–0.06) *per* 10 dB L_{den} . No clear association was observed between railway noise exposure and waist circumference increase. Moreover, we did not observe any association for weight gain except for a borderline statistically significant association between aircraft noise and weight change (0.03 kg/year; 95% CI 0.01–0.04) *per* 10 dB L_{den} . The results were not affected by additional adjustments for other transportation noise sources, road traffic related NOx or contextual confounding (area based mean income) or following exclusion of those with exposure to railway or aircraft noise ≥ 45 dB L_{den} or address change during follow-up. Traffic related NOx was moderately correlated to road traffic noise ($r=0.56$) but not to railway ($r=0.14$) or aircraft noise ($r=-0.02$).

Aircraft and road traffic noise exposure were related to an increased incidence of central obesity with IRRs of 1.19 (95% CI 1.14–1.24) and 1.07 (95% CI 1.00, 1.14) *per* 10 dB L_{den} , respectively (Table 2). Moreover, aircraft noise was associated with an increased risk of overweight with an IRR of 1.06 (95% CI 1.01–1.12) *per* 10 dB L_{den} . Categorical and restricted cubic splines analyses did not suggest any clear departure from linearity in the association between aircraft traffic noise exposure and waist circumference increase or IRR of central obesity (Table 2, Figure 6).

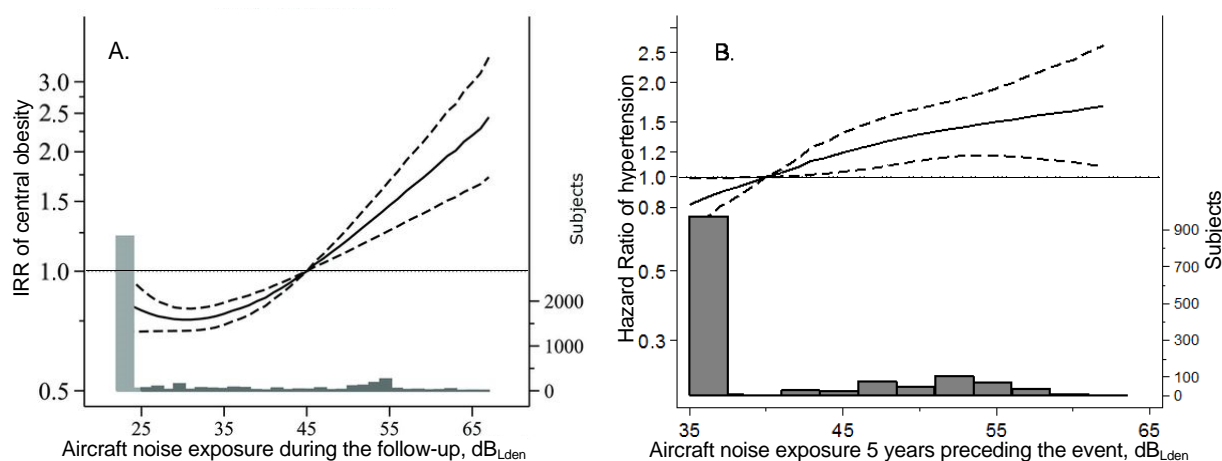


Figure 6. Incidence rate ratio (IRR) of central obesity (A) and hazard ratio for hypertension (B) in a cohort from Stockholm County in relation to noise exposure from aircraft in the fully adjusted model based on restricted cubic spline analyses.

Note: 45 dB L_{den} is used as a reference level, IRR of central obesity or hazard ratio of hypertension are indicated with bold central line, 95% CIs are dashed outer bands. Bars indicate the number of subjects in different exposure groups.

Table 2. Risks of central obesity and hypertension in a cohort from Stockholm County in relation to transportation noise exposure from different sources.

Noise source ^e	Central obesity ^a		Hypertension ^b		
	No. of subjects / cases	Main Model ^c IRR (95% CI)	person-years	No. of cases	Main Model ^d HR (95% CI)
Road traffic noise					
Categorical, dB L _{den}					
<45	2,932 /548	1.00 (ref.)	21,934	992	1.00 (ref.)
45–49	796 /154	1.00 (0.85–1.17)	5,023	238	1.10 (0.96–1.27)
50–54	479 /124	1.33 (1.12–1.58)	2,953	118	0.92 (0.77–1.12)
≥55	179 /46	1.26 (0.96–1.64)	1,075	38	0.89 (0.65–1.23)
Continuous					
per 10 dB L _{den}	4,386 /872	1.07 (1.00–1.14)	30,985	1,386	0.93 (0.86–1.01)
Railway noise					
Categorical, dB L _{den}					
<45	4,057 /791	1.00 (ref.)	28,475	1289	1.00 (ref.)
45–49	128 /25	0.97 (0.68–1.38)	987	43	0.97 (0.72–1.31)
50–54	110 /33	1.43 (1.07–1.92)	739	28	0.83 (0.58–1.20)
≥55	91 /23	1.27 (0.88–1.81)	784	26	0.79 (0.54–1.17)
Continuous					
per 10 dB L _{den}	4,386 /872	1.05 (0.99–1.12)	30,985	1,386	0.91 (0.82–1.02)
Aircraft traffic noise					
Categorical, dB L _{den}					
<45	3,590 /647	1.00 (ref.)	25,275	1025	1.00 (ref.)
45–49	103 /22	1.27 (0.87–1.85)	2,486	135	1.18 (0.99–1.41)
50–54	508 /145	1.62 (1.39–1.89)	2,512	172	1.31 (1.12–1.54)
≥55	185 /58	1.99 (1.58–2.50)	681	53	1.33 (1.02–1.75)
Continuous					
per 10 dB L _{den}	4,386 /872	1.19 (1.14–1.24)	30,953	1,385	1.16 (1.08–1.24)

^a Gender-specific cut-off values for central obesity were applied for waist circumference: ≥88 cm for women and ≥102 cm for men. Subjects with central obesity at baseline were excluded from analysis.

^b Hypertension cases identified from questionnaires, measurements and registers.

^c Incidence rate ratios (IRR) and 95% confidence intervals (CI) adjusted for sex, age, dietary habits, alcohol consumption, education level, physical activity, smoking status, psychological distress, job strain and shift work.

^d Hazard ratios (HR) and 95% confidence intervals (95% CI) adjusted for sex, educational level, physical activity during leisure time, psychological distress and diabetes heredity at recruitment.

^e Time-weighted noise exposures expressed as L_{den} taking into account all addresses where the subject had lived during follow-up period for central obesity and where the subject lived 5-years preceding hypertension diagnosis.

