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HEALTH EFFECTS OF ROAD TRAFFIC NOISE IN CHILDHOOD AND ADOLESCENCE

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Health effects of road traffic noise in childhood and adolescence
THESIS FOR DOCTORAL DEGREE (Ph.D.)

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Für Papa, Mamma und Nils

ABSTRACT

Traffic noise is an increasing environmental exposure, primarily as a consequence of continuous urbanisation and growth of the transport sector. The burden of disease from noise is the second highest in Europe among all environmental exposures, after air pollution, and WHO recently proposed more strict environmental noise guidelines. Evidence on noise effects early in life is limited, although existing data indicate an onset of harmful effects in childhood and adolescence, with a possible role of exposure already in utero. The overall aim of this thesis was to investigate effects of pre- and postnatal exposure to road traffic noise and/or maternal occupational noise exposure during pregnancy on birth outcomes as well as on certain cardiovascular, metabolic and respiratory health effects during childhood and adolescence.

All studies in this thesis were based on the BAMSE birth cohort, which includes more than 4000 children from Stockholm County born during 1994-1996. Individual assessment of residential exposure to noise from road traffic was based on a newly developed database containing longitudinal information on determinants of traffic noise levels in Stockholm County. Data on health outcomes and covariates were obtained from questionnaires, medical examinations and health registers.

Road traffic noise exposure was not associated with saliva cortisol in 16-year-olds. However, the levels were markedly increased in the highest exposure group among those very annoyed by road traffic noise. Furthermore, BMI was increased in school children in relation to road traffic noise exposure, with increments of 0.11 kg/m^2 and 0.20 kg/m^2 per 10 dB Lden in the age groups 8-11 and 12- 16 years, respectively. Maternal noise exposure during pregnancy was not related to birth weight, however, an inverse association was observed between maternal road traffic noise exposure during pregnancy and preterm birth (OR 0.72, 95 % CI 0.59– 0.90 per 10 dB L_{den}). There was no clear association between road traffic noise exposure and systolic or diastolic blood pressure, but a tendency to elevated systolic blood pressure was noted in 16-year olds when their mother was heavily exposed to noise in the workplace during pregnancy. Asthma and wheezing during childhood and adolescence were generally not related to road traffic noise exposure in infancy or to maternal noise exposure during pregnancy. However, there were tendencies towards increased risks for asthma ever up to 16 years with residential road traffic noise exposure in infancy ≥55 dB L_{den} (adjusted OR=1.22; 95 % CI 0.90-1.65), as well as with prenatal occupational noise exposure ≥80 dB L_{Aeq8h} (OR=1.18; 95 % CI 0.85-1.62).

In conclusion, our findings suggest effects of road traffic noise exposure on saliva cortisol levels, in combination with annoyance, and on BMI development. However, no clear associations were observed for blood pressure in adolescence or asthma/wheezing from childhood to adolescence.

LIST OF SCIENTIFIC PAPERS IN THESIS

1. Wallas, A., C. Eriksson, O. Gruzieva, T. Lind, A. Pyko, M. Sjöström, M. Ögren and G. Pershagen (2018). "Road traffic noise and determinants of saliva cortisol levels among adolescents." Int J Hyg Environ Health 221(2): 276-282.
2. Wallas, A., S. Ekström, A. Bergström, C. Eriksson, O. Gruzieva, M. Sjöström, A. Pyko, M. Ögren, M. Bottai and G. Pershagen (2018). "Traffic noise exposure in relation to adverse birth outcomes and body mass between birth and adolescence." Environ Res 169: 362-367.
3. Enoksson Wallas, A., C. Eriksson, A. K. Edstedt Bonamy, O. Gruzieva, I. Kull, M. Ögren, A. Pyko, M. Sjöström and G. Pershagen (2019). "Traffic noise and other determinants of blood pressure in adolescence." Int J Hyg Environ Health 222(5): 824-830.
4. Enoksson Wallas, A., C. Eriksson, M. Ögren, A. Pyko, M. Sjöström, E. Melen, G. Pershagen, and O. Gruzieva. “Noise exposure and childhood asthma up to adolescence” (under revision for Environ Res).

RELATED PAPERS

5. Pyko, A., C. Eriksson, T. Lind, N. Mitkovskaya, A. Wallas, M. Ögren, C. G. Östenson and G. Pershagen (2017). "Long-term exposure to transportation noise in relation to development of obesity-a cohort study." Environ Health Perspect 125(11): 117005.
6. Pyko, A., T. Lind, N. Mitkovskaya, M. Ögren, C. G. Östenson, A. Wallas, G. Pershagen and C. Eriksson (2018). "Transportation noise and incidence of hypertension." Int J Hyg Environ Health 221(8): 1133-1141.
7. Pyko, A., N. Andersson, C. Eriksson, U. de Faire, T. Lind, N. Mitkovskaya, M. Ögren, C. G. Östenson, N. L. Pedersen, D. Rizzuto, A. K. Wallas and G. Pershagen (2019). "Long-term transportation noise exposure and incidence of ischaemic heart disease and stroke: A cohort study." Occup Environ Med 76(4): 201-207.

OTHER COAUTHORED PAPERS

8. Almqvist, C., A. K. Örtqvist, T. Gong, A. Wallas, K. M. Ahlen, W. Ye and C. Lundholm (2015). "Individual maternal and child exposure to antibiotics in hospital - a national population-based validation study." Acta Paediatrica 104(4): 392-395.
9. Ahlen, K. M., A. K. Örtqvist, T. Gong, A. Wallas, W. Ye, C. Lundholm and C. Almqvist (2016). "Antibiotic treatment and length of hospital stay in relation to delivery mode and prematurity." PLoS One 11(10): e0164126.

LIST OF ABBREVIATIONS

3D	Three-dimensional
BAMSE	Barn, Allergy, Milieu, Stockholm, Epidemiology
BMI	Body mass index (kg/m^2)
CI	Confidence interval
CVD	Cardiovascular disease
dB	Decibel
ENS	Endocrine nervous system
ESC	Evening saliva cortisol
EU	European Union
GIS	Geographic information systems
HPA axis	Hypothalamic–Pituitary–Adrenal axis
Hz	Hertz
IHD	Ischemic heart disease
IOTF	International Obesity Task Force
ISAAC	International Study of Asthma and Allergies in Childhood
JEM	Job-exposure matrix
kg	Kilogram
L_{Aeq24h}	Continuous A-weighted equivalent sound pressure level for 24 hours
L_{Aeq8h}	Continuous A-weighted equivalent sound pressure level for 8 hours
L_{den}	L_{Aeq24h} with a penalty added for night time noise (10 dB) and evening noise (5 dB) to account for the higher noise sensitivity during these periods
m	Meter
MBR	Medical birth register
MeDALL	Mechanisms of the Development of Allergy
mmHg	mm vertical column of mercury
MONE	Maternal occupational noise exposure
MSC	Morning saliva cortisol
N	Number
nmol/l	Nanomole per litre
NO_x	Nitrogen oxides
NYK	Nordisk yrkesklassificering
OR	Odds ratio
P1- P4	Thesis paper 1-4
SEI	Socio-economic index
TWA	Time-weighted average

1 INTRODUCTION

Traffic noise is an increasing environmental exposure, primarily as a consequence of continuous urbanisation and growth of the transport sector. In 2012 it was estimated that approximately 125 million people in Europe were exposed to noise levels from road traffic exceeding 55 dB L_{den}, which is the European Environment Agency noise indicator level and has been linked to harmful health effects (EEA 2014). Corresponding exposure to railway and aircraft noise affected 19 and 4.1 million, respectively. In Sweden close to two million people are exposed to traffic noise exceeding 55 dB L_{Aeq24h} (Eriksson et al. 2013). The World Health Organisation (WHO) has estimated that at least one million healthy years of life are lost every year from traffic-related environmental noise in Western Europe, mainly due to sleep disturbance and annoyance, but cardiovascular disease also contributes (WHO 2018b). Amongst all environmental exposures, the burden of disease from noise is the second highest in Europe, after air pollution. In view of the evidence on adverse health effects WHO recently proposed more strict environmental noise guidelines (WHO 2018b).

Evidence examining the effects of noise early in life is limited, although existing data indicate an onset of harmful effects in childhood and adolescence, with a possible role for noise exposure *in utero* (Dzhambov et al. 2014, Selander et al. 2016, Weyde et al. 2018). There are several reasons why children may be a vulnerable group in relation to noise exposure (van Kamp and Davies 2013) They may be more susceptible to noise exposure than adults as their organs are not fully developed and in addition, children are not always aware of the dangers and do not have possibilities to change their exposure situation in the same way as adults.

The following sections aim to give a background to the exposures and outcomes investigated in the research articles conducted for this doctoral thesis. The purpose is to describe the types of noise exposure that were studied and to summarize the current state-of-the-art regarding research on some potentially noise induced health effects in children and adolescents as well as possible underlying mechanisms behind these effects.

1.1 ROAD TRAFFIC NOISE EXPOSURE

Road traffic is the dominant source of transportation noise for most populations. Other sources that contribute to traffic noise exposure such as noise from railways and aircraft are not examined in the papers conducted for this thesis and will therefore not be discussed in depth. An overview of the health effects related to noise can be found in section 1.4.

The perception of noise is subjective which explains the complexity of the term *noise*. Commonly, noise could be described as loud and unpleasant sounds. The interpretation thus depends on how an individual perceives a sound and relates to the source. For instance, some people consider the

music at a rock concert as entertainment, whereas others describe it as noise. The abbreviation *dB(A)* describes the logarithmic unit for sound pressure in *decibel* with the sound spectrum A-weighted. A-weighting indicates that lower frequencies are considered to be less important compared to middle- or high frequencies, which has a closer resemblance to human sound perception. Figure 1 describes the sound pressure in some common exposure situations.

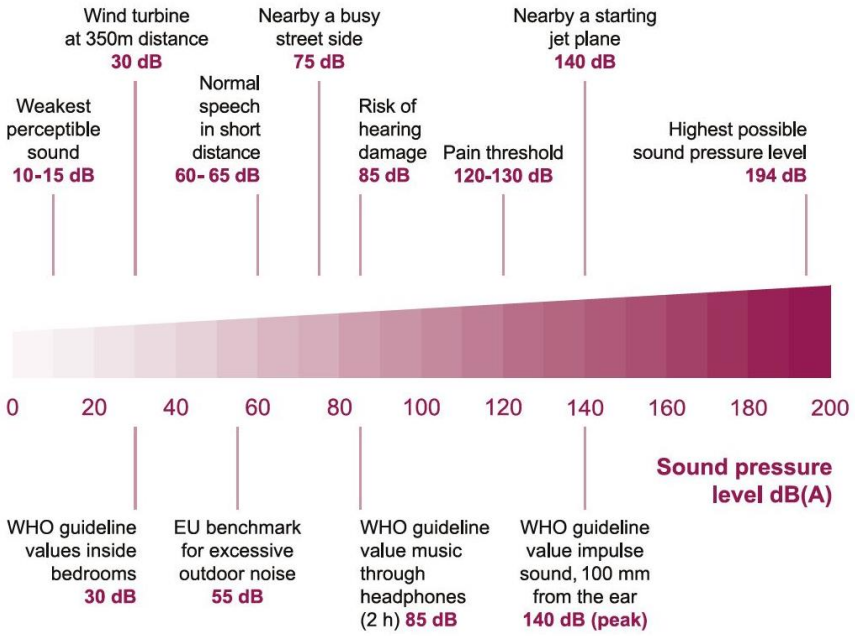

Figure 1. Selected noise sources in relation to sound pressure levels in the environment.

The European Union (EU) uses L_{den} and L_{night} as representative noise indicators for sound pressure levels (Table 1). The choice was based on various factors such as validity (relationship with effects) in the scientific literature, practical applicability and transparency, as well as enforceability and consistency (EEA 2010). In this thesis the noise indicators L_{den} and L_{Aeq8h} are used. More strict road traffic guideline values of 53 dB L_{den} and 45 dB L_{night} were recently proposed by (WHO 2018b) in view of new evidence on adverse health effects.

Table 1: Characteristics of noise indicators used in this thesis

Noise indicator	Characteristics
L_{Aeq24h}	Continuous A-weighted equivalent sound pressure level for 24 hours
L_{Aeq8h}	Continuous A-weighted equivalent sound pressure level for 8 hours
L_{den}	L_{Aeq24h} with a penalty added for night time noise (10 dB) and evening noise (5 dB) to account for the higher noise sensitivity during these periods
L_{night}	Continuous A-weighted equivalent sound pressure level during night time

1.2 OCCUPATIONAL NOISE EXPOSURE

Occupational noise exposure can be associated with auditory and non-auditory health outcomes. Worldwide about 16 % (and in some regions up to 21 %) of hearing loss in adults is associated with noise exposure at the workplace (Nelson et al. 2005). Job-exposure matrices (JEM) can be used to identify occupations with particularly high exposure. Briefly, JEMs are commonly built on occupational exposure measurements, and if such are not available, assessments from experts with an understanding of the exposure are applied (Coughlin and Chiazze 1990). Published literature and staff interviews may also be used to fill gaps in the exposure assessment (Sjöström et al. 2013). For the development of a Swedish JEM on occupational noise exposure, measurement reports were collected from clinics, health services and large companies nationwide (Sjöström et al. 2013). The JEM is used in this thesis and contains measurement report data as well as actual measurements for over 100 different occupation groups.

Occupational noise exposure is mostly characterised as the time-weighted average of an 8-hour workday (L_{Aeq8h}). In Sweden a few occupations have levels above 85 dB L_{Aeq8h} , such as concrete worker, locomotive engineer and plastic industry worker (Sjöström et al. 2013). Safety instructions in such occupations generally involve the use of hearing protection. However, in other noisy occupations like that of a preschool teacher, such prevention is often not provided, although noise levels may exceed 84 dB(A) (Persson Waye et al. 2019). Health consequences observed in a cohort of Swedish preschool teachers included auditory fatigue, tinnitus and hyperacusis (Fredriksson et al. 2019). Health hazards from occupational noise exposure may not be found only in the working population. Occupational noise exposure of the mother during pregnancy has been associated with adverse outcomes and hearing dysfunction (Dzhambov et al. 2014, Selander et al. 2016). A more detailed description regarding noise exposure and health effects in children and adolescents is provided in section 1.4.

1.3 HEALTH EFFECTS UNDER STUDY IN CHILDHOOD AND ADOLESCENCE

This section aims to give a brief overview on a variety of health outcomes which were assessed in relation to noise exposure in the four research articles that comprise this this thesis. Not all of the outcomes are of major concern in children and adolescents, but may lead to serious manifestations in adulthood, such as poor lung function and overweight/obesity.

