Cardiovascular effects of environmental noise: Research in Austria

Review of studies in alpine valleys over 25 years – exposure response and
effect modification

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Abstract

Cardiovascular effects of noise rank second in terms of DALYs after annoyance. Although research during the past decade has consolidated the available data base the most recent meta-analysis still shows wide confidence intervals – indicating imprecise information for public health risk assessment. The alpine area of the Tyrol in the Austrian part of the Alps has experienced a massive increase in car and heavy goods traffic (road and rail) during the last 35 years. Over the past 25 years small, middle and large sized epidemiologic health surveys have been conducted – mostly within the framework of environmental health impact assessments. By design these studies have emphasized a contextually driven environmental stress perspective where the of adverse health effects by noise are studied in the broader framework of environmental health, susceptibility and coping. Furthermore, innovative exposure assessment strategies were implemented. This paper reviews existing knowledge from those studies over time, presents exposure-response curves with and without interaction assessment based on standardized re-analyses and discusses it in the light of past and current cardio-vascular noise effects research. The findings support relevant moderation by age, gender and family history in nearly all studies and suggest a strong need for consideration of non-linearity in exposure-response analyses. On the other hand, air pollution did not play a relevant role as moderator for the noise-hypertension or the noise-angina pectoris relationship. Finally, different noise modeling procedures can introduce variation in exposure response curves with substantive consequences for public health risk assessment of noise exposure.
Keywords
Traffic noise, blood pressure, hypertension, angina pectoris, noise, exposure-response relationship, effect modification
Introduction

Through its geographical position in central Europe Austria has experienced transit-traffic since Roman times. Since the early seventies the Austrian part of the Alps has experienced a massive increase in car and especially in heavy goods traffic (road and rail). Currently, about 32% of the population is exposed to road noise levels $\geq 60$ dBA and 60% $\geq 55$ dBA. While the increase occurred foremost on the road, first complaints were issued about highway traffic by the end of the seventies. In 1984 we started a first pilot study in a small community ("noise village") which was surrounded by a highway and an associated toll station (Lercher 1988, Lercher 1990) to explore the problem. Later, the intentions to move heavy goods transport from road to rail led to an increase of heavy rail traffic during the night resulting in higher noise levels than through the daytime (+3 dBA). Therefore, multi-community health surveys followed to study the supposed adverse effects of noise and air pollution in those alpine valleys where the transit-traffic was on the increase or where large rail infrastructure projects required environmental health impact assessment (EHIA) (Lercher 1992, Lercher et al. 1995, 1996a, 2000, Heimann et al., 2007). In these studies we emphasized a contextually driven environmental stress perspective (Cohen et al. 1996) and placed the study of noise related adverse health effects in the broader framework of environmental health, susceptibility and coping (Lercher 1994, Lercher 1996a, 1998b, 1998b, Lercher 2007).

Cardiovascular effects of noise rank second in terms of disability adjusted life years (DALYs) after annoyance. Although research during the past decade has consolidated the available data base the most recent meta-analysis - based on road traffic noise studies - reveals wide confidence intervals. It is not also sufficiently clear what the inconsistent results concerning standard potential effect modifiers such as sex, age and education mean. Furthermore, the quantitative role of psychological and physiological vulnerability factors that can promote adverse effects of noise such as noise sensitivity, health status or family history of hypertension has not yet been fully understood. Even the strong data base on the
cardiovascular effects of aircraft noise shows a substantial diversity in terms of exposure response shapes and slopes and in terms of observed effect modifiers. The conclusions about the effects of road traffic noise rest mainly on the Caerphilly & Speedwell and the Berlin studies. Insufficient data are available on the potential cardiovascular effects due to railway noise exposure.

In earlier papers we have suggested that the large variability of noise effects observed is partly due to the strong moderation and/or mediation by the context where the noise exposure occurs and partly due to the effectiveness of coping strategies (Lercher 1994, Lercher 1996b, Lercher et al 1998a, Lercher 2007). Related to this argument, factors such as regional differences in the underlying population morbidity structure (susceptibility and health status) and the overall exposure load (at work, environment, socio-economic)) may in addition be responsible for the often observed heterogeneous results. A specific argument is related to the potential difference in the experienced noise exposure in alpine areas. This may be either related to the perception of noise (perceived exposure contrast, signal