4.3 TRANSPORTATION NOISE EXPOSURE AND HYPERTENSION

From 5,712 participants completing both baseline and follow-up SDPP investigations 4,854 were included in the final analysis of [paper III](#). Those 858 excluded did not differ in exposure status for the three transportation noise sources. In total, 1,392 cases of hypertension developed during more than 30,900 person-years in the study base.

In the fully adjusted models, we observed a statistically significant association between aircraft noise exposure and incidence of hypertension with a HR of 1.16 (95% CI 1.08–1.24) *per* 10 dB L_{den} using the 5-year exposure window (Table 2). No positive associations were observed for road traffic or railway noise. This was similar to the results for the 1-year and 10-year exposure period, although the exposure-response trends were less obvious for the 10-year window. Spline analysis did not indicate any deviation from linearity in the exposure-response relationship for aircraft noise focussing on the 5-year period prior to diagnosis (Figure 6).

4.4 TRANSPORTATION NOISE EXPOSURE AND INCIDENCE OF ISCHEMIC HEART DISEASE AND STROKE

Paper IV was based on the CEANS cohort. From the original sample of 22,314 individuals, 241 (0.1%) were excluded due to missing exposure data and 2,061 (9.2%) because of missing data on covariates. The remaining 20,012 subjects had a mean age at study entry of 60 years (range 35–104) and provided more than 245,000 person-years of observation. During follow-up, we registered 1,363 incident IHD and 902 incident stroke events.

Table 3 shows associations between transportation noise exposure from different sources 1–5 years preceding the event and incidence of IHD. Overall, no clear or consistent associations were observed between noise exposure from any of the three transportation sources and IHD incidence. However, there were statistically significant associations between exposure to road traffic as well as aircraft noise and incidence of IHD in women, with HRs of 1.11 (95% CI 1.00–1.22) and 1.25 (95% CI 1.09–1.44) *per* 10 dB L_{den} , respectively. On the other hand, a statistically significant inverse relation was seen in men for road traffic noise (HR 0.86; 95% CI 0.79–0.94 *per* 10 dB L_{den}), while no clear association was observed for railway or aircraft noise exposure.

Similar to IHD, there were no strong overall associations between noise exposure from any of the transportation noise sources and stroke incidence (Table 4). This also held true in the sex-specific analyses, however, a borderline statistically significant relation was observed in women for railway noise (HR 1.13; 95% CI 1.00–1.27 *per* 10 dB L_{den}).

In cohort-specific analyses of IHD incidence in relation to road traffic exposure we observed a positive association in the SDPP cohort (HR 1.19; 95% CI 1.02–1.39 *per* 10 dB L_{den}), and inverse association in the SALT cohort (HR 0.87; 95% CI 0.78–0.97 *per* 10 dB L_{den}) (data not shown). Overall, moderate heterogeneity across cohorts was suggested (Higgin's I^2 statistic 68.2%). Meta-analysed estimates for IHD incidence due to road traffic noise were comparable to the main results with a HR of 0.96 (95% CI 0.84–1.08) *per* 10 dB L_{den} . Only low heterogeneity was noted between the cohorts for other transportation noise sources and for stroke (results not shown).

Table 3. Overall and sex-specific hazard ratios of ischemic heart disease incidence in relation to transportation noise exposure 1–5 years preceding the event from different sources in the fully the adjusted model¹.

Exposure	Road traffic noise exposure years 1–5			Railway noise exposure years 1–5			Aircraft noise exposure years 1–5		
	Person-years	HR ¹ (95%CI)	No. of cases	Person-years	HR ¹ (95% CI)	No. of cases	Person-years	HR ¹ (95% CI)	No. of cases
Overall									
Categorical, dB L _{den}									
<45	125,126	1.00 (ref.)	542	210,185	1.00 (ref.)	1,111	207,957	1.00 (ref.)	1,110
45–49	44,516	1.05 (0.91–1.23)	245	15,940	0.98 (0.81–1.18)	123	21,949	0.98 (0.82–1.17)	144
50–54	36,413	1.02 (0.87–1.19)	254	9,832	0.97 (0.75–1.24)	67	12,153	1.05 (0.84–1.31)	91
55–60	39,045	0.86 (0.73–1.01)	322	9,143	1.02 (0.79–1.31)	62	2,949	1.23 (0.76–2.00)	17
Continuous									
per 10 dB L _{den}	245,100	0.96 (0.90–1.03)	1,363	245,100	1.01 (0.93–1.09)	1,363	245,008	1.04 (0.94–1.15)	1,362
Women									
Categorical, dB L _{den}									
<45	68,743	1.00 (ref.)	171	119,340	1.00 (ref.)	463	119,944	1.00 (ref.)	458
45–49	26,387	1.11 (0.86–1.43)	96	9,745	1.15 (0.89–1.49)	70	12,533	1.04 (0.80–1.35)	67
50–54	21,912	1.36 (1.08–1.73)	133	6,291	0.97 (0.68–1.38)	33	6,727	1.28 (0.95–1.72)	53
55–60	23,715	1.19 (0.95–1.50)	189	5,381	0.82 (0.54–1.25)	23	1,484	2.05 (1.09–3.84)	10
Continuous									
per 10 dB L _{den}	140,757	1.11 (1.00–1.22)	589	140,757	1.02 (0.91–1.14)	589	140,688	1.25 (1.09–1.44)	588
Men									
Categorical, dB L _{den}									
<45	56,383	1.00 (ref.)	371	90,845	1.00 (ref.)	648	88,013	1.00 (ref.)	652
45–49	18,129	1.04 (0.86–1.26)	149	6,195	0.82 (0.62–1.09)	53	9,416	0.94 (0.73–1.19)	77
50–54	14,501	0.83 (0.67–1.02)	121	3,541	0.96 (0.68–1.36)	34	5,426	0.85 (0.61–1.19)	38
55–60	15,330	0.65 (0.52–0.81)	133	3,762	1.18 (0.85–1.63)	39	1,465	0.78 (0.37–1.65)	7
Continuous									
per 10 dB L _{den}	104,343	0.86 (0.79–0.94)	774	104,343	1.00 (0.90–1.11)	774	104,320	0.90 (0.78–1.03)	774

¹Hazard ratio (HR) adjusted for sex, enrolment year, year of the event, smoking status, alcohol consumption, occupational status, educational level, physical activity during leisure time, marital status and socioeconomic index.

Table 4. Overall and sex-specific hazard ratios of stroke incidence in relation to transportation noise exposure 1–5 years preceding the event from different sources in the fully adjusted model¹.