1.3.1 STRESS AND ANNOYANCE

Stress is primarily induced by two different systems: the Sympathetic-Adrenal-Medullary axis and the Hypothalamic-Pituitary-Adrenal (HPA) axis. The Sympathetic-Adrenal-Medullary axis is mainly triggered by acute stress and involves secretion of adrenaline and noradrenaline. The Hypothalamic-Pituitary-Adrenal axis is more involved in long-term effects of both acute and chronic stress and is

characterised by a release of the glucocorticoid hormone cortisol from the adrenal cortex (Hannibal and Bishop 2014). Cortisol is an important regulatory hormone of lipid and glucose metabolism, and long-term increased levels may result in several adverse health effects, including hypertension, centralisation of body fat, dyslipidaemia and insulin resistance (Rosmond and Björntorp 2000). Cortisol release commonly follows a diurnal pattern with high levels after awakening and decreasing levels during the day with the lowest levels in the evening (Dahlgren et al. 2009).

Sources for stress in children and their perception of it are diverse as well as the adverse health outcomes associated with stress (Thomas Boyce and Hertzman 2018). There is evidence that maternal stress perception during pregnancy is associated with adverse birth outcomes, e. g. preterm birth and foetal growth retardation (Entringer et al. 2010). Maternal stress during pregnancy may also be associated with an increased risk of the offspring being overweight or obese (Li et al. 2010, Hohwü et al. 2014). Furthermore, low socio-economic status (childhood poverty) has been associated with psychological stress in teenagers, indicated by elevated cortisol levels and significantly lower cardiovascular reactivity (Evans and Kim 2007). A constantly elevated stress hormone response in children has been related to alterations in brain development and immune function, as well as adverse metabolic and cardiovascular outcomes (Johnson et al. 2013). Some of these outcomes such as obesity and/or cardiovascular effects were manifested also in adults.

Annoyance is a negative reaction triggered by an agent or a condition leading to symptoms such as anger, discomfort, or impatience (WHO 1999). In the context of this thesis noise annoyance is focused. In a comprehensive review Guski et al. (1999) show that annoyance is a main effect of environmental noise. Evidence regarding annoyance and traffic noise exposure in children and adults is described in section 1.4.1.

1.3.2 WEIGHT DEVELOPMENT AND BIRTH OUTCOMES

The body mass index (BMI) is calculated as the person's weight in kilograms divided by the height in square meters. The BMI is often used to define if an individual is overweight or obese (Table 2).

Table 2: Definition of BMI categories*

BMI (kg/m^2)	Definition
<18.5	Underweight
18.5-24.9	Normal
25-29.9	Overweight
≥30	Obese
**According to WHO (2018b)*	

However, the BMI does not consider the body composition of fat and muscle, thus it does not assess how bodyweight is related to the proportion of lean tissue and muscles in relation to percentage of

body fat. BMI-defined overweight and obesity are linked to morbidity and mortality at a population level (Flegal et al. 2009, Huxley et al. 2010, Engin 2017).

According to the WHO being overweight or obese has reached epidemic proportions. In the mid-1970s about 4 % of the 5-19-year-olds worldwide were overweight (with exception of sub-Saharan regions and parts of Asia), while in 2016 the prevalence had increased to over 18 %. For obesity the prevalence changed from 1 % to around 7 %, corresponding to over 340 million people (WHO 2018a). Childhood overweight increases the risk of being overweight and/or obese in adulthood, thereby augmenting the risk of severe health outcomes such as cardiovascular diseases, diabetes, and skeletal disorders. However, already at a young age, being overweight or obese can lead to complications in breathing, high blood pressure and insulin resistance (WHO 2018a).

The definition of BMI from infancy up to adulthood differs from that used in adults. To measure BMI in children and adolescents z-scores are used. Z-scores are reference values which are specific to the child's age and sex. From the ages 2- 20 years, z-scores are prepared by the WHO and the US Centre for Disease Control and Prevention. These scores define overweight and obesity in children either by values ≥85th and ≥95th percentile, respectively, or by +1 and +2 standard deviation scores (Kuczmarski et al. 2002, de Onis et al. 2007). To provide an international standard for overweight and obesity in children, the International Obesity Task Force (IOTF) developed centile curves in 2012, which correspond to adult cut-offs. Compared to the WHO classification the prevalence values were lower using the IOTF classification. Validations show that the WHO classification captured more cases, whereas the IOTF included less non-cases (Brann et al. 2015). In this thesis BMI definitions according to the IOTF classification are used.

Birth weight is an important marker for the development and health of the new-born. Low birthweight (defined as <2500g) is a risk factor for neonatal death (within the first 28 days of life) as well as for long-term consequences, such as impaired physical development (UNICEF and WHO 2019). Even adult-onset health effects have been associated with low birth weight, such as obesity and diabetes (Jornayvaz et al. 2016, UNICEF and WHO 2019). According to a recent report the prevalence of babies born with low birthweight in 2015 ranged between ca. 7 % in "more developed countries" to 17 % in Asia (UNICEF and WHO 2019). Some sub-regions in south Asia even reported a prevalence of over 26 %. These figures correspond to 20.5 million new-borns worldwide. In Sweden the proportion of new-borns with low birthweight in 2015 was around 4 % (OECD 2019). The global prevalence is likely to be underestimated as birthweight data for over 21 million new-borns in Africa were not available in the UNICEF report. Some potential risk factors associated with low birth weight include low socio-economic status, poor maternal nutritional status (maternal BMI/ weight gain during pregnancy), low height and weight of the mother, anaemia and primiparity (Voigt et al. 2004, Khan et al. 2016). Furthermore, maternal environmental exposures

such as air pollution and neighbourhood greenness have also been associated with birth weight (Pedersen et al. 2013, Eriksson et al. 2019).

Another important indicator for impaired health development in children is preterm birth. Preterm birth is defined as a gestational age of <37 weeks/259 days (Chawanpaiboon et al. 2019). According to a recent review the global proportion of preterm livebirths in 2014 was around 11 % (nearly 15 million new-borns). Over 80 % of the preterm births occurred in Asia and sub-Saharan Africa (Chawanpaiboon et al. 2019). The proportion of preterm new-borns in 2017 in Sweden was 5.5 % (Socialstyrelsen 2019). Just as for birthweight data the reported rates may be an underestimation as data for some African regions were unavailable.

1.3.3 BLOOD PRESSURE

It has been projected that about 1.3 billion worldwide and approximately 2 million in Sweden have hypertension (Läkartidningen 2013, WHO 2016). Hypertension is also referred to as high blood pressure and is often defined as a systolic blood pressure of ≥140 mmHg and a diastolic blood pressure of ≥90 mmHg in adults (WHO 1999). The definition of hypertension and prehypertension in children and adolescents differs from that in adults. It depends on age, sex, and height and is defined according to standardised tables where blood pressure ≥90th percentile is defined as prehypertension and ≥95th percentile as hypertension. The prevalence of prehypertension and hypertension in children is estimated to be around 6 % and 3 %, respectively, and both conditions are often underdiagnosed (Riley et al. 2018).

Increased blood pressure has become a growing health risk in children. A recent American cohort study with over 15000 children found that the prevalence of elevated blood pressure in children had increased from 12 % to over 14 % (Sharma et al. 2018). There is strong evidence for an association between childhood blood pressure and blood pressure later in life (Chen and Wang 2008). Furthermore, hypertension in children is correlated with being overweight and obese (Riley et al. 2018). High blood pressure in children can be tackled through changes in lifestyle such as diet and physical activity, recommendations for adults additionally recommend restrictions in tobacco and alcohol consumption (WHO 2016, Riley et al. 2018).

1.3.4 ASTHMA AND WHEEZING

Asthma is a condition characterised by symptoms like coughing, difficulties in breathing and shortness of breath, as well as spasmodic contractions of airway smooth muscle. A further indicator that may characterise an asthma attack is a whistling sound in the chest during breathing, often described as wheezing. Asthma is an inflammation of the airways leading to airway obstruction (Ferrante and La Grutta 2018). Treatment with medication can reduce the symptoms, however, the disease is not curable with drugs. It leads to a major economic impact on the public health system

and paediatric asthma is one of the most common chronic diseases in children and adolescents (WHO 2011). In Sweden the prevalence of asthma among children and adolescents is between 8 and 10 % (Environmental Health Report 2013). Besides genetic predisposition, lifestyle and environmental factors have been identified as risk factors for asthma (Moffatt et al. 2010, Thacher et al. 2014, Gehring et al. 2015, Ekström et al. 2017). Some factors, like air pollution, mould and house dust mites are related to crowdedness and/or urbanisation, and may contribute to higher asthma occurrence in urban areas (Robinson et al. 2011).

1.4 HEALTH EFFECTS OF ENVIRONMENTAL NOISE EXPOSURE

This section summarises the evidence on health effects related to exposure to road traffic noise exposure as well as to noise in the workplace. As previously mentioned, WHO recently published updated guidelines on environmental noise for the European region (WHO 2018b). New developments in these guidelines were the inclusion of further environmental noise sources (such as wind turbines and leisure noise) as well as growing evidence on serious adverse health risks associated with environmental noise exposure, such as cardiovascular and metabolic diseases. Although evidence in adults is more comprehensive, data are also available pointing to associations between environmental noise exposure and adverse health effects early in life.

1.4.1 STRESS AND ANNOYANCE

It has been suggested that noise-induced release of stress hormones is associated to a variety of health disorders, including cardiovascular conditions in adults (Babisch et al. 2001). Also, annoyance and sleep disturbances are related to road traffic noise exposure. An extensive review summarised studies examining the association between occupational or traffic noise exposure and stress hormones in both adults and children (Babisch 2003). The evidence on effects of traffic noise from sources such as roads, railways and aviation on cortisol measured in saliva or urine appears inconsistent. Studies including adult subjects showed varying results from decreasing to increasing levels in relation to noise exposure, whereas children's levels were either unchanged or increased (Evans et al. 1995, Haines et al. 2001b, Bigert et al. 2005). Raised levels of adrenaline and noradrenaline were found among children in relation to aircraft noise in a study near Munich airport, whereas no association was observed in a corresponding study near Heathrow airport (Hygge et al. 1996, Evans et al. 1998, Haines et al. 2001b). One study on noise from road traffic and railways found higher overnight urinary cortisol levels in children in noisier areas (Evans et al. 2001). Although there are indications that aircraft noise exposure is related to elevated morning saliva cortisol among adults, and particularly in women (Selander et al. 2009), evidence on environmental noise and stress hormones in children and adolescents is conflicting. Stansfeld and Clark (2015) suggested that measures of prolonged raised cortisol may be appropriate as a stress marker.

Annoyance is associated with environmental noise exposure (WHO 2011). In adults annoyance is strongly correlated with the exposure to different sources of traffic noise (Guski et al. 2017). Evidence from a cross-sectional multicentre study on traffic noise exposure and annoyance in children showed aircraft noise exposure to be associated with severe annoyance in 9-11-year-olds (van Kempen et al. 2009). Associations appeared stronger in combination with road traffic noise exposure. Furthermore, a nationwide survey in German 8-14-year-olds found that annoyance to road traffic noise increased with age (Babisch et al. 2012a). In a French cross-sectional study in children 7- 11 years old noise annoyance was associated with exposure levels in outdoor areas near to the bedroom (Grelat et al. 2016).

In conclusion, evidence shows that traffic noise exposure is related to annoyance and stress in adults, but data are more limited in children and adolescents. There is a need for longitudinal data, as well as more harmonised exposure and outcome measures, to assess the role of environmental noise exposure for annoyance and stress reactions early in life.

1.4.2 WEIGHT DEVELOPMENT AND BIRTH OUTCOMES

Only a few studies have investigated associations between noise exposure and obesity markers or weight development in adults. A relationship between noise exposure and obesity markers may be mediated by noise induced activation of the Hypothalamic-Pituitary-Adrenal axis and/or sleep disturbances (see section 1.5). Findings in adults show associations between traffic noise exposure and markers of obesity, assessed by BMI, waist circumference and other measures (Eriksson et al. 2014, Oftedal et al. 2015, Pyko et al. 2015, Christensen et al. 2016b, Foraster et al. 2018, Cramer et al. 2019). Recent studies have examined associations in children. A Danish cross-sectional study investigated overweight at 7 years of age in relation to traffic (road and railway) noise exposure during foetal life and childhood. Exposure to road traffic noise of the mother during pregnancy or during childhood was associated with overweight, however, no association was found with railway noise (Christensen et al. 2016a). Furthermore, a Norwegian cohort study found associations between maternal noise exposure during pregnancy and an increase in BMI from birth to 8 years of age (Weyde et al. 2018). In conclusion, sparse evidence in children and adolescents suggests adverse effects by noise exposure on body weight in children, and more evidence is needed to understand if the findings regarding weight development in adults originate during childhood and adolescence.

Prenatal exposure to noise has been associated with adverse health outcomes in infancy and later in life. Maternal noise exposure to traffic noise or to occupational noise during pregnancy have shown associations to a variety of outcomes such as hearing disorders, BMI development, and pregnancy related outcomes (Dzhambov et al. 2014, Selander et al. 2016, Weyde et al. 2018). However, the evidence is limited and inconsistent. A systematic review did not find sufficient

evidence for associations of prenatal noise exposure and adverse birth related outcomes (Hohmann et al. 2013). However, a meta-analysis examining maternal occupational noise exposure (MONE) and pregnancy related outcomes found evidence for an increased risk for small-for-gestational-age, and also the risks for preterm birth, perinatal death, spontaneous abortion and preeclampsia were elevated, albeit not significantly. Furthermore, pooled analyses showed statistically significant risks for MONE and gestational hypertension and/or congenital malformations (Dzhambov et al. 2014). High MONE during pregnancy has been associated with hearing dysfunction in children (Selander et al. 2016). Recent studies also found associations between prenatal road traffic noise and childhood overweight as well as BMI trajectories in children, respectively (Christensen et al. 2016a, Weyde et al. 2018). The inconsistency of the findings suggests that relationships between environmental noise exposure and birth outcomes as well as weight development from infancy to adolescence need to be further examined.

1.4.3 CARDIOVASCULAR EFFECTS

Exposure to road traffic noise has been shown to increase the risk for cardiovascular diseases (van Kempen et al. 2018). However, the number of high-quality studies examining potential associations varies for different outcomes. Combined evidence from cohort and case-control studies showed that road traffic noise exposure was associated with incident ischemic heart disease (IHD) in adults. Within the range of approximately 40- 80 dB L_{den} the risk for incident IHD increased by 8 % per 10 dB $L_{den.}$ Road traffic noise exposure was also positively associated with incident self-reported hypertension in adults in a pooled meta-analysis combining seven cohort studies (Fuks et al. 2017). Associations were less clear with measured hypertension. So far there is only limited evidence showing associations between road traffic noise exposure and the incidence of stroke. Sørensen et al. (2014) found a statistically significant increased risk of 14 % per 10 dB L_{den} in a Danish cohort with more than 50000 participants.

Substantial research has been conducted to assess associations between traffic noise exposure and cardiovascular effects in adults, but the evidence in children and adolescents is limited. However, it has been indicated that children with a low sleep quality, which may be caused by noise disturbance, have an unhealthy heart rate variability pattern (Michels et al. 2013). In cross-sectional analyses of school children in two birth cohorts exposure to noise was associated with diastolic blood pressure in one study (Liu et al. 2014), whilst the results from the other study primarily suggested associations with traffic related air pollution exposure (Bilenko et al. 2015). In a review it was concluded that despite methodological diversity in the assessment of exposures, as well as in blood pressure measurements and in the study design, there appeared to be a positive association between noise exposure and children's blood pressure (Paunovic et al. 2011). However, it was indicated that the causal relationship between noise exposure and changes in blood pressure still

needs to be confirmed through further epidemiological studies and the role of other risk factors also needs to be investigated.

1.4.4 RESPIRATORY EFFECTS

There are a few studies indicating relationships between noise exposure and asthma/wheezing and/or rhinitis (Duhme et al. 1996, Behrens et al. 2004, Bockelbrink et al. 2008), as well as bronchitis (Ising et al. 2004, Niemann et al. 2006). Duhme et al. (1996) and Behrens et al. (2004) used self-reported traffic density and noise annoyance as measures of exposure. Both found positive associations between noise exposure and respiratory symptoms in children. However, after stratifying solely for self-reported traffic noise, Behrens et al. (2004) observed weaker associations, which might indicate that adverse health effects were stronger in relation to annoyance rather than noise exposure. This hypothesis is supported by the findings from Bockelbrink et al. (2008), who found positive associations between noise annoyance from indoor noise sources and prevalent asthma in children. Furthermore, Ising et al. (2004) and Niemann et al. (2006) found positive associations between noise exposure and bronchitis in children and respiratory effects in adults, respectively. The authors concluded that stress and activation of the HPA axis triggered by noise may be responsible for the observed associations.

It appears that a possible association between environmental noise and asthma or other respiratory diseases remains unclear. This may be explained by various factors including: (1) all presented findings were based on cross-sectional study design, (2) the exposure assessment varied among the studies, which makes it difficult to compare findings, and (3) confounding factors such as traffic related air pollution was in part not considered, which may in turn cause spurious associations. Overall, there is a lack of longitudinal and objective data on respiratory outcomes in relation to environmental noise exposure.

1.5 MECHANISMS OF NOISE EFFECTS

The underlying mechanisms behind possible effects of exposure to traffic noise and the above described health outcomes have been investigated to some extent. Traffic noise is a stressor that triggers the activation of the Hypothalamic-Pituitary-Adrenal and Sympathetic-Adrenal-Medullary axes (Babisch 2014) (Figure 2). The activation may be triggered through the auditory system, which continues to function even during sleep. A chronic activation may induce alterations in the metabolic system leading to visceral fat deposition, distress, and/or anxiety (Henry 1992, Björntorp 1997). It has been suggested that long-term elevated levels of stress hormones, such as cortisol, are associated with weight gain and increase in BMI (Hewagalamulage et al. 2016). Noise induced sleeping disorders could also result in a malfunction of the HPA axis (Van Cauter and Knutson

2008), and lead to a variety of non-auditory short- and long-term health effects, which are further discussed below.

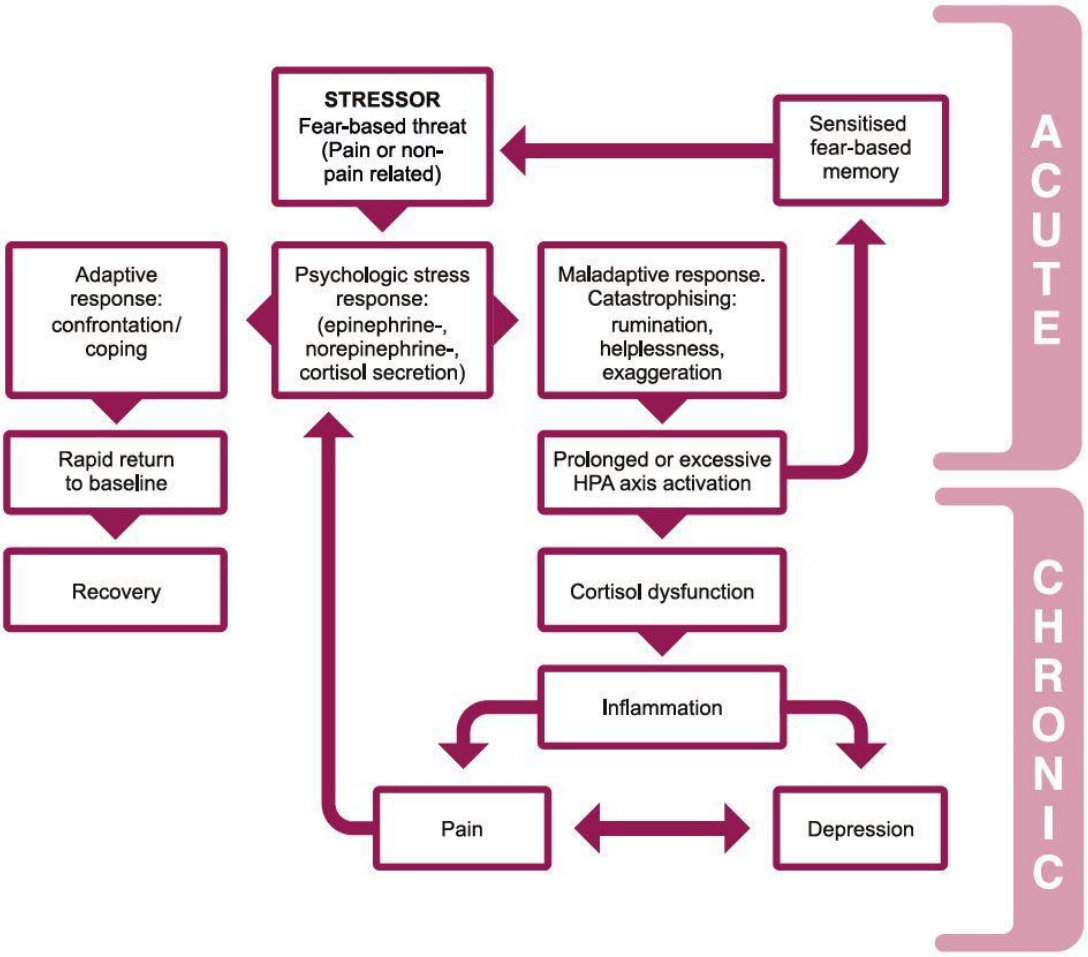

Figure 2. Potential mechanisms of an acute and chronic stress reaction.

Traffic noise exposure may cause sleep disturbances and short sleep duration (WHO 2009, WHO 2011). Sleep disturbances caused by noise may also contribute to obesity by influencing the levels of growth hormone, prolactin, cortisol, thyrotropin and insulin (Taheri et al. 2004, Chaput et al. 2007). Furthermore, sleep disturbance leads to downregulation of leptin (satiety-stimulating hormone) and upregulation of ghrelin (hunger-stimulating hormone), which may lead to a higher caloric intake (Brondel et al. 2010). Overall, an association between sleep and body weight is supported by a recent population-based study in Korean adolescents, where it was shown that increased sleep duration was associated with a reduction in BMI, as well as a decreasing risk for overweight and obesity (Do 2019). Eriksson et al. (2014) and Christensen et al. (2016a) have found associations between noise exposure and an increased risk of developing obesity or overweight in both adults and children, respectively, which partly may be related to sleep disturbances (WHO 2018b). In addition, deprived sleep affects the carbohydrate metabolism, identifiable in a reduced glucose tolerance and type-2 diabetes (Spiegel et al. 1999, Eriksson et al. 2008). An increased risk for diabetes in turn has been associated to traffic related noise (Sørensen et al. 2013). Individual

perception to noise may also be important, but this has only rarely been taken into account in the studies on noise exposure and obesity.

Noise induced cardiovascular disorders may result from direct synaptic nervous interactions, or indirectly through individual perception of sound. Noise exposure and individual annoyance to noise may be interacting thereby affecting the relationship between noise and cardiovascular outcomes (Babisch 2010). Daytime sleepiness and adverse sleep quality was associated with road traffic noise exposure in children (Öhrström et al. 2006). Children may be susceptible to noise induced sleep disturbances and stress reactions which may lead to adverse changes in blood pressure (Knutson et al. 2009, WHO 2009).

The understanding of potential mechanisms behind an association between traffic noise exposure and symptoms of the respiratory tract such as asthma and wheezing is poor. One hypothesis is that an altered immune function increases the risk for immune-mediated diseases including asthma and allergies (Kilpeläinen et al. 2002). As described earlier, noise can cause psychological and/or physiological stress which may also exacerbate these types of diseases.

2 OBJECTIVES

The overall aim of this thesis was to investigate associations between exposure to road traffic noise and development of body weight and asthma during childhood and adolescence, as well as stress hormone levels and blood pressure in adolescence. The role of maternal noise exposure in the workplace and to road traffic during pregnancy was additionally considered. The results of this thesis aim to contribute to the understanding of how exposure to noise may lead to long-term health consequences, and what characteristics mediate or moderate the relationship between exposure and outcome.

The specific objectives of the individual thesis projects were:

- To investigate the role of exposure to road traffic noise and annoyance for stress hormone levels in adolescents.
- To examine changes in the body mass index from infancy to adolescence, as well as adverse birth outcomes, in relation to maternal occupational and road traffic noise exposure during pregnancy as well as individual road traffic noise exposure from birth to adolescence.
- To assess how exposure to road traffic noise and maternal noise exposure during pregnancy may affect systolic and diastolic blood pressure, as well as prehypertension at 16 years of age.
- To study the association between pre- and postnatal exposure to road traffic noise, as well as maternal occupational noise exposure, and occurrence of asthma and wheezing from infancy to adolescence.

3 MATERIAL AND METHODS

3.1 THE BAMSE BIRTH COHORT

All studies in this thesis were conducted with data from individuals in the BAMSE cohort (Wickman et al. 2002). *BAMSE* is an acronym based on the Swedish words *barn*, *allergi*, *miljö*, *Stockholm* and *epidemiologi,* which translate to *children*, *allergy*, *environment*, *Stockholm* and *epidemiology*. It constitutes an ongoing prospective birth cohort study where individuals born in four predefined areas of Stockholm County are followed, recently for up to 24 years. The original aim of the BAMSE project was to assess environmental and socio-economic risk factors for asthma and allergic diseases, but the scope has widened over time.

The recruitment of the BAMSE study population started in 1994 and by the end of 1996 more than 4000 study participants had been included. Briefly, 7221 children were born in the study area during the recruitment period, and after exclusion and non-accessibility of some individuals, 5488 subjects were eligible according to the inclusion criteria. Finally, 4098 new-borns (corresponding to 75 % of the eligible individuals) were recruited to the BAMSE cohort (Figure 3).

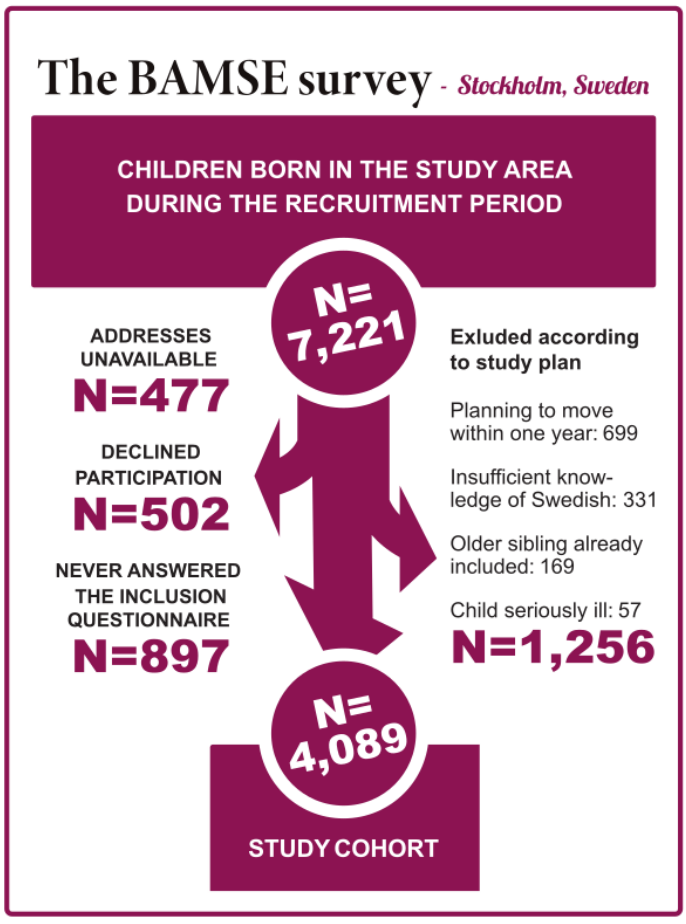

Figure 3. Description of the BAMSE birth cohort recruitment.

The study area included urban and sub-urban districts with a variety of housing, environmental and socio-economic conditions. It comprised the three municipalities Järfälla (suburban), Solna and Sundbyberg (mostly urban), and a part of Stockholm municipality (urban).

The first data collection was made at 3- 4 months of age, when a questionnaire was filled out by the parents, focusing on exposure, heredity and socio-economic factors. Similar, but more detailed questionnaires were sent to the parents when the child was 1, 2, 4 and 8 years of age and to the parents and children at 12 and 16 years. Where applicable, questions were harmonised with those used in the projects: International Study of Asthma and Allergies in Childhood (ISAAC) (Asher et al. 1995) and Mechanisms of the Development of Allergy (MeDALL) (Hohmann et al. 2014). Response rates for the questionnaires ranged from 78 to 96 % for the parents and from 68 to 76 % for the children. At the 4, 8, and 16 year-follow-ups all children were invited to take part in clinical examinations. During the clinical examinations, which were performed by trained nurses, blood samples were taken, and measurements of height and weight were made (further described under 3.4.2 and 3.4.4). At 16 years blood pressure measurements were additionally performed and the participants were provided with instructions and sampling kits for saliva cortisol measurement (further described under 3.4.1 and 3.4.3) (Figure 4).