Exposure	Road traffic noise exposure years 1–5			Railway noise exposure years 1–5			Aircraft noise exposure years 1–5		
	Person-years	No. of cases	HR ¹ (95%CI)	Person-years	No. of cases	HR ¹ (95% CI)	Person-years	No. of cases	HR ¹ (95% CI)
Overall									
Categorical, dB L _{den}									
<45	127,275	307	1.00 (ref.)	214,554	710	1.00 (ref.)	212,064	726	1.00 (ref.)
45–49	45,441	150	1.01 (0.83–1.23)	16,180	91	1.02 (0.82–1.27)	22,460	113	0.99 (0.80–1.22)
50–54	37,209	192	1.10 (0.90–1.33)	10,034	59	1.20 (0.92–1.57)	12,568	51	0.73 (0.54–0.98)
55–60	40,258	253	0.86 (0.70–1.05)	9,415	42	0.99 (0.73–1.36)	2,996	12	1.36 (0.77–2.43)
Continuous									
per 10 dB	250,183	902	1.00 (0.92–1.09)	250,183	902	1.05 (0.96–1.15)	250,088	902	0.96 (0.84–1.09)
Women									
Categorical, dB L _{den}									
<45	69,082	134	1.00 (ref.)	120,551	339	1.00 (ref.)	120,961	362	1.00 (ref.)
45–49	26,517	68	0.90 (0.67–1.21)	9,694	58	1.23 (0.93–1.63)	12,654	58	0.98 (0.74–1.31)
50–54	22,160	107	1.16 (0.89–1.51)	6,372	36	1.34 (0.95–1.90)	6,890	32	0.80 (0.55–1.16)
55–60	24,328	149	0.89 (0.68–1.15)	5,470	25	1.13 (0.75–1.70)	1,510	6	1.38 (0.61–3.10)
Continuous									
per 10 dB	142,087	458	1.02 (0.91–1.14)	142,087	458	1.13 (1.00–1.27)	142,015	458	1.06 (0.89–1.25)
Men									
Categorical, dB L _{den}									
<45	58,193	173	1.00 (ref.)	94,003	371	1.00 (ref.)	91,103	364	1.00 (ref.)
45–49	18,924	82	1.11 (0.85–1.45)	6,486	33	0.79 (0.55–1.13)	9,806	55	1.00 (0.74–1.33)
50–54	15,049	85	1.03 (0.78–1.35)	3,662	23	1.04 (0.68–1.59)	5,678	19	0.63 (0.40–1.01)
55–60	15,930	104	0.83 (0.63–1.08)	3,945	17	0.85 (0.52–1.38)	1,486	6	1.35 (0.60–3.06)
Continuous									
per 10 dB	108,096	444	0.99 (0.89–1.11)	108,096	444	0.97 (0.84–1.11)	108,073	444	0.86 (0.72–1.03)

¹Hazard ratio (HR) adjusted for sex, enrolment year, year of the event, smoking status, alcohol consumption, occupational status, educational level, physical activity during leisure time, marital status and socioeconomic index.

4.5 COMBINED EXPOSURE TO SEVERAL SOURCES OF TRANSPORTATION NOISE

We observed an exposure-response relation between the number of transportation noise sources and risk of central obesity with the IRR increasing from 1.22 (95% CI 1.08–1.39) among those exposed to only one source to 2.26 (95% CI 1.55–3.29) among those exposed to all three transportation noise sources (Figure 7). Higher risks appeared of both IHD and stroke incidence with a HR of 1.57 (95% CI 1.06–2.32) and 1.42 (95% CI 0.87–2.32), respectively, in those exposed to all three noise sources simultaneously, although not statistically significant for stroke. On the other hand, no association was indicated for hypertension in relation to the number of transportation noise sources.

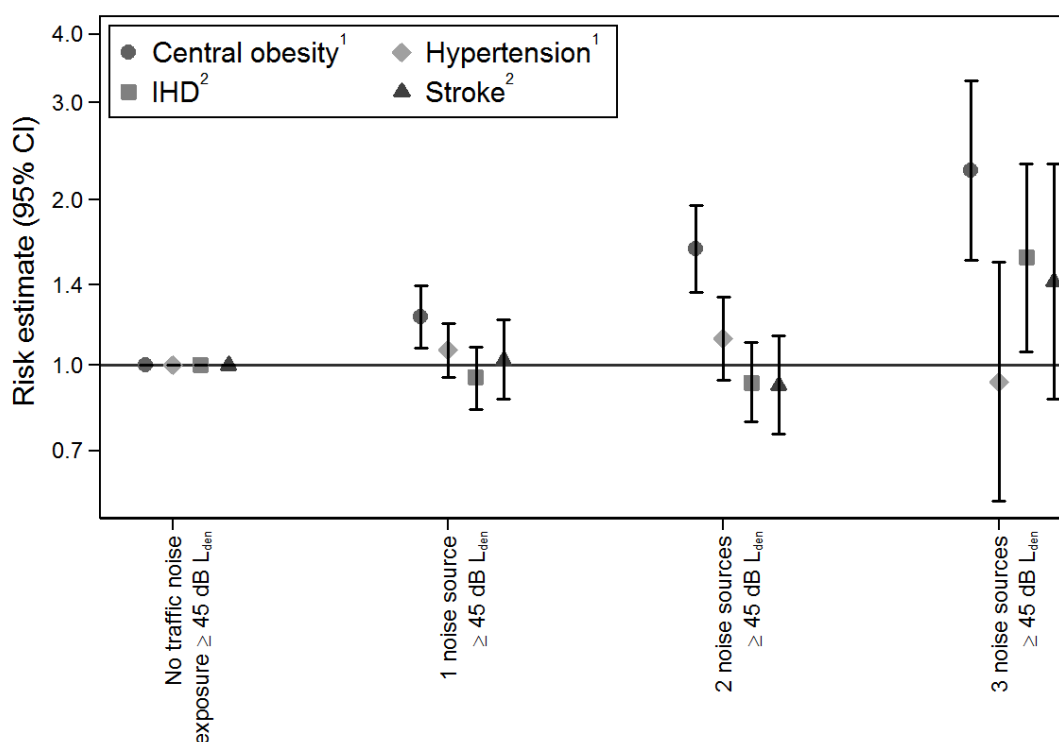


Figure 7. Risks of central obesity, hypertension, ischemic heart disease incidence and stroke in cohorts from Stockholm County in relation to noise exposure ≥ 45 dB L_{den} from road traffic, railways, and/or aircraft.