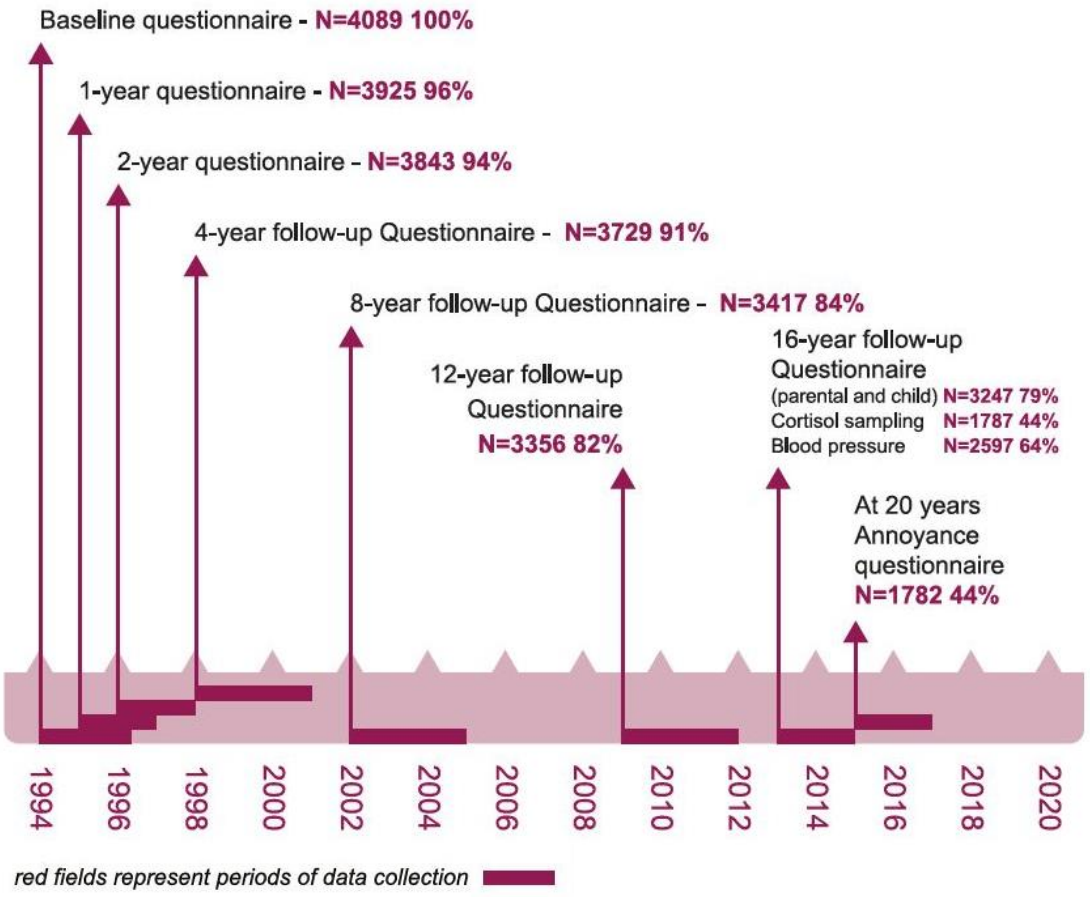

Figure 4. Description of the data collection in the BAMSE birth cohort.

The data collection for the most recent follow-up of the BAMSE cohort at 22- 24 years of age was finalised in May 2019, and these data are not included in this thesis.

3.2 ROAD TRAFFIC NOISE EXPOSURE ASSESSMENT

All information on road traffic noise exposure used in this thesis was assessed on an individual level and based on a recently developed noise exposure database. This database enables assessment of noise levels from transportation sources at any residence in Stockholm County based on geocoded addresses. For estimation of road traffic noise exposure, we used information provided by the Swedish Mapping, Cadastral and Land registration Authority (Lantmäteriet), Stockholm Air and Noise Analysis (SLB-analys), the Swedish transportation administration (Trafikverket), and Stockholm municipality (Figure 5). Data on railway and aircraft noise exposures were also included in the database, but these exposures were uncommon in the study population and not used in the thesis.

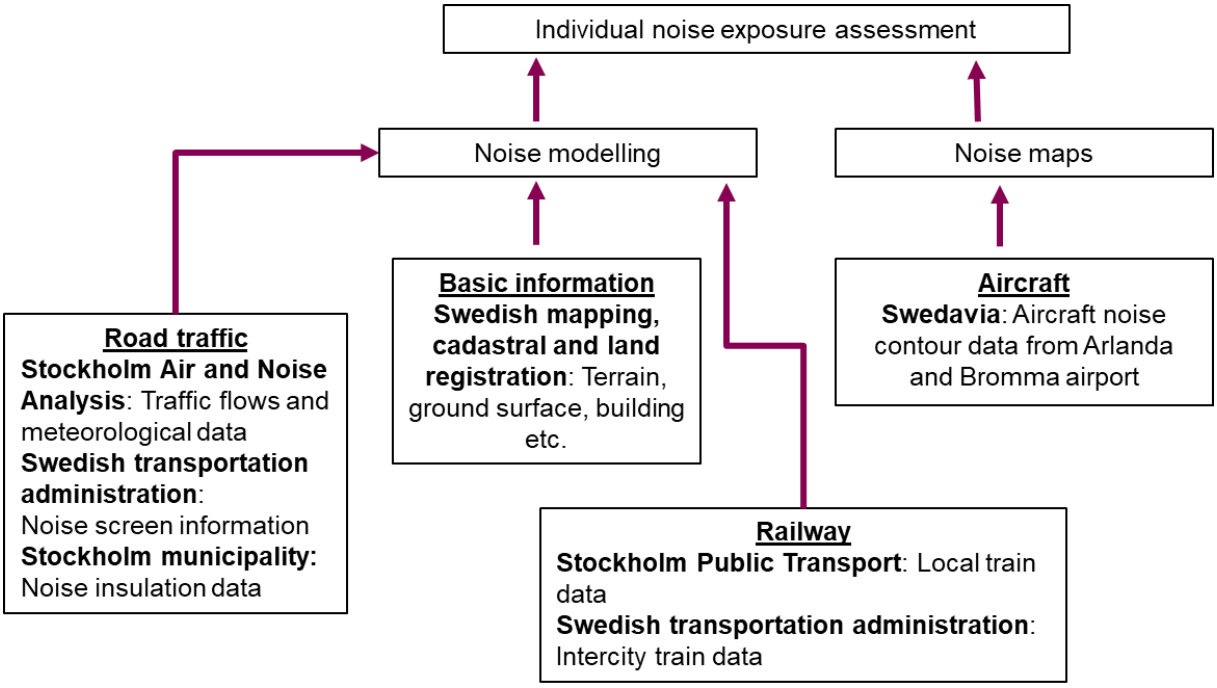

Figure 5. Sources and data included in the noise exposure data base.

For the exposure assessment in this thesis noise modelling was based on the following information:

- 3D shape of the terrain surface
- Road traffic flows on different road segments in 5-year intervals from 1990 to 2010
- Speed limits for road traffic
- Number of heavy vehicles on the road
- GIS shapes of all buildings

To assess individual residential noise exposure history, we used the address information of each participant from birth and onwards. Addresses were obtained from the questionnaires and by using

the property register each address was assigned a geographic coordinate. Incomplete or inconsistent address information was supplemented with data from the Swedish tax authority. Applying a simplified version of the Nordic prediction method (Nielsen 1997) and information from the database, we modelled the 24h- A-weighted sound pressure level for each address of interest. Ögren and Barregård (2016) have validated the methodology of estimating noise levels from road traffic against the full Nordic prediction method with acceptable results.

The modelled noise exposure levels were obtained in L_{Aeq24h} and to facilitate international comparisons we translated them to L_{den}. This implies the use of penalties of 5 dB for the evening period (19- 23) and 10 dB for the night time (23- 7) (Murphy and King 2010). For road traffic there is an underlying assumption of traffic flows of 75 %, 20 % and 5 % during day, evening and night, respectively. This leads to an addition of 3.4 dB to the equivalent level (L_{Aeq24h}) to obtain the corresponding L_{den} noise level. To enable the assessment of average lifetime road traffic noise exposure we used linear interpolation to model noise levels between the 5-year intervals (from 1990 to 2010) and based calculations on the residential history of each study subject. Time-weighted average (TWA) exposure was estimated using the noise levels at each address for an individual and the residential time at the respective address during the time period of interest.

3.3 MATERNAL OCCUPATIONAL NOISE EXPOSURE ASSESSMENT

To assess maternal occupational noise exposure (MONE) during pregnancy we used information on employment from the baseline questionnaire. The answer to the question "What is the mother's profession or trade" was transferred from text to *NYK85/90*-codes (Statistiska centralbyrån 1989). Then we applied the codes to a job-exposure matrix (JEM) containing noise exposure information for more than 300 occupational groups (Sjöström et al. 2013). Occupational noise exposure was assessed in five-year intervals from 1974 to 2014. The classification was based on multiple measurement reports from occupational medicine clinics, occupational health services and large companies, as well as individual measurements. The noise categories rank from <70 dB ("low exposure") to >85 dB ("high exposure") and were recently expanded from three to five categories. Noise levels are presented as equivalent noise levels (L_{Aeq8h}) corresponding to time-weighted averages of an 8-h workday. Occupations coded as "student" and "housewife" were considered as low exposed and classified with an exposure level of <70 dB. Codes categorised as "not classified" were considered as missing in the analyses. For the analyses in this thesis we had access to information on occupational noise exposure during pregnancy for 3886 mothers (95 % of the BAMSE cohort).

3.4 HEALTH OUTCOMES

This thesis elucidates associations between pre- or postnatal noise exposure and a variety of health outcomes from infancy to adolescence in individuals from the BAMSE cohort. Data collection for the different outcomes was conducted at multiple time points during the follow-up period and information was retrieved from questionnaires to the parents and/or the participant as well as from clinical examinations and other sources. The following sections describe the assessed outcomes and the data collection procedures in detail.

3.4.1 STRESS AND ANNOYANCE

Cortisol measurements in saliva samples were used to assess individual stress levels and we also considered questionnaire data to examine annoyance to various noise sources such as traffic, neighbours and the school environment. Two months after the clinical examinations during the 16- year follow-up had started it was decided to invite subsequent participants to provide two samples of saliva for measurements of cortisol. One sample was to be taken in the morning after awakening and the other in the evening prior to bedtime. The saliva sampling kit was distributed at the clinical examination with instructions on how the samples should be collected. A kit contained two tubes marked with the participant's BAMSE identification number, each containing a sterile cotton roll (Salivette®, SARSTEDT AG & Co., D-51582 Nümbrecht). The participants were instructed to take the sample before they cleaned their teeth. Morning samples were to be collected 15 minutes after wake-up and the evening sample just before bedtime. The participants should keep the cotton roll in their mouth until it was soaked thoroughly with saliva and then put it in the tube, which was labelled by the participant with the exact time of sampling. Both tubes were then sent to the laboratory where the samples were centrifuged and stored at -80 °C until analysis. The CORT-CT2 Cortisol RIA (125I) kit from CISBIOassays, Sollentuna, Sweden, was used for the analyses (Hansen et al. 2003). A total of 1794 subjects sent in morning and evening saliva samples, however, 22 morning and 20 evening saliva samples contained insufficient material for analysis.

In 2015 a short supplementary questionnaire was sent to 3154 participants who had taken part in the 16-year follow-up, primarily to assess noise annoyance to different environmental sources. Furthermore, questions on hearing disorders, tinnitus, as well as listening behaviour regarding portable music devices and the use of ear plugs were included. The participants were asked to rank their subjective experience of annoyance in the 12-months prior to the questionnaire at home, school and/or work in relation to a variety of environmental noise sources such as traffic and wind turbines but also from people/neighbours. The degree of annoyance was assessed by a verbal rating scale with five alternatives (not at all, slightly, moderately, very, and extremely). A total of 1782 subjects sent back a completed supplementary questionnaire.

For some of the analyses in **P1** we combined the information from the annoyance questionnaire and the data from the cortisol sampling. We focused on the 737 individuals who lived at the same address in 2015 as when the cortisol-sampling during the 16-year follow-up was performed and conducted our analyses with the underlying assumption that no significant changes in their residential environment had occurred (Figure 6). Out of these, 705 fulfilled additional inclusion criteria and were included in the sub-analysis on annoyance and saliva cortisol.

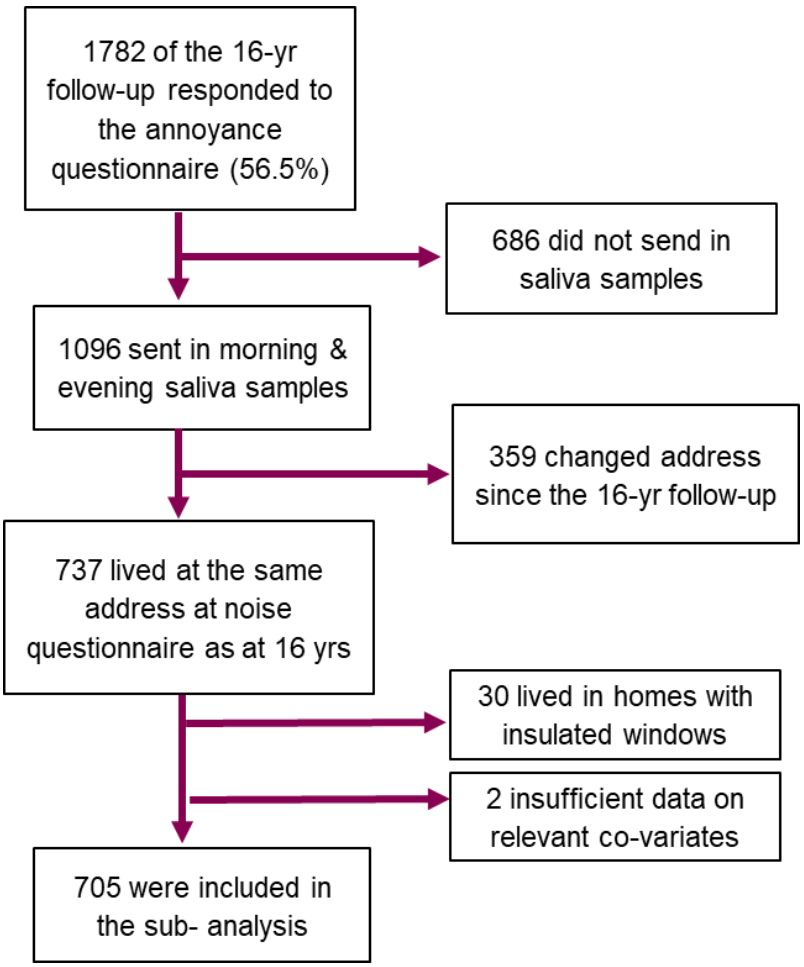

Figure 6. Flowchart on inclusion criteria for sub-analysis on noise annoyance and saliva cortisol.

3.4.2 WEIGHT DEVELOPMENT AND BIRTH OUTCOMES

To assess changes in BMI from infancy to adolescence in the BAMSE cohort we used information on height and weight from the clinical examinations at the 4, 8, and 16-year follow-ups. Furthermore, we retrieved information from school and health-care records at 10 different time points: 6 months (±2 weeks), 12 and 18 months (±4 weeks), 2, 3, 4 and 5 years (±6 months), and 7, 10 and 12 years (−6 to +11 months) (Magnusson et al. 2012). If an individual was lacking information on weight and height from records or examinations, we supplemented with data from self-reporting in the 12- and 16-year questionnaires (Table 4). The self-reported information was validated using data from the other sources and considered as sufficiently accurate (Ekström et al.

2015). To define those that were overweight (including obesity) we followed the definition of gender and age-specific cut-offs from the International Obesity Task Force (Cole and Lobstein 2012).

Table 3: Data on height and weight from birth to adolescence among individuals in the BAMSE birth cohort (n=4072).

Age (years)	Source	Females (n=2015)		Males (n=2057)	
		n	%	n	%
0	MBR	1950	96.8	2009	97.7
0.5	SHR	1117	55.4	1173	57.0
1	SHR	1109	55.0	1155	56.1
1.5	SHR	1062	52.7	1126	54.7
2	SHR	751	37.3	775	37.7
3	SHR	628	31.2	634	30.8
4	CE+ SHR	1612	80.0	1662	80.8
5	SHR	1087	53.9	1117	54.3
7	SHR	1221	60.6	1250	60.8
8	CE	1286	63.8	1334	64.9
10	SHR	1104	54.8	1135	55.2
12	SHR+SR	1453	72.1	1475	71.7
16	CE+SR	1576	78.2	1531	74.4

MBR: Medical Birth Register, SHR: School/ health care records, CE: Clinical Examination, SR: Self-reported

For the analyses in this thesis height and weight data to calculate the BMI at pre-defined ages were available for 4072 individuals at one or more time points during the follow-up (Table 4). Data availability ranged from 31 % to 98 % at different ages and was particularly low 2 and 3 years of age.

We also assessed associations in relation to preterm birth (<37 weeks) and low birth weight (<2500 g) with data collected from the Swedish Medical Birth Register (MBR). Weight and height data for calculating maternal BMI were also obtained from the MBR. Information on weight has been

included in MBR since 1983 and height since 1992. Both are commonly assessed at an antenatal care centre during the first visit in week 9-10 of a pregnancy and most women have this information registered before the end of the first trimester (Socialstyrelsen 2008). Maternal overweight was defined as a BMI of 25 to <30 kg/m^2 and obesity as ≥30 kg/m^2.

A total of 3760 study subjects had completed information on gestational age and birth weight, while weight and height information to calculate maternal BMI was available for 3533 mothers.

3.4.3 BLOOD PRESSURE

The clinical examinations at the 16-year follow-up of the BAMSE participants included measurements by trained nurses of resting systolic and diastolic blood pressure. The measurements were performed with an automatic blood pressure meter (Omron M6, AJ Medical, Lidingö, Sweden), which has also been validated for use in children and adolescents (Stergiou et al. 2006).

To enable accurate blood pressure values each individual underwent three measurements following a standard protocol. The protocol specified that the arm cuff be placed on the upper part of the right arm. Cuff sizes were available from small to large. A one-minute pause was taken between the respective measurements. For the analyses blood pressure levels were evaluated according to WHO standards with respect to the child's age, sex and height-for-age z-scores (de Onis et al. 2007).

We analysed the associations between pre- or postnatal road traffic noise exposure, or MONE during pregnancy, and blood pressure as well as prehypertension in adolescents. Prehypertension was diagnosed if the systolic or diastolic blood pressure was ≥90th percentile for age, sex and height and/or ≥120/ 80 mmHg (NIH 2004, Rosner et al. 2013). Data on blood pressure were available for 2597 adolescents and 387 were classified as prehypertensive.

3.4.4 ASTHMA AND WHEEZING

Road traffic noise exposure and MONE was examined in relation to asthma and wheeze up to adolescence. To assess the prevalence and incidence of asthma we used the reported information from the parental questionnaires at 1, 2, 4, 8, 12, and 16 years. A detailed description of the definition of asthma and wheeze is available in Table 5. Wheeze was defined as at least 1 episode of wheeze during the last 12 months prior to the questionnaires at 1, 2, 4, 8, 12 or 16 years (Gruzieva et al. 2013).

Table 4: Definitions of asthma in the BAMSE study.	
Follow-up	**Definition**
1 year	At least 3 episodes of wheeze after 3 months of age in combination with treatment with inhaled glucocorticoids and/or sign of suspected hyperreactivity without concurrent upper respiratory infection.
2 years	At least 3 episodes of wheeze after 1 year and up to the date of questionnaire 2 in combination with treatment with inhaled glucocorticoids and/or sign of suspected hyperreactivity without concurrent upper respiratory infection.
4, 8, 12, and 16 years	More than 3 episodes of wheeze in the last 12 months prior to the date of the respective questionnaire and/or at least 1 episode of wheeze in the last 12 months prior to the date of the questionnaire combined with prescription of inhaled steroids for symptoms of asthma.

Incidence of asthma and wheeze were defined as first time diagnosis/occurrence of the respective outcome definition during a specified age period without the fulfilment of the outcome at any previous time point. For analyses in **P4** we included 2764 individuals from the baseline cohort to assess asthma/wheeze in relation to MONE during pregnancy and for maternal exposure to road traffic noise during pregnancy 2875 individuals were included. Assessments examining associations with noise exposure during infancy and average noise exposure since birth were based on 2835 and 2185 individuals, respectively.

3.5 STATISTICAL METHODS

Results in **P1** to **P4** on categorical road traffic noise exposure were presented in three categories from <45, between 45-54, to ≥55 dB and the exposure levels were expressed in L_{den}. When results were provided in relation to continuous exposure, we used an increment of 10 dB. MONE was only available as a categorical variable and varied slightly between the different articles. In **P1** the noise exposure categories were <70, 70- <85, and ≥85 dB, however, in **P2, P3** and **P4** cut-offs of <70, 70-79, and ≥80 dB were used. MONE was always expressed as L_{Aeq8h}. Throughout the analysis of all papers, the models tested the assumption of linearity between the respective exposure and the outcome of interest.

The data availability of the assessed outcomes determined the type of study design in the different papers. With data available only at 16 years, **P1** and **P3** used a cross-sectional study design, whereas the studies **P2** and **P4** were conducted with a longitudinal design since outcome data were available at several occasions during the 16-year follow-up. In **P1** we used linear regression models to assess the associations between road traffic noise exposure or MONE and morning as well as

evening saliva cortisol levels expressed as geometric means. To achieve near-normally distributed saliva cortisol levels we used a logarithmic transformation of the values. In a sub-sample we assessed geometric mean saliva cortisol levels in relation to reported noise annoyance to road traffic noise and road traffic noise levels at the residence. Annoyance was expressed in three categories (not, moderately, very annoyed). Linear regression models were also used in **P3** to investigate the association between noise exposure from various sources and systolic as well as diastolic blood pressure.

The analyses in **P2** were conducted using quantile regression, which implies the investigation of associations between exposure and outcome at different percentiles of the outcome. We focused on the 10^{th}, 50^{th}, and 90^{th} percentiles of the BMI distribution. Associations were specified as coefficients expressing the mean changes in BMI per each unit increase (10 dB) in noise exposure. Furthermore, we used logistic regression models in **P3** and **P4** to calculate ORs for prehypertension and asthma and/or wheeze, respectively, in relation to noise exposure. In **P4** we also used generalised estimating equation (GEE) models to assess longitudinal associations between noise exposure and the prevalence/incidence of asthma and/or wheeze from infancy to adolescence (Thacher et al. 2014). GEE models take into account that repeated measurements in one individual are correlated.

All estimates of associations were expressed with 95 % confidence intervals (CI). To control confounding factors, we used adjustments for selected covariates in each paper. The selection of potential confounders was made based on previous literature (**P1**, **P2**, **P3**, **P4**), association with the outcome (**P2, P3**), by using forward selection stepwise regression models to identify high-impact-covariates (**P1**), as well as chi-square tests for significant differences (**P4**). A detailed description of the adjustment variables included in the analyses of the four papers included in this thesis is provided in Table 5.

Information on covariates used for analyses were obtained from the questionnaires and medical examinations from baseline to the 16-year follow-up. In addition, for two articles (**P3**, **P4**) we estimated levels of nitrogen oxides (NO_x), as an indicator of local air pollution from road traffic, using dispersion models (Schultz et al. 2016). NO_x levels were estimated at specific geocoded address points (i.e. residence, day care, and/or school). The dispersion model contained information on air quality and wind obtained from the Airviro Air Quality Management System (http://airviro.smhi.se) and was combined with an emission database calculating an average of annual levels of air pollution for the years 1990, 1995, 2000, 2002, 2003, 2004, 2006, 2010 and 2015. Linear interpolation was used to assess exposure between the years without information on emissions. The model considered only addresses within Stockholm County and for each study subject the exposure to NO_x was estimated as a time-weighted average level based on the time

spent at different addresses. The dispersion model was regularly validated against measurements at air quality monitoring stations.

Table 5: Covariates used for adjustment in P1- P4

Adjustment variable	Type	Indicator/ category	Study where adjustment was used
Age	continuous	years	1, 3
Age group	categorical	<1, 1- 4, 4- 8, 8- 12, 12- 16 years	2
Asthma heredity	binary	yes/no	4
Duration of exclusive breastfeeding	binary	<4/ ≥4 months	3
Eczema	binary	yes/no	1
Height	continuous	meter	3
Maternal BMI during pregnancy	binary	normal, overweight/obese	2, 3
Maternal education	categorical	university, >2 years high school, middle school or less	3
MONE	categorical	<70, 70-79, ≥80 dB	2
Municipality at birth	categorical	Stockholm, Solna, Järfälla, Sundbyberg	2, 3, 4
Nicotine use at 16 years	binary	yes/no	3
NO_x	continuous	$\mu g/m^3$	4
Parental occupation at baseline	categorical	Blue collar, white collar, other	2, 4
Parental smoking during infancy	binary	yes/no	2, 4
Parental smoking during pregnancy	binary	yes/no	2, 3, 4
Physical activity	binary	<5/ ≥5 hours	2, 3
Rhinitis	binary	yes/no	1
Sampling season	categorical	Jan- Mar, Apr- Jun, Jul- Sep, Oct- Dec	1
Sex	binary	male/female	1, 3, 4

3.6 ETHICAL PERMISSION

All surveys, clinical investigations, data handling and analyses in the BAMSE project were approved by the Ethics committee of Karolinska Institutet, Stockholm, Sweden. The parents of the participants, as well as the participants where applicable, provided informed consent. Information was given on the possibility to withdraw from the BAMSE study at any stage.

4 RESULTS

This chapter gives an overview on the most important results obtained in the different papers on which the thesis is based. The results focus on associations between pre- or postnatal road traffic noise exposure, as well as maternal occupational noise exposure, and the outcomes in the respective studies. **P1** focused on associations in relation to morning and evening saliva cortisol, as well as levels of annoyance: **P2** considered changes in BMI and becoming overweight from birth to adolescence and also outcomes related to pregnancy: **P3** investigated relationships regarding systolic and diastolic blood pressure along with prehypertension: and **P4** examined the associations with prevalent and incident asthma or wheeze from infancy to adolescence.

Overall, average road traffic noise exposure levels varied very little from birth to 16 years of age. At 16 years of age the median noise level was 48.7 dB L_{den} (n= 2811) (Figure 7), the median level at birth was 51.7 dB L_{den} (n= 4002), and the median TWA lifetime noise exposure level from birth to adolescence was 48.4 dB L_{den} (n= 2519). The estimates are influenced by differences in the individuals included in the different analyses.

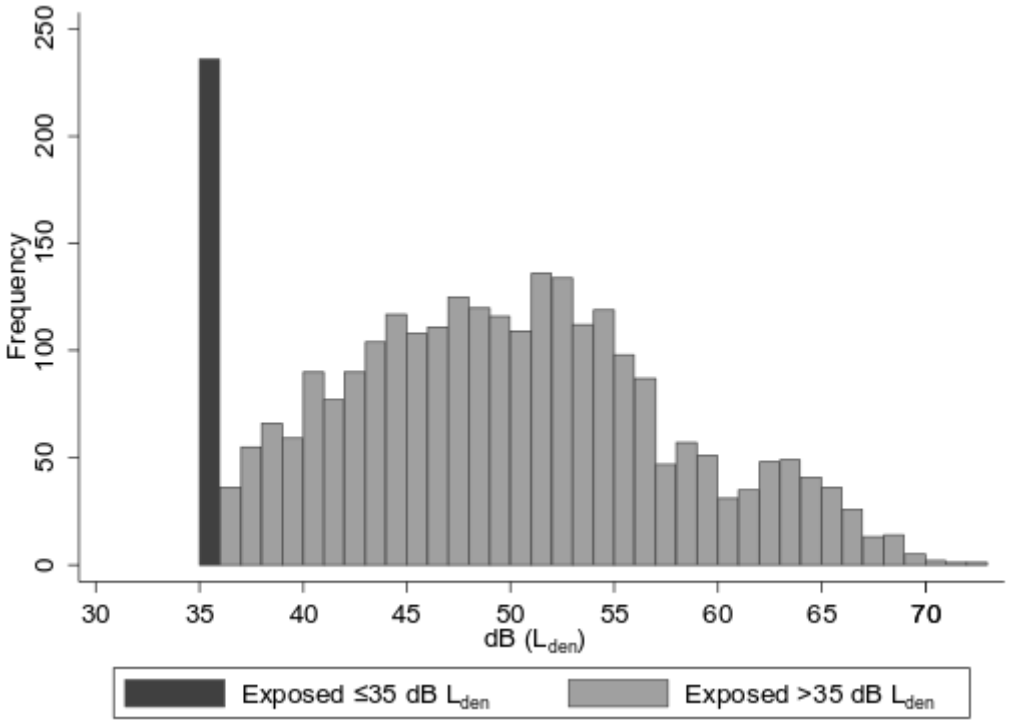

Figure 7. Distribution road traffic noise exposure at 16 years of age.