Note: ¹ Based on the SDPP cohort;
² Based on the CEANS cohort.

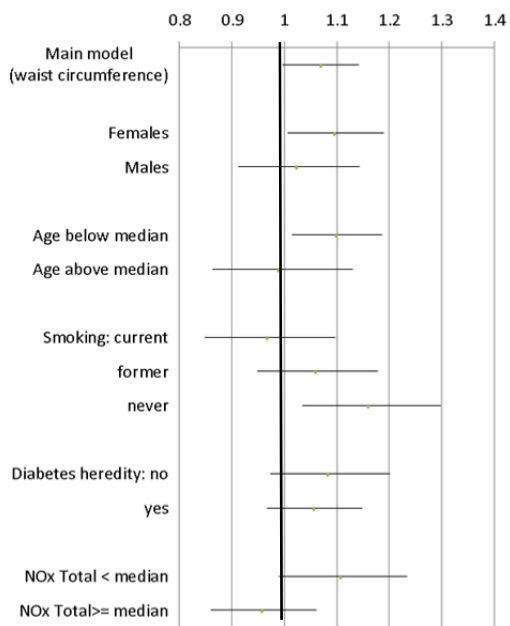
4.6 INTERACTIONS

Interactions for different outcomes in relation to transportation noise are assessed in Figure 8. In paper II statistically significant interactions in relation to road traffic noise exposure and *central* obesity were seen only for smoking status ($p=0.099$) and air pollution ($p=0.058$) (Figure 8A). The risk was increased among never smokers with an IRR of 1.16 (95% CI 1.04–1.30) *per* 10 dB L_{den} but not in those currently smoking (IRR of 0.96; 95% CI 0.85–1.10 *per* 10 dB L_{den}). The risk was higher in those exposed to an NO_x level below the median value of $2.9 \mu\text{g}/\text{m}^3$ with an IRR of 1.10 (95% CI 0.99–1.23) *per* 10 dB L_{den} compared to those exposed to air pollution levels above the median with an IRR of 0.96 (95% CI 0.86–1.06) *per* 10 dB L_{den} .

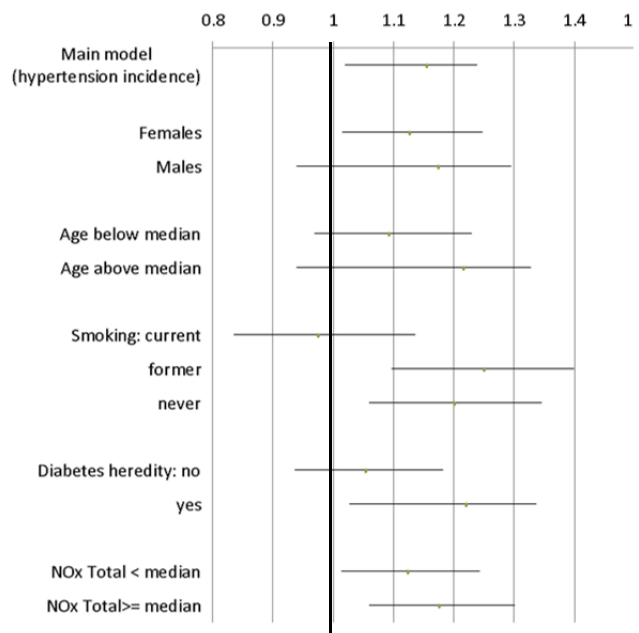
There were no statistically significant interactions in relation to aircraft noise exposure 5 years preceding the event and risk of hypertension, except for smoking status ($p=0.02$) and diabetes heredity ($p=0.06$) (Figure 8B). An association was only seen for those not currently smoking, with a HR of 1.29 (95% CI 1.16–1.40) among former smokers and 1.20 (95% CI 1.07–1.35) among never smokers. Those with a family history of diabetes had a HR of 1.22 (95% CI 1.11–1.34) *per* 10 dB L_{den} compared to 1.05 (95% CI 0.93–1.18) *per* 10 dB L_{den} among those with no diabetes heredity.

A statistically significant interaction in relation to road traffic noise exposure 1–5 years preceding the event and risk of IHD was observed for sex ($p<0.001$). Furthermore, the association between road traffic noise and IHD incidence tended to be stronger in the younger age group (*i. e.* below the median of 56 years) (Figure 8C).

A. IRR of central obesity *per* 10 dB L_{den}



B. IRR of hypertension *per* 10 dB L_{den}



C. HR of ischemic hear disease *per* 10 dB L_{den}

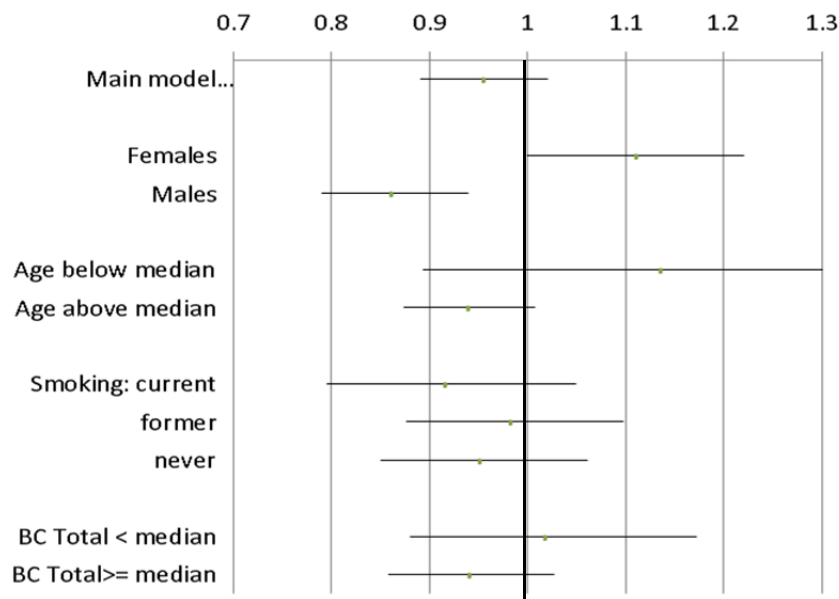


Figure 8. Measures of association and 95% confidence intervals for selected metabolic or cardiovascular outcomes related to transportation noise exposure in fully adjusted models considering interactions with covariates.

A. Incidence rate ratio (IRR) of central obesity in relation to road traffic noise exposure during follow-up.

B. IRR of hypertension in relation to aircraft noise 5 years preceding the event.

C. Hazard ratio (HR) of IHD in relation to road traffic noise exposure 1–5 years preceding the event.

5 DISCUSSION

In this thesis we wanted to explore long-term effects of transportation noise exposure on metabolic and cardiovascular outcomes. Furthermore, we aimed to investigate the role of combined exposure to multiple sources of transportation noise as well as to evaluate interactions between noise exposure and different risk factors, including air pollution, in relation to obesity and cardiovascular diseases. Below, the main findings are discussed in relation to available scientific evidence. Furthermore, methodological aspects which may have influenced the results are brought up and evaluated.

5.1 MAIN FINDINGS

5.1.1 Obesity

The results from the first two papers in this thesis, which were based on the same study population, are in line with each other and show associations between long-term exposure to certain types of transportation noise and waist circumference as well as risk of *central* obesity. In general, no corresponding association was observed for BMI defined *general* obesity, however, BMI defined *overweight* was associated with exposure to aircraft noise. Moreover, relationships were observed between transportation noise exposure and markers of central obesity as well as waist-circumference increase. Only few epidemiologic studies have considered the effects of transportation noise exposure on obesity in adults (Eriksson et al., 2014; Oftedal et al., 2015; Christensen et al., 2016, 2015). Our findings cover noise from road traffic, railways and aircraft, and are discussed separately for each noise source.

The results of paper I indicate an association between road traffic noise and prevalence of central obesity as well as waist circumference, but not BMI. This partly confirms findings of a cross-sectional Danish study by Christensen et al. (2016) reporting statistically significant associations between exposure to road traffic noise and waist circumference as well as BMI. However, a cross-sectional study from Norway by Oftedal et al. (2015) found associations between road traffic noise and BMI only in noise sensitive women. Our longitudinal study described in paper II showed an association between exposure to road traffic noise and waist circumference increase, but not for weight gain. These findings confirm results from a longitudinal Danish study regarding waist circumference, however, unlike us they also found statistically significant associations for weight gain (Christensen et al., 2015). The effect size in our and the Danish studies on road traffic noise and waist circumference increase recalculated for 10 years of follow-up and expressed per 10 dB L_{den} were comparable.

With regard to railway noise we did not see any associations for BMI and inconsistent results for waist circumference. In the cross-sectional study (paper I) a statistically significant association was observed between railway noise and waist circumference, but this was not confirmed in the longitudinal study (paper II). The findings are in line with those from the Danish cohort where results from the cross-sectional analyses showed associations between railway noise >60 dB L_{den} and waist circumference as well as BMI, which were not confirmed in subsequent longitudinal analyses (Christensen et al., 2015, 2016).

Our results on aircraft noise in relation to obesity are in line with the previous longitudinal investigation by Eriksson et al. (2014), performed on the same cohort. However, our new analysis used a much more detailed methodology for assessment of aircraft noise exposure as well as other noise sources and showed associations both for waist circumference increase in relation to road traffic or aircraft noise exposure and for weight gain related to aircraft noise exposure. Obesity outcomes were more strongly related to aircraft noise in our studies than to other noise sources. This is similar to the pattern for annoyance and sleep disturbances (Miedema and Oudshoorn, 2001; Miedema and Vos, 2007) showing aircraft noise to cause more pronounced effects than road traffic or railway noise at the same levels (WHO, 2009).

In paper I and II we assessed several potential confounding factors for the association between transportation noise exposure and obesity. Experimental studies have shown that exposure to air pollution may induce adipose inflammation and visceral adiposity (Sun et al., 2009; Xu et al., 2010). Moreover, a recent study by Li et al. (2016) reported associations between distance to major roads and both overall and abdominal adiposity. In our papers I and II additional adjustment for traffic-related air pollution did not markedly affect results for road traffic noise and central obesity prevalence (paper I) or waist circumference increase in paper II but tended to weaken the association for central obesity. Other studies on road traffic noise and obesity by Oftedal et al. (2015) and Christensen et al. (2016) did not report major changes in the associations following adjustment for air pollution from road traffic. We cannot exclude that air pollution exposure contributed to the association between road traffic noise and obesity in our study population. However, confounding by air pollution is unlikely for the association between aircraft noise and obesity because of the low correlation between the two exposures.

Our data support a role of transportation noise exposure in development of central obesity, particularly for aircraft and road traffic noise. The stronger associations for central than for general obesity suggest that primarily stress-related mechanisms are involved.

5.1.2 Hypertension

The results of the cohort study described in paper III show a positive association between aircraft noise exposure and incidence of hypertension. For the 5-year exposure window prior to diagnosis a linear exposure-response relationship was indicated. Road traffic and railway noise did not seem to be associated with the risk of hypertension.

Despite an increasing number of studies on transportation noise and hypertension, the evidence is still inconclusive according to a recent systematic review (van Kempen et al., 2017). This is mainly due to a lack of high-quality longitudinal investigations. A majority of the evaluated studies were of a cross-sectional design and most of these also had a high risk of bias, e.g. due to low response rates, lack of adjustment for potential confounders and self-reporting of the outcome.

In the systematic review by van Kempen et al. (2017), a positive association between aircraft noise and prevalence of hypertension was suggested, although it did not reach statistical

significance (RR 1.05; 95% CI 0.95–1.17 *per* 10 dB L_{den} increase). In previous analyses of aircraft noise and cumulative incidence of hypertension performed in the same cohort as our study (Eriksson et al., 2007, 2010), a positive association was indicated in men but not in women. In the current investigation, several methodological improvements made it possible to assess the association more accurately. Firstly, we performed a new exposure assessment based on each participant's yearly average aircraft noise exposure instead of using just one point in time for the complete follow-up period. Secondly, we supplemented the outcome assessment with register data on diagnosis of hypertension. Thirdly, we now use a Cox regression model, assessing incidence of hypertension during the follow-up period rather than cumulative incidence at the end of the study. This implies that we take into account the difference in average follow-up time between the sexes, which may have contributed to the apparent differences in the previous studies. In the present analyses, an association was indicated in both men and women. The risk increased by approximately 16% *per* 10 dB L_{den} and appeared to be somewhat stronger in men. Our results are in line with recent findings by Dimakopoulou et al. (2017), who found a positive association (OR 2.63; 95% CI 1.21–5.71 *per* 10 dB L_{den}) between night-time aircraft noise and incidence of hypertension in a cohort study in Athens, Greece. However, a case-control study by Zeeb et al. (2017) around the Frankfurt airport in Germany did not find an association between aircraft noise and hypertension (OR 0.99; 95% CI 0.98–1.01 *per* 10 dB $L_{Aeq,24h}$).