Most of the mothers in the BAMSE birth cohort (79%) were exposed to MONE levels <70 dB L_{Aeq8h}, 13 % to levels between 70 and 79 dB L_{Aeq8h}, and less than 9 % to levels of ≥80 dB L_{Aeq8h} (Table 6).

Table 6: Distribution of occupational noise exposure during pregnancy in mothers of the BAMSE participants.		
Noise category	**N**	**%**
<70	3081	79
70-74	334	9
75-79	149	4
80-85	311	8
>85	11	<1

4.1 CORTISOL AND ANNOYANCE

Morning saliva cortisol (MSC) levels in the study sample (n= 1751) had a geometric mean of 39 nmol/l (total range 1- 318 nmol/l). The evening saliva cortisol (ESC) levels were substantially lower with a geometric mean of 7 nmol/l (Figure 8). For girls the MSC was higher than in boys (geometric means 42 and 35 nmol/l, respectively).

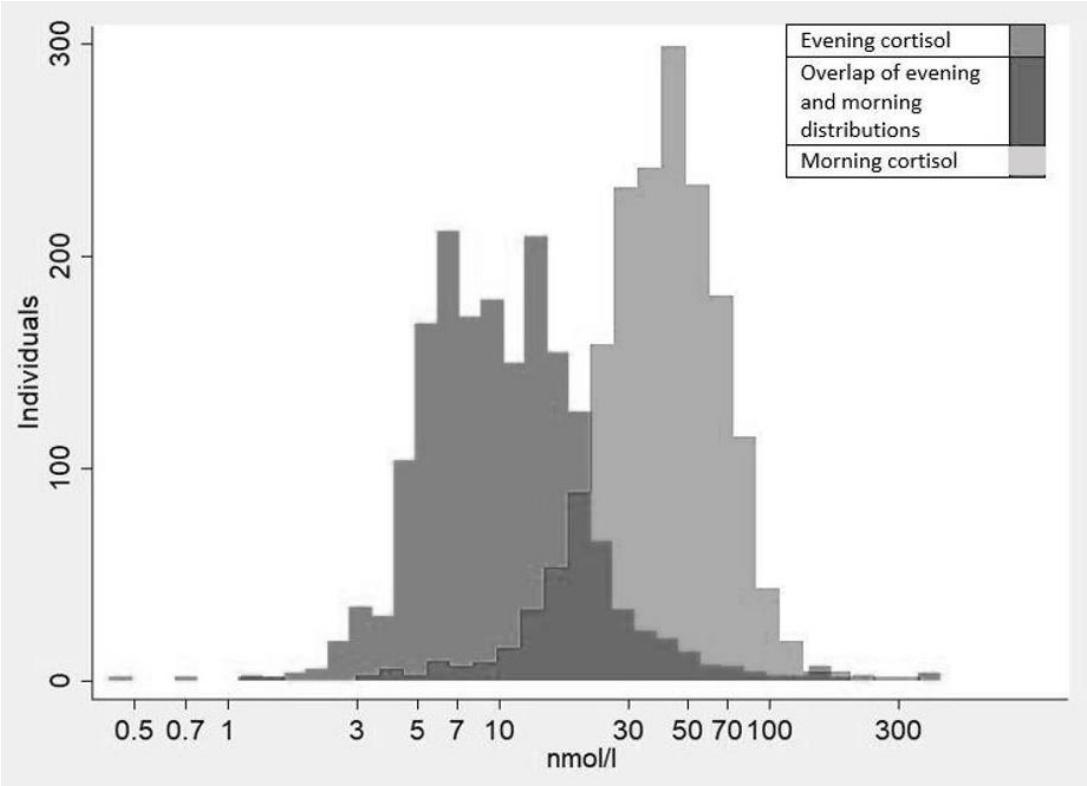

Figure 8. Logarithmic distribution of saliva cortisol at 16 years of age in the BAMSE birth cohort.

No significant associations were observed between categorical or continuous road traffic noise exposure and MSC levels. There was a non-significant decrease in MSC with increasing noise

exposure (Figure 9). Analyses based on the ESC levels did not show any clear influence by road traffic noise.

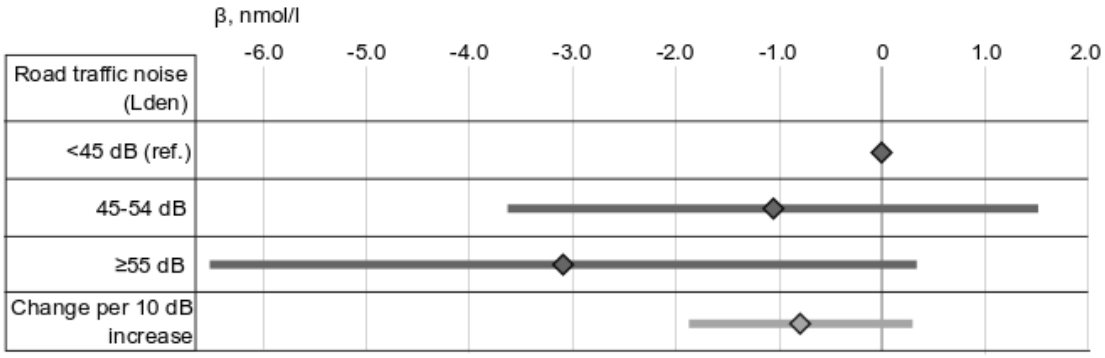

Figure 9. Morning saliva cortisol in relation to residential road traffic noise among 16-year olds from the BAMSE birth cohort.

The analyses of the sub-sample of 705 individuals showed positive trends between noise annoyance and MSC, especially noise annoyance related to residential road traffic and neighbours (p-value 0.1). There were increased prevalence rates of very-annoyed individuals (25 %) in the highest exposure group compared to 15 % in the group exposed to levels <45 dB L_{den}. Furthermore, those who were highly exposed and very annoyed to road traffic noise at home had the highest MSC levels (50.5 nmol/l) (Table 7). Results for ESC did not show comparable associations.

Table 7: Morning saliva cortisol levels in relation to annoyance and residential road traffic noise exposure among 705 adolescents from Stockholm

Residential road traffic, L_{den}	Not annoyed		Moderately annoyed		Very annoyed		Total
	N (%)	Geometric mean (nmol/l)	N (%)	Geometric mean (nmol/l)	N (%)	Geometric mean (nmol/l)	
<45	208 (58)	41.0	97 (27)	38.3	55 (15)	43.1	360
45-54	134 (52)	36.4	78 (30)	43.9	48 (18)	41.1	260
≥55	42 (49)	36.4	22 (26)	31.8	21 (25)	50.5	85
Total	384		197		124		705

4.2 WEIGHT DEVELOPMENT AND BIRTH OUTCOMES

A third of the study population (n= 1232) were overweight on at least one occasion during the follow-up time of our study. There were significant differences in characteristics between normal and overweight individuals, i.e. overweight persons were more likely to have been born prematurely (< 37 weeks) and have overweight mothers. We did not observe any consistent change in median BMI related to road traffic noise exposure in the age groups < 4 years, however in the group 4- < 7 years the association was slightly but significantly inverse, whereas BMI increased with noise

exposure in the older age groups. Road traffic noise exposure in the age groups 8-11 and 12-16 years was associated with increases of 0.11 kg/m² and 0.20 kg/m², respectively (Table 8).

Table 8: Changes in median BMI in relation to road traffic noise exposure in different age groups (per 10 dB L_{den}).

Age group	Beta coefficient	95% CI
<1y	-0.03	-0.11; 0.06
1-3	-0.01	-0.11; 0.09
4-7	-0.06	-0.08; -0.04
8-11	0.11	0.08; 0.13
12-16	0.20	0.17; 0.22

A similar pattern was seen for the 10th and 90th percentiles. However, we did not observe corresponding results for the risk of being overweight in relation to road traffic noise exposure with no statistically significant associations in any of the age groups (Figure 10).

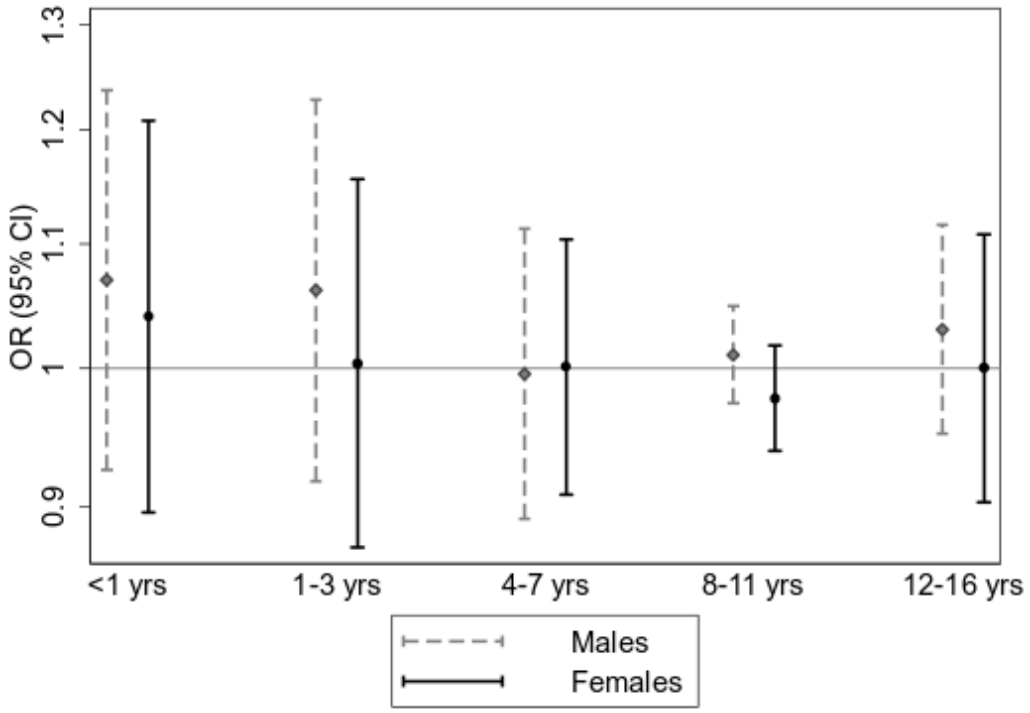

Figure 10. Odds ratio for being overweight in relation to road traffic noise exposure per 10 dB L_{den} in different age groups.

MONE and maternal road traffic noise during pregnancy were not associated with low birth weight or BMI development until adolescence. However, there was an inverse association between maternal

road traffic noise exposure during pregnancy and preterm birth (OR 0.72, 95 % CI 0.59– 0.90 per 10 dB L_{den}).

4.3 BLOOD PRESSURE

More than twice as many boys as girls were prehypertensive (22 % and 8 %, respectively) among the 16-year-olds from the BAMSE cohort (n= 2595). Median systolic blood pressure was 120.5 mmHg and corresponding diastolic blood pressure was 67 mmHg with a close to normal distribution. The systolic and diastolic blood pressure levels (mmHg) were similar in the three categories of TWA noise exposure from birth to adolescence (Figure 11). A majority of the study population lived at addresses with <55 dB L_{den} as pre- or postnatal exposure to road traffic noise, with no apparent difference for those classified as prehypertensive. For TWA exposure, 18 % of those with prehypertension had residential noise levels from road traffic of ≥55 dB L_{den}, while in the total sample this was 20 %.

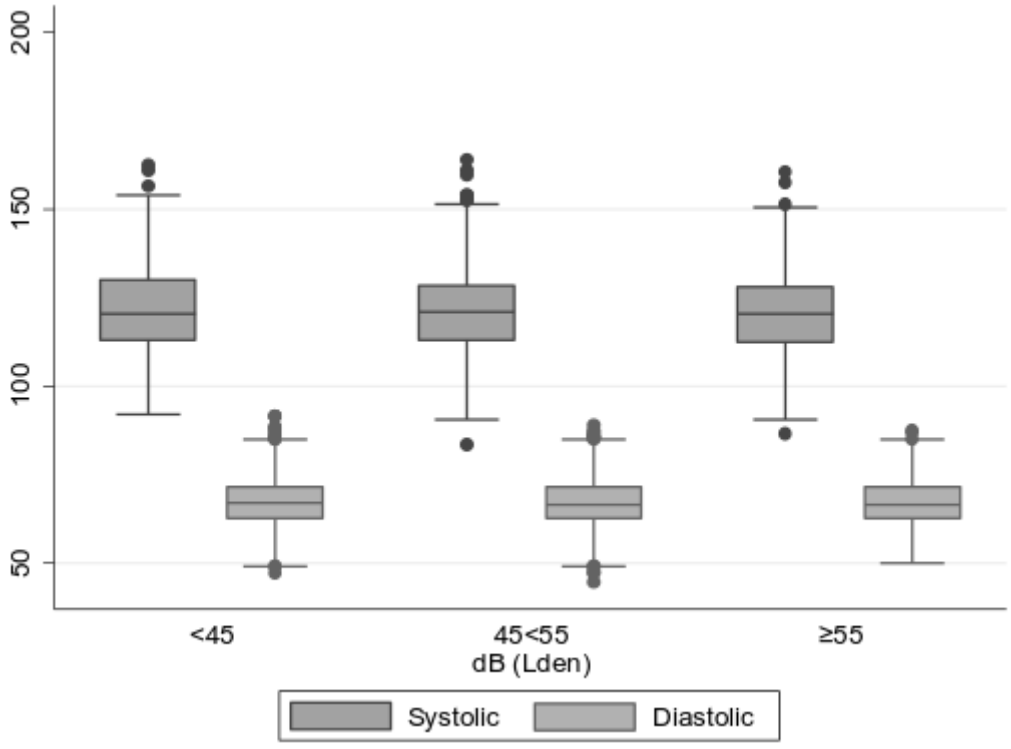

Figure 11. Distribution of diastolic and systolic blood pressure (mmHg) at 16 years of age in relation to TWA residential road traffic noise exposure from birth and onwards.

Non-significant inverse associations were observed between road traffic noise exposure and systolic or diastolic blood pressure. There was, however, a tendency towards elevated systolic blood pressure in individuals from the MONE exposure group 70- 79 dB L_{Aeq8h}. Results for diastolic blood pressure were similar but appeared weaker. For prehypertension we observed decreased OR in relation to both road traffic noise exposure and MONE, however, statistical significance did not remain after adjustment for potential confounders. Analyses of associations between air pollution

exposure (NO_x) in relation to prehypertension and/or blood pressure showed similar results as for noise.