The systematic review by van Kempen et al. (2017) also reported a positive association between exposure to road traffic noise and prevalence of hypertension (RR 1.05; 95% CI 1.02–1.08 *per* 10 dB L_{den}) but in contrast, the only available cohort study did not show a significant association (IRR 0.97; 95% CI 0.90–1.05 *per* 10 dB L_{den}) (Sørensen et al., 2011b). In a recent case-control study by Zeeb et al. (2017), there was no association between road traffic noise and hypertension (OR: 1.00; 95% CI 0.99–1.01). In a cohort study by Fuks et al. (2017), only a weak association was suggested for self-reported hypertension (OR 1.03; 95% CI 0.99–1.07) but not for measured. Our results differ from the findings of the recent meta-analysis of cross-sectional studies but are in line with the findings from the longitudinal investigations, thus not providing evidence of an association between road traffic noise exposure and incidence of hypertension.

For railway noise, the meta-analysis by van Kempen et al. (2017) aggregated data from four cross-sectional studies. The results showed a tendency of an association with prevalence of hypertension, although not statistically significant, RR 1.05 (95% CI 0.88–1.26) *per* 10 dB L_{den} . In the cohort study by Sørensen et al. (2011b), there was no association between railway noise and incidence of hypertension, with an IRR of 0.96 (95% CI 0.88–1.04) *per* 10 dB L_{den} . Similarly, in the recent case-control investigation by Zeeb et al. (2017), no association was evident (OR 1.00; 95% CI 0.99–1.01). The results of the present investigation did not support an association between railway noise and incidence of hypertension, and are thus in line with previous findings.

It is not clear from the scientific literature if a particular time period of noise exposure is of importance in causing hypertension. Most of the evidence is based on cross-sectional studies, which are unsuitable for investigating time-related aspects in exposure-response relationships. In an attempt to investigate the role of different induction times of transportation noise exposure for the risk of hypertension, we used three exposure periods, i.e. 1, 5 and 10 years prior to the event. Our results indicate an elevated risk of hypertension already after the first year of exposure to aircraft noise remaining the same for 5 years preceding the event, however, somewhat less clear for the longest exposure period of 10 years. This could be due to a smaller sample in the analyses of the longest period.

Furthermore, a high correlation between different time windows of exposure implies that the power is limited to detect differences in exposure-response relationships. Previous studies have shown that aircraft noise during night-time may cause acute elevations of the blood pressure (Haralabidis et al., 2008). Acute effects of noise can involve activation of the autonomic nervous system (SAM-axis) and the endocrine system (HPA-axis), resulting in an elevation of stress hormones such as adrenaline, noradrenaline and cortisol (Lundberg, 1999; Selander et al., 2009a), as well as affecting vascular function (Schmidt et al., 2013).

Moreover, night-time traffic noise has been associated with subclinical atherosclerosis (Kälsch et al., 2014), which speaks in favour of long-term effects of noise exposure on hypertension. More epidemiological evidence from studies with longitudinal design is needed to elucidate induction-latency periods for noise-induced hypertension.

Overall, our findings indicate a role for aircraft noise in induction of hypertension, but not for road traffic or railway noise, confirming results from other longitudinal studies. The risk of hypertension related to aircraft noise in our study remained stable after additional adjustments for area-based mean income, local traffic-related NO_x and other noise sources.

5.1.3 Ischemic heart disease and stroke

The results presented in [paper IV](#) do not provide clear and consistent evidence of associations between exposure to transportation noise and incidence of IHD. However, there appeared to be increased risks of IHD in women in relation to exposure to road traffic or aircraft noise.

There is an increasing number of studies on transportation noise and IHD. A recent meta-analysis of 3 cohort and 4 case-control studies calculated a RR of 1.08 (95% CI 1.01–1.15) *per* 10 dB L_{den} for IHD following exposure to noise from road traffic (van Kempen et al., 2017). In our study, the overall result was comparable to a recent Swedish cohort study on myocardial infarction and road traffic noise showing a RR of 0.99 (95% CI 0.86–1.14) *per* 10 dB L_{den} (Bodin et al., 2016). For IHD mortality our results are similar to the WHO-review reporting a pooled RR of 1.05 (95% CI 0.97–1.13) *per* 10 dB L_{den} based on 1 case-control and 2 cohort studies. Data are limited for aircraft noise exposure and IHD incidence or mortality. The WHO-review reported a pooled RR of 1.09 (95% CI 1.04–1.15) *per* 10 dB L_{den} for IHD incidence based on two ecological studies while we did not see an association. One cohort study reported a RR for IHD mortality of 1.04 (95% CI 0.98–1.11) *per* 10 dB L_{den} related to aircraft noise (Huss et al., 2010). In the present study, we also observed a tendency to

increased IHD mortality due to aircraft noise exposure. For railway noise, the WHO-report did not find any longitudinal studies on IHD incidence or mortality, but two subsequent studies indicated positive associations for IHD mortality (Héritier et al., 2017; Seidler et al., 2016) with risk estimates consistent with our findings. One possible explanation for the absence of clear associations for different sources of transportation noise in our study may be the comparatively low exposure levels.

The evidence on transportation noise and stroke is limited (van Kempen et al., 2017). Our study did not show an association between road traffic exposure and stroke in contrast to a Danish cohort study reporting a RR of 1.14 (95% CI 1.03–1.25) *per* 10 dB L_{den} and a pooled RR estimate for aircraft noise from the WHO-review with RR of 1.05 (95% CI 0.96–1.15) *per* 10 dB L_{den} . Our results showed a tendency of an association between railway noise and stroke incidence. For stroke mortality, our results suggested associations both for railway and aircraft noise in contrast to the WHO-review. Overall, the evidence on transportation noise and stroke appears less consistent than for IHD, which is in line with our data.

The risk of IHD due to transportation noise remained stable after adjustments for a number of potential confounders, including individual and contextual socioeconomic characteristics as well as exposure to BC. However, we cannot rule out that residual or unmeasured confounding may be present.

5.1.4 Exposure to multiple sources of noise

We evaluated the role of combined exposure to several transportation noise sources for each of the outcomes under the study in this thesis. Clear exposure-response associations related to number of noise sources were seen for obesity-related outcomes, IHD and stroke where a particularly high risk appeared in the group exposed to all three noise sources, although not statistically significant for stroke. No corresponding association was reported for hypertension.

Several studies on sleep and annoyance suggested effects of combined exposure to different noise sources (Griefahn et al., 2006; Miedema, 2004). These and our findings regarding obesity, IHD and stroke go in line with the multiple environmental stressor theory of Stansfeld and Matheson (2003), implying that several stressors may enhance the effect of each other. The theory is also supported by the study of Selander et al. (2013), where an interaction was seen between traffic noise, occupational noise and job strain in relation to myocardial infarction.

5.1.5 Interactions

We did not observe consistent interactions between transportation noise exposure and the tested risk factors in papers I–IV. A strong interaction between road traffic noise exposure and sex in relation to IHD incidence was found in paper IV. Available evidence on sex differences in associations between noise and cardiovascular disease is limited. Babisch et al. (2005) reported that road traffic exposure >70 dB $L_{day(6-22)}$ was associated with myocardial

infarction only in men (OR 1.81; 95% CI 1.02–3.21). Results of a Danish cohort study also suggested stronger effects in men with a RR for myocardial infarction related to road traffic noise of 1.14 (95% CI 1.03–1.26) *per* 10 dB L_{den} (Sørensen et al., 2012). However, Selander et al. (2009b) and Beelen et al. (2009) did not find gender differences in cardiovascular incidence and mortality related to road traffic noise. Moreover, Gan et al. (2012) reported main results with no gender differences but found a 7% non-significant excess risk of coronary mortality in women after adjustment for traffic-related air pollutants. In our results, associations between transportation noise and cardiovascular outcomes were primarily seen in women. This observation is supported by findings that women had particularly elevated levels of salivary cortisol in response to noise exposure (Selander et al., 2009a; Paris et al., 2010), suggesting a higher susceptibility to noise-induced stress responses. However, no consistent gender related interactions were observed in papers I–III focused on obesity markers and hypertension.

We did not observe clear interactions between noise exposure and age in relation to any of the outcomes. This goes in line with studies on road traffic noise and CVD outcomes (Beelen et al., 2009; Selander et al., 2009b). In papers II and IV the association tended to be stronger in the younger age group, just as in some noise studies on hypertension (Bodin et al., 2009; de Kluizenaar et al., 2007). On the other hand, Gan et al. (2012) and Sørensen et al. (2012) reported stronger associations in higher age groups in studies focused on acute coronary events. All in all, it is not clear if age modifies the association between noise and metabolic or cardiovascular outcomes.

Smoking status modified associations for central obesity and hypertension in paper II and III. The association between transportation noise and the outcomes was seen only among those not currently smoking. Nicotine has been associated with a lower blood pressure (Baron, 1996; Mehboudi et al., 2017), which may explain why the association with hypertension was only evident in never and former smokers. The relationship between smoking and obesity is complex and not completely understood. It is suggested that current smoking, as well as smoking cessation, can be associated with obesity (Dare et al., 2015; Klesges et al., 1989), which might make it difficult to assess the association between transportation noise and central obesity among smokers.

In papers I–III performed on the SDPP cohort a family history of diabetes (FHD) modified the effect only for hypertension where the association was mainly seen in persons with FHD, suggesting that those with diabetes heredity may be particularly vulnerable.

The only interaction between transportation noise and traffic-related air pollution was observed in relation to central obesity with significant associations confined to those with low exposure to air pollution. There is some evidence of associations between air pollution and obesity (Li et al., 2016; Sun et al., 2009; Xu et al., 2010), and it is difficult to explain the interaction found in our study biologically. Correlations between air pollution and noise from road traffic may have contributed to spurious associations when both exposures are included in the same model.

5.2 METHODOLOGICAL CONSIDERATIONS

Papers I–III were based on the SDPP cohort recruited in five municipalities of Stockholm County. We have detailed information on potential individual and contextual confounders, health outcome data from detailed measurements by trained nurses and several high quality Swedish medical registers as well as a unique exposure assessment methodology, together providing excellent opportunities to study effects of long-term transportation noise exposure on the metabolic and cardiovascular system. However, there are some methodological issues which have to be taken into account.

First of all, the SDPP cohort by design enriched the fraction of persons with a family history of diabetes. Therefore, approximately 52% of the participants in the SDPP cohort at the baseline and 56% at the follow-up investigation had a positive family history of diabetes (FHD). The proportion of FHD in the general population of the corresponding age group varies from 20 to 25% (Östenson, personal communication). Thus, our results may not be generalizable to the population as a whole. In all three papers, we therefore performed effect modification analyses to assess if and how the FHD oversampling affected the associations between transportation noise and obesity markers or hypertension. Papers I and II focused on obesity and suggested that the association with noise exposure was unaffected by FHD. However, in paper III focused on hypertension a statistically significant interaction between transportation noise and FHD was detected in relation to family history of diabetes, suggesting that those with diabetes heredity may be particularly vulnerable, therefore the results may not be generalizable to the whole population.

Furthermore, one of the main aims of the SDPP was to implement and evaluate methods for prevention of type 2 diabetes through community based interventions. Successful interventions can affect population health and, therefore, could possibly interfere with the associations between exposure and health outcomes. Interventions were performed in three of the five recruitment municipalities (Sigtuna, Värmdö and Upplands Väsby) and the effects of the interventions were evaluated with measurements of blood pressure, body weight and glucose tolerance. However, only small statistically insignificant differences were found between municipalities with and without interventions and are not believed to have influenced our results (Östenson, personal communication).

Exposure misclassification is another source of bias in epidemiological studies. Noise exposure from road traffic, railway and aircraft was assessed with different methodologies. First of all, aircraft and railway noise could not be assessed at baseline for the SDPP cohort. While road traffic noise data could be obtained from 1990, aircraft and railway noise data were available only since 1995 and 1998, respectively. Therefore, we needed to make assumptions of noise levels for these sources to be the same earlier during follow-up. This issue potentially more affects SDPP men (recruited 1992–1994) than women (recruited 1996–1998), while the rest of the cohorts were recruited starting from 1998. However, in studies focused on SDPP only (papers I–III) no clear gender differences were observed.

Another limitation relates to the low number of highly exposed persons. The rather limited exposure contrast may well be a reason for the lack of associations for road traffic and railway noise regarding cardiovascular outcomes. Furthermore, we only have limited information on evening and night-time exposures, although these exposure periods may be particularly relevant for noise-related cardiovascular disease (Héritier et al., 2018). In addition, the lack of objective data on exposure modifiers, such as façade and window insulation as well as bedroom location and information on exposure to noise from other sources, including occupational noise, may result in imprecision of the noise estimates. However, the assessments of exposure for all three noise sources were performed objectively and are not likely to be dependent on the outcome status, thus, most likely leading to a dilution of any effects.