4.4 ASTHMA AND WHEEZE

There was an inverse relation between exposure to road traffic noise during infancy and occupational noise exposure among the mothers during pregnancy. A strong correlation between road traffic noise and traffic related air pollution (NO_x) was observed in the urban residential areas of the study sample (Stockholm and Solna). Asthma prevalence did not vary much between the follow- ups and ranged from 6 % at 2 years to 7 % at 16 years. On the other hand, the prevalence of wheeze decreased from 23 % to 9 % between infancy and adolescence (Table 9).

Table 9: Prevalence and incidence of asthma and wheeze up to 16 years at different ages in the BAMSE birth cohort.

Outcome	Prevalence*	Incidence**
	Total/ Cases (%)	Total/ Cases (%)
Asthma		
1 year	3466/ 140 (4)	3466/ 140 (4)
2 years	3368/ 211 (6)	3271/ 132 (4)
4 years	3314/ 248 (7)	3078/ 132 (4)
8 years	3063/ 204 (7)	2679/ 92 (3)
12 years	2993/ 214 (7)	2441/ 82 (3)
16 years	2801/ 194 (7)	2146/ 62 (3)
Wheeze (≥1 episode)		
1 year	2927/ 505 (17)	2927/ 505 (17)
2 years	2712/ 629 (23)	2468/ 357 (14)
4 years	2823/ 486 (17)	2231/ 178 (8)
8 years	2654/ 297 (11)	1873/ 82 (4)
12 years	2616/ 258 (10)	1695/ 60 (4)
16 years	2287/ 206 (9)	1401/ 50 (4)
* Prevalent cases are defined as total number of cases at the respective follow-up occasion.		
** Incident cases are defined as first-time outcome in the respective age without fulfilling the definition at any previous time point.		

A statistically significant increased OR of ever having had asthma was observed in relation to MONE. However, the association became non-significant after full adjustment (OR= 1.2, 95 % CI 0.9- 1.6 for those exposed to ≥80 dB L_{Aeq8h} compared to the reference group). When assessing asthma ever

in relation to road traffic noise exposure during infancy the risks showed increasing tendencies in the highest category (≥55 dB L_{den}). No corresponding results were observed in relation to maternal exposure to road traffic during pregnancy.

Longitudinal analyses assessing associations between pre- and/or postnatal road traffic noise exposure and asthma incidence up to adolescence showed non-significant results (Figure 12). At 12 years of age a close to statistically significant odds ratios were observed, both in relation to maternal and infancy exposure. Overall, results remained insignificant in relation to prevalent asthma as well as incident/prevalent wheeze. The analyses were not sensitive to adjustment for traffic related air pollution (NO_x).

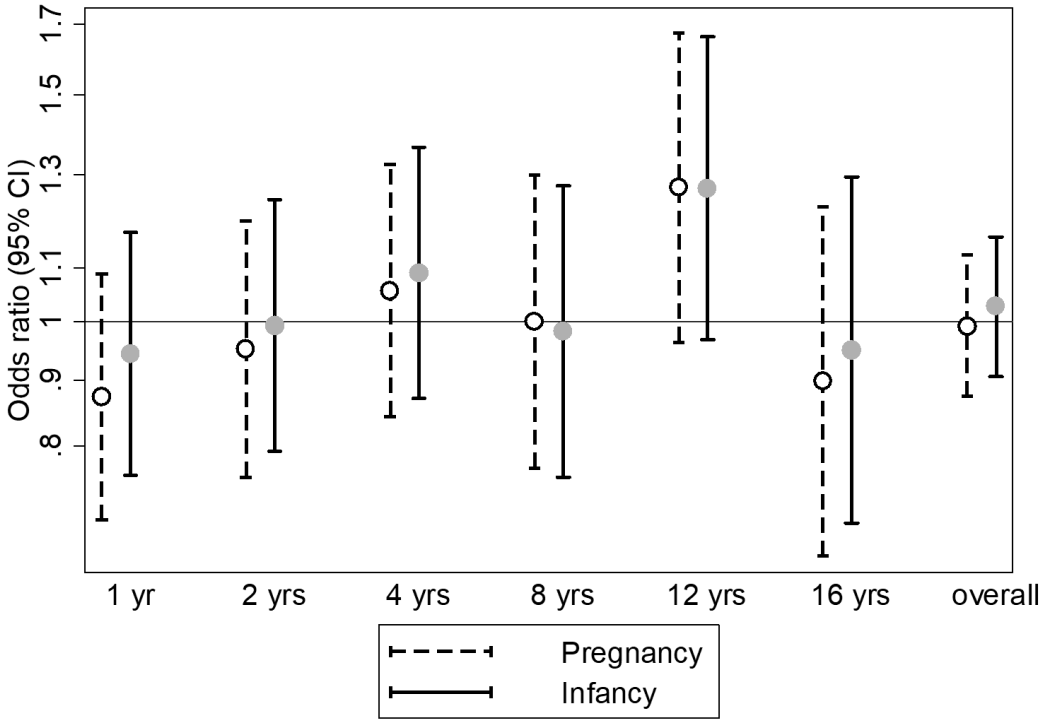

Figure 12. Associations between exposure to maternal residential road traffic noise exposure during pregnancy as well as residential road traffic noise exposure during infancy and incident asthma up to adolescence in the BAMSE cohort (odds ratios expressed in relation to a 10 dB increase in noise exposure).

5 DISCUSSION

This chapter discusses the main findings of the individual studies conducted for this thesis. The potential effects of postnatal exposure to road traffic noise, as well as prenatal maternal exposure during pregnancy, including occupational noise exposure, were investigated in relation to a variety of outcomes such as saliva cortisol and blood pressure levels, as well as the development of BMI and asthma. Both noise exposure and outcomes were assessed during different time windows, making it possible to address a broad spectrum of associations from childhood to adolescence. Besides the discussion of scientific evidence, methodological considerations are taken up to assess how systematic and/or random errors may have influenced the findings and how they were handled in the individual studies. Potential systematic errors (bias) in epidemiological research can result from selection, misclassification, and confounding factors (Rothman et al. 2008). A systematic error can occur due to the study design, measurement of the exposure and/or the outcome, as well as in the selection or follow-up of participants (Matsui and Keet 2017).

Random errors are the consequence of instabilities around a true value due to statistical variability which can be indicated by the width of the confidence intervals (Rothman et al. 2008). A random error may be related to various aspects like the sample size, the prevalence and/or the quality of exposure and outcome assessments. The random error can be larger in studies with small sample sizes or when outcome or exposure are rare. Confidence intervals may then be wider compared to a large sample with a more common exposure or outcome. In the studies conducted for this thesis confidence intervals were often rather narrow because of relatively large sample sizes (n >1700 **P1**, >3700 and >2500 in **P2**+ **P3**, and >2800 in **P4**). However, a paucity of highly noise exposed individuals made results in these categories uncertain.

5.1 CORTISOL AND ANNOYANCE

We did not observe clear associations between road traffic noise exposure and saliva cortisol levels in our study sample. A contributing reason for the lacking association may be the low exposure levels our study population, where the average exposure levels were below 55 dB for approximately 85 % of the individuals. Evidence on traffic related noise exposure and the association with cortisol levels in children and adolescents is limited and inconsistent. Evans et al. (2001) found elevated urinary cortisol levels in children living in areas with high average exposure (62 dB $L_{day\text{-}night}$) to road and railway noise compared to levels in low-noise exposed children (mean 46 dB $L_{day\text{-}night}$). Ising et al. (2004) observed an association between night time road traffic noise exposure and cortisol levels comparing high exposed children (mean levels of 62 dB $L_{A8night}$) to moderately and non-exposed children. Assessing associations with aircraft noise exposure and stress in children Evans et al. (1998) did not find significant associations with cortisol, but rather with other stress hormones such

as epinephrine and norepinephrine in relation to average noise levels of 62 dB and higher. On the other hand, Ising et al. (2003) found road traffic noise exposure to be associated with cortisol and cortisone levels but not with other stress hormones. Significant associations were also observed in a study of children focussing on cortisol levels and exposure to road and railway noise (mean levels of 62 dB L_{Aeq24h}) (Evans et al. 2001). Furthermore, Ising et al. (2002) found significant increases in cortisol levels in relation to night time road traffic noise exposure with measured noise levels indoors <55 dB. However, several studies did not find significant associations between cortisol levels and traffic noise exposure although average exposure levels for those categorised as exposed were rather high (mean ≥62 dB) (Evans et al. 1995, Haines et al. 2001a, Haines et al. 2001b). This suggests that noise exposure may not be directly responsible for the observed associations and that noise induced alterations of stress responses due to sleep disturbances could contribute. In a WHO report on biological mechanisms in relation to environmental noise, Eriksson and Nilsson (2018) describe that a dysregulated HPA axis has an dominant role for a number of known risk factors and that sleep disturbances may affect hormonal release.

No clear conclusion can be drawn comparing our results with previous studies, this is partly related to differences in study design, cortisol sampling material, and noise exposure sources. Additionally, levels of stress hormones may be related to the individual's perception of noise rather than the actual noise levels. We found suggestive trends in morning saliva cortisol in relation to noise annoyance from particular sources such as neighbours and road traffic. This could be an indication of a modifying effect by noise annoyance as found by Babisch et al. (2012b, 2013), as well as Frei et al. (2014) in relation to sleep quality and hypertension. Eze et al. (2018) found noise related annoyance to be associated with current asthma in adults and Bockelbrink documented that noise annoyance from different sources was associated with asthma prevalence in girls (Bockelbrink et al. 2008). Although we used standardised questionnaires to assess the degree of noise annoyance there may be important psycho-social factors which we lacked information on.

Our results need to be interpreted carefully due to the time gap between the cortisol sampling and the assessment of annoyance. There is a risk for misclassification of relevant residential noise exposure and saliva cortisol levels in the annoyance sub-sample. Although we only included individuals who had not changed addresses since the cortisol sampling, assuming noise exposure at the residential address had not changed, we cannot rule out that exposure differs between the timepoints of cortisol sampling and annoyance assessment. Another source for error may be selection bias related to differences of the groups who responded to the annoyance questionnaire and the non-responders. However, in sensitivity analyses we did not see significant differences in the distribution of selected covariates among the groups. Also, random error is of concern due to the rather small size of the sub-sample.

To conclude, we found that that annoyance in combination with traffic noise exposure was associated with increased stress hormone levels, however, there is a lack of longitudinal studies investigating this relation.

5.2 WEIGHT DEVELOPMENT AND BIRTH OUTCOMES

We did not observe consistent changes in median BMI related to road traffic noise exposure in the different age groups. A marginally significant inverse association was observed for age group 4- <7 years, whereas BMI increased in the older age groups (8-11 and 12-16 years). However, there was no corresponding excess risk of being overweight in relation to road traffic noise exposure in the different age groups. MONE and maternal road traffic noise during pregnancy were generally not associated with low birth weight, prematurity or BMI development until adolescence. However, there was an inverse association between maternal road traffic noise exposure during pregnancy and preterm birth.

There are different hypotheses as to why noise exposure could influence weight development and markers of obesity. One potential explanation could be that noise exposure triggers the HPA-axis leading to the release of cortisol (described in 1.5). High stress hormone levels may then result in weight gain (Spiegel et al. 1999, van Cauter et al. 2008). In their prospective study examining perceived stress in children and adolescents van Jaarsveld et al. (2009) observed increased BMI and/or waist scores. A second hypothesis is that noise-induced sleep deprivation results in weight gain due to changes in the levels in hormones responsible for the regulation of appetite (Taheri et al. 2004, Chaput et al. 2007). In a literature review Viet et al. (2014) report that noise induced maternal stress during pregnancy could lead to a dysregulation of hormones and decreased human placental lactogen, which affects the energy supply to the foetus, as well as vasoconstriction causing negative effects on the blood flow in the placenta.

Although we did not observe associations between road traffic noise exposure and BMI in the younger age groups, we found consistent associations from school age up to adolescence. There are some studies on environmental noise exposure showing positive associations with regard to the development of BMI and/or weight in adults (Eriksson et al. 2014, Christensen et al. 2015, Oftedal et al. 2015, Pyko et al. 2015, Christensen et al. 2016b). Christensen et al. (2016a) examined exposure to road traffic noise during pregnancy and childhood in relation to adiposity at 7 years, and found positive associations with overweight but not with BMI. A longitudinal study from Norway assessed the development of BMI in relation to road traffic noise exposure from birth to 8 years of age (Weyde et al. 2018). No significant associations were found between road traffic noise exposure during childhood and BMI trajectories from birth to age 8 years, which is comparable to our findings. There is some evidence pointing to associations between road traffic noise exposure and waist circumference (Pyko et al. 2017), however, we did not have data on waist circumference in the

BAMSE cohort. It appears that at this point the evidence is too limited to enable an overall conclusion on effects of road traffic noise exposure on BMI development in children and adolescents.

We did not observe significant associations between prenatal road traffic noise exposure and adverse birth outcomes. Only a few studies have examined traffic noise exposure during pregnancy in relation to birth weight and childhood BMI with varying findings. One study found an inverse relationship between road traffic noise exposure during pregnancy and birth weight (Gehring et al. 2014), Weyde et al. (2018) in turn, found positive associations regarding BMI trajectories from birth to age 8 years, and Wu et al. (1996) explained the lack of association between prenatal road traffic noise exposure and birth weight with too low exposure levels in their study sample. The latter may also partly explain the absence of associations in our study.

Although we did not observe clear associations between MONE and adverse postnatal health outcomes, there is some evidence on adverse health effect related to such exposure A systematic review based on cohort studies, case-control studies and surveys indicated that MONE (exposure levels between >78 and 85 dB L_{Aeq8h}) is associated with low birth weight, gestational length, spontaneous abortion (before 3rd trimester), as well as with preterm birth and intrauterine growth retardation (Ristovska et al. 2014). Furthermore, a recent Swedish cohort study found significant associations between MONE and small-for-gestational-age and low birth weight (Selander et al. 2019). Earlier findings also showed associations between MONE and hearing dysfunction in children (Selander et al. 2016). There is a great need for further studies to confirm the risks associated with MONE during pregnancy and the effects on the unborn child.

We did not find an obvious explanation for the inverse association between prenatal road traffic noise exposure and preterm birth. Studies from Magann et al. (2005) and Saurel-Cubizolles et al. (2004) found conflicting associations between noise exposure during pregnancy and preterm birth. It is possible that our observations may be the result of residual confounding related to a positive relationship between socio-economic status and road traffic exposure in the BAMSE cohort. Gruzieva et al. (2012) showed that socio-economy and road traffic are positively related in the BAMSE birth cohort. This is explained by higher noise levels in inner-city areas with higher apartment prices, primarily affordable for individuals from higher socio-economic strata. Another explanation might be random error due to few individuals with adverse birth outcomes in our study population. Furthermore, there is uncertainty regarding the duration of MONE in the BAMSE study as we do not know until which gestational age mothers continued working. Selander et al. (2016, 2019) found statistically significant results between MONE and childhood hearing dysfunction and reduced foetal growth, respectively, in mothers working full-time during pregnancy (less than 20 days leave of absence). In conclusion, it is not clear if maternal noise exposure during pregnancy has effects on the risk of preterm birth.

5.3 BLOOD PRESSURE

We did not observe strong and consistent associations between road traffic noise exposure and systolic or diastolic blood pressure in adolescence. Prehypertension showed a trend towards decreasing ORs in relation to road traffic noise, however, only in the crude models. These observations were partly different for those with MONE, where we observed a tendency for elevated systolic blood pressure, as well as a suggested excess risk of prehypertension in adolescents whose mothers were exposed to levels between 70- 79 dB L_{Aeq8h}. Similar but weaker associations were also found with diastolic blood pressure. Our results with regard to air pollution exposure (NO_x) were comparable to those for noise exposure.

A systematic review examined a total of 13 studies which focused on associations between road traffic noise and blood pressure in children (Dzhambov and Dimitrova 2017). Most of the studies were conducted in the last 10 years, except for three studies which were published between 1995 and 2008. The authors also performed a meta-analysis even though most of the studies included in the review varied with regard to both the exposure and outcome assessment.

The suggested inverse associations with road traffic noise exposure observed for systolic and diastolic blood pressure in our study are in line with findings in previous cross-sectional studies (van Kempen et al. 2006, Lepore et al. 2010, Belojevic and Evans 2012, Clark et al. 2012, Paunovic et al. 2013, Belojevic et al. 2015, Bilenko et al. 2015). However, other studies have shown positive associations between road traffic noise exposure and blood pressure in children (Regecova and Kellerova 1995, Belojevic et al. 2008, Babisch et al. 2009, Sughis et al. 2012, Lercher et al. 2013, Liu et al. 2014). Belojevic and Evans (2012) found positive associations only with systolic blood pressure and Belojevic et al. (2015) only with blood pressure measured at school and Bilenko et al. (2015) only in diastolic blood pressure measured at school. The overall results of the aforementioned meta-analysis conducted by Dzhambov and Dimitrova (2017) showed small positive, although non-significant associations between road traffic noise and systolic or diastolic blood pressure in children. Results from a meta-analysis of studies in adults on road traffic noise and hypertension also found positive significant associations (van Kempen et al. 2018). The authors pooled the findings from 26 cross-sectional studies, however the evidence was considered to be of very low quality due to a variety of methodological deficiencies.

It is worth taking into account that there are a number of limitations regarding both our own and previous studies. Due to the cross-sectional design we cannot draw conclusions on causality as we are uncertain about the time sequence of exposure and outcome. Additionally, the current evidence regarding childhood blood pressure varies with regard to the assessment of road traffic noise exposure which makes the comparison of the results and an overall conclusion difficult (Dzhambov and Dimitrova 2017). In our studies however, we do not expect there to be a high risk for systematic

misclassification of pre-hypertension as we used WHO- z-score- definitions for sex, height and age in our assessment of blood pressure. It should be noted, however, that there may be a risk for random error due to the single measurement occasion and the relatively small sample of individuals with pre-hypertension, primarily leading to dilutions of any associations.

We did not find a clear association between traffic related air pollution (NO_x) and blood pressure at 16 years of age. However, the findings resembled those seen with road traffic noise exposure where we also found suggestive inverse associations. Lui et al. (2014) found similar results to ours for 4 different air pollutants and blood pressure in 10- year olds. One explanation for the decreased blood pressure levels could be due to widening of blood vessels resulting from inhalation of nitrogen oxide from traffic emissions (Sørensen et al. 2012). A cross-sectional study by Bilenko et al. (2015) examining 12-year-olds found positive associations between long term exposure to particular air pollutants and diastolic blood pressure. However, these observations were not consistent for systolic blood pressure and they mirror the divergent evidence seen in adults. Studies have shown inconsistent results with both inverse as well as positive associations between air pollution and hypertension (Ibald-Mulli et al. 2004, Harrabi et al. 2006, Sørensen et al. 2012, Fuks et al. 2017). Air pollution and traffic noise are difficult to examine separately from one another, even when both factors are included in the analyses, due to strong correlations which result from road traffic being the major source for both.

5.4 ASTHMA AND WHEEZING

No consistent associations were found neither between MONE during pregnancy nor pre- or postnatal road traffic noise exposure and the incidence and/or prevalence of asthma or wheezing. Some results however, suggested an increased risk of having asthma at any point up to adolescence in relation to both MONE and road traffic noise exposure during infancy.

There is limited evidence on the possible influence of noise exposure on respiratory outcomes. It has been suggested that alterations in the immune system and connective tissue could be underlying biological pathways involved in the occurrence of respiratory symptoms in relation to noise (Recio et al. 2016). As mentioned earlier, noise can act as a stressor. Aich et al. (2009) summarised in their review on stress and disease susceptibility that psychological stressors acutely activate the production of pro-inflammatory cytokines. This can affect the central nervous system and lead to a reaction of the adrenal cortex and cortisol release. The reaction may lead to a vicious circle where cytokine release leads to further cortisol release and exacerbation of the stress response through constant positive feedback.

In adults associations have been observed between short-term exposure to environmental noise and hospital admissions as well as mortality due to respiratory causes (Tobias et al. 2001, Tobias

et al. 2014, Recio et al. 2017). These findings still held true after controlling for traffic related air pollution. Eze et al. (2018) found noise exposure from different traffic sources to be associated with exacerbations in adult asthma. As in adults, evidence for associations between noise exposure and respiratory outcomes in children and adolescents is sparse. Lineares et al. (2006) found that >4 % of the admissions due to pneumonia in children may be related to environmental noise exposure. There is some evidence on effects by long-term noise exposure on respiratory and allergic outcomes in children. A majority of the studies show positive associations with bronchitis and asthma-related symptoms (Duhme et al. 1996, Ising 2003, Ising et al. 2004, Niemann et al. 2006, Bockelbrink et al. 2008). One study found statistically significant associations between self-reported lorry traffic and wheezing in early adolescence, however, not during childhood and no statistically significant associations were observed with self-reported asthma (Behrens et al. 2004). Most of these studies did not have objective data on noise exposure and used questionnaire-reported traffic noise. In our study there was a tendency for increased risks of asthma ever up to 16 years of age in relation to residential road traffic noise during infancy, which is generally in line with some earlier studies. However, we did not find a clear overall association in the longitudinal analyses. To our knowledge ours is the first study that longitudinally examined allergic outcomes such as asthma and wheeze in relation to objectively assessed noise exposure.

We did not observe any associations between MONE during pregnancy and asthma ever up to 16 years. This could be explained by limited statistical power due to low number of asthmatic children exposed to high levels of occupational noise in utero. In their nationwide cohort study Selander et al. (2016) found MONE during pregnancy to be associated with hearing dysfunction mainly in children of mothers in the highest exposure group with noise levels of ≥85 dB L_{Aeq8h}. In our sample we only had 66 mothers in the highest exposure category of ≥80 dB L_{Aeq8h}. All in all, more research is needed to elucidate if and how pre- and postnatal environmental noise exposure may affect the respiratory system early in life.

5.5 STRENGTHS AND GENERALISABILITY

There are a number of strengths in the individual studies presented in this thesis despite the random and systematic errors that have occurred. Using the comprehensive data available from the BAMSE birth cohort is a major strength. As described earlier exposure and outcome data were prospectively available for a large population-based cohort with a follow-up time of up to 16 years. Moreover, response rates remained high throughout the follow-up period.

Several outcomes examined in this thesis, such as weight and height, saliva cortisol and blood pressure were assessed objectively for most of the participants and information on development of asthma and BMI was available longitudinally from childhood to adolescence. The occurrence of respiratory outcomes, such as asthma, was repeatedly assessed following standardised

questionnaires. Objective TWA lifetime road traffic noise exposure information was available for every study participant for addresses in the study area and through the application of an extensive JEM maternal occupational noise exposure during pregnancy was also accessible.

Briefly, generalisability addresses the comparability of the findings in individuals from the study population and those outside of the study population (Rothman et al. 2008). As described earlier new-borns from 4 different areas of Stockholm County were recruited to take part in the study and 75 % of the eligible children were included in the study sample. Through this broad inclusion it was possible to cover a broad spectrum of housing, environmental, and socio-economic conditions. To assess whether the non-responders of the BAMSE project differed from the final cohort they received a short questionnaire, and the responses indicated that no strong differences in selected characteristics existed between the participants and those who did not participate or were excluded. The only difference between the groups was found for parental smoking which was slightly more common among the non-responders. Another exclusion criterion was insufficient knowledge of Swedish. This resulted in a lower representation of families with non-Swedish origin. We do not believe that underlying biological mechanisms for noise induced health effects differ across ethnicity groups. However, generalisability might be reduced with regard to occurrence of parental smoking and characteristics of children with non-Swedish origin.

To conclude, the design of the BAMSE study indicates that the findings in this thesis should be relevant also outside the study population. However, the generalisability in the individual studies may be affected because of more limited inclusion of study subjects.

6 CONCLUSION

This thesis is based on the high-quality birth cohort BAMSE, combined with a newly developed traffic noise exposure database as well as a job-exposure matrix, enabling longitudinal prospective studies of associations between road traffic noise exposure or maternal occupational noise exposure and different outcomes from birth to adolescence. Such studies are rare or non-existent in the literature. Some of the important findings of the thesis are:

- No clear associations were found between exposure to road traffic noise and saliva cortisol levels in the morning or evening among adolescents.
- Reported annoyance to noise combined with high levels of road traffic noise exposure was related to increased morning saliva cortisol levels, suggesting that individual noise perception is of importance for stress hormone levels.
- Road traffic noise exposure was associated with an increase in body mass index from school age to adolescence. Maternal exposure to occupational noise or road traffic noise during pregnancy was not consistently related to birth weight or BMI development. However, an inverse association was observed between maternal road traffic noise exposure and preterm birth.
- No strong or consistent associations were noted between road traffic noise exposure and blood pressure levels or prehypertension in adolescents. This also held true for maternal exposure to noise from road traffic or in the workplace during pregnancy.
- Asthma and/or wheeze from infancy to adolescence were not related to road traffic noise during infancy or to maternal occupational noise exposure during pregnancy.

Research has been very limited on health effects of noise exposure in childhood and adolescence. Consequently, based on the findings in this thesis together with earlier evidence it is not possible to arrive at strong conclusions on causality. The most consistent results relate to noise effects on weight development, which is supported by evidence in adults. Several circumstances may contribute to the limited evidence on associations between noise exposure and different outcomes in this thesis, including comparatively low noise exposures, the spot measurements of some outcomes (saliva cortisol and blood pressure) and imprecise exposure assessments. Serious adverse health effects related to traffic noise exposure have been observed in adults, primarily for cardiovascular and metabolic outcomes. Since several of these may have an origin in childhood it seems important with further studies on health effects by environmental noise exposure in children and adolescents, preferable with longitudinal design.

7 SVENSK SAMMANFATTNING

Trafikbuller är en ökande miljöexponering, främst som en följd av en fortlöpande urbanisering och tillväxt av transportsektorn. Sjukdomsbördan från buller är den näst högsta i Europa bland alla miljöexponeringar, efter luftföroreningar, och Världshälsoorganisationen har nyligen skärpt riktvärdena för omgivningsbuller. Kunskaperna om bullers effekter tidigt i livet är begränsade, även om tillgängliga data antyder att skadliga effekter uppkommer redan i barndomen och tonåren, med en möjlig roll även av exponering under fosterlivet. Det övergripande syftet med denna avhandling var att undersöka effekterna av exponering för vägtrafikbuller och/eller yrkesmässig bullerexponering under graviditeten hos modern för graviditetsutfall samt vissa kardiovaskulära, metabola och respiratoriska hälsoeffekter under barndomen och ungdomsåren.

Alla studier i avhandlingen baserades på födelsekohorten BAMSE, som inkluderar mer än 4000 barn från Stockholms län födda 1994–1996. Individuell bedömning av exponering för buller utanför bostaden från vägtrafik baserades på en nyutvecklad databas som innehåller longitudinell information för uppskattning av trafikbullernivåer i Stockholms län. Uppgifter om hälsoutfall och olika riskfaktorer erhölls från frågeformulär, medicinska undersökningar och hälsoregister.

Exponering för vägtrafikbuller var inte förknippad med salivkortisolnivåer hos 16-åringar, men nivåerna ökade markant i den högsta exponeringsgruppen bland dem som var mycket besvärade av vägtrafikbuller. Dessutom ökade BMI hos skolbarn i relation till exponering för vägtrafikbuller, med ökningar på 0,11 kg/m² och 0,20 kg/m² per 10 dB L_{den} i åldersgrupperna 8-11 respektive 12-16 år. Bullerexponering hos modern under graviditeten var inte relaterad till födelsevikt, dock observerades ett omvänt samband mellan moderns exponering för vägtrafikbuller under graviditet och prematuritet (oddskvot 0,72; 95 % konfidensintervall 0,59- 0,90 per 10 dB L_{den}). Det förelåg ingen tydlig koppling mellan vägbullerexponering och systoliskt eller diastoliskt blodtryck, men en tendens till förhöjt systoliskt blodtryck noterades hos 16-åringar när deras mor var utsatt för höga bullernivåer på arbetsplatsen under graviditeten. Astma och väsande/pipande andning under barndomen och tonåren var inte relaterade till vägtrafikbullerexponering i spädbarnsåldern eller till moderns bullerexponering under graviditeten. Det förelåg emellertid en tendens till ökad risk för astma upp till 16 års ålder i relation till vägbullerexponering under spädbarnstiden ≥55 dB L_{den} (oddskvot 1,22; 95 % konfidensintervall 0,90- 1,65), så väl som till moderns yrkesexponering för buller ≥80 dB L_{Aeq8h} (1,18; 0,85- 1,62). Sammanfattningsvis tyder resultaten på samband mellan vägtrafikbullernivåer och salivkortisol, vid rapporterade bullerbesvär, samt med BMI-utveckling, medan inga tydliga samband sågs för blodtryck hos ungdomar eller astma från barndomen till ungdomsåren.

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