Paper IV was based on the CEANS cohort constituted from four cohorts and focused on transportation noise in relation to IHD and stroke incidence. The four cohorts differed in some respects. To address these differences the main results were additionally adjusted for enrolment year of each participant (varies across cohorts), year of diagnosis as well as a cohort indicator. Moreover, we estimated cohort-specific associations with subsequent meta-analysis to test heterogeneity across cohorts. A moderate heterogeneity was suggested for IHD, however, not for stroke. Several studies focused on acute coronary events and stroke in relation to air pollution reported heterogeneity to be more apparent for stroke compared to coronary events (Cesaroni et al., 2014; Stafoggia et al., 2014; Korek et al., 2015). Age has been suggested to be a major source of heterogeneity. The SDPP participants were youngest at entry and lived in sub-urban areas with lower exposure levels, while the SNAC-K cohort participants were considerably older, had the highest exposure levels and lived in a comparatively small area in central Stockholm. However, meta-analysed estimates for IHD incidence related to road traffic noise was comparable to the main pooled results.

In all four papers we addressed confounding by adjustments for a number of individual risk factors. Additional adjustment for area based contextual indicators as well as local traffic related air pollution did generally not affect our findings. However, we cannot rule out that residual or unmeasured confounding may be present.

6 CONCLUSIONS

This thesis focused on longitudinal studies regarding the role of long-term exposure to noise from different transportation noise source for development of metabolic and cardiovascular diseases. In view of the paucity of such evidence for most transportation noise sources and outcomes the studies contribute significantly to the body of available evidence.

Associations were documented between long-term transportation noise exposure and development of central obesity, particularly for road traffic and aircraft noise. Road traffic noise was associated with waist circumference increase but not weight gain, while aircraft noise was related to both of these outcomes. In general, aircraft noise showed stronger associations than the other transportation noise sources, similar to the situation for annoyance and sleep disturbances.

With regard to cardiovascular outcomes, long-term aircraft noise exposure was associated with incidence of hypertension but no corresponding relations were observed for road traffic or railway noise. Furthermore no clear or consistent associations were observed between transportation noise exposure and risk of ischemic heart disease or stroke. However, there appeared to be an increased risk of ischemic heart disease in women related to road traffic noise exposure, while the opposite held true for men. Comparatively low noise exposure levels may have contributed to the absence of clear associations between noise exposure and cardiovascular diseases.

Our results show pronounced exposure-response trends for the number of transportation noise sources and obesity-related outcomes. For IHD and stroke, a particularly high risk appeared only in the group exposed to all three transportation noise sources, but this was not observed for hypertension. In view of the very limited available evidence more studies are urgently needed on effects of combined exposure to several noise sources.

We did not observe consistent interactions between noise exposure and air pollution or other risk factors in relation to metabolic and cardiovascular outcomes. However, our findings suggest that some groups may be particularly susceptible to the adverse health effects of transportation noise, for example related to sex, age and smoking habits.

Overall, the findings of this thesis provide further evidence on a link between long-term transportation noise exposure and metabolic effects, in particular central obesity. Combined exposure to different noise sources in relation to obesity and some CVD outcomes appears particularly harmful. Stronger action is called for to reduce noise exposure in the population and prevent serious health effects induced by noise.

7 SVENSK SAMMANFATNING

Trafikbullerexponeringen ökar på grund av snabb urbanisering och transporttillväxt. Exponering för buller i miljön påverkar en stor del av befolkningen och ger upphov till omfattande besvärreaktioner och sömnstörningar. Det vetenskapliga underlaget rörande metabola och kardiovaskulära effekter av långvarig exponering för trafikbuller från olika källor är dock oftast begränsat och av låg kvalitet, vilket gör riskbedömningen osäker, trots att bullerrelaterade hälsoeffekter skulle kunna vara av stor folkhälsomässig betydelse. Det främsta syftet med detta avhandlingsarbete var att studera utvecklingen av övervikt, hypertoni, ischemisk hjärtsjukdom och stroke i förhållande till exponering för buller från vägtrafiken, järnvägar och flygplan, och särskilt betydelsen av samverkans effekter.

De fyra kohorterna i studien baserades i Stockholms län och omfattade totalt mer än 22 000 vuxna som följdes i upp till 20 år. Tre av arbetena i avhandlingen utnyttjar endast en av dessa kohorter, SDPP kohorten, som innehöll nära 8 000 personer vid rekryteringen. Individuell exponeringsbedömning för buller från vägtrafiken, järnvägar eller flygplan var baserad på detaljerad boendehistorik för varje studiedeltagare samt på en nyutvecklade databas, som innehåller longitudinell information om faktorer som påverkar bullernivåer från de tre bullerkällorna. Uppgifter om luftförorenings exponering erhöles från spridningsmodeller baserad på en liknande metodik. Information om övriga riskfaktorer baserades på frågeformulär och register, medan utfallsdata även erhöles från kliniska undersökningar.

Då det gäller överviktsmarkörer observerades de starkaste sambanden för flygbuller. En 10 dB högre bullernivå var relaterad till en ökning av midjemåttet och vikten på 0,16 cm/år (95% KI 0,14–0,17) respektive 0,03 kg/år (95% KI 0,01–0,04). Vägtrafikbuller var associerat med en ökning av midjemåttet med 0,04 cm/år (95% KI 0,02–0,06) per 10 dB L_{den} , medan inga klara samband observerades för järnvägsbuller. Den relativa risken för bukfetma relaterad till exponering för olika trafikbullerkällor ökade från 1,22 (95% KI 1,08–1,39) bland de som utsattes för endast en källa till 2,26 (95% CI 1,55–3,29) hos de som exponerades för alla tre trafikbullerkällorna. Dessutom var flygbullerexponering associerad med risken för hypertension (HR 1,16; 95% KI 1,08–1,24 per 10 dB L_{den}), medan inga samband sågs för andra trafikbullerkällor. Inga tydliga samband observerades mellan trafikbullerexponering och risken för ischemisk hjärtsjukdom eller stroke. Dock förelåg en ökad risk för ischemisk hjärtsjukdom hos kvinnor relaterad till vägtrafikbullerexponering, medan motsatsen gällde för män. Högre risker sågs för både ischemisk hjärtsjukdom och stroke hos de som utsattes för alla tre bullerkällorna, med en HR på 1,57 (95% KI 1,06–2,32) respektive 1,42 (95% KI 0,87–2,32).

Sammanfattningsvis tyder våra resultat på negativa hälsoeffekter av långvarig exponering för trafikbuller från olika källor då det gäller vissa metabola och kardiovaskulära sjukdomar, och på att kombinerad exponering för flera olika bullerkällor är särskilt skadlig.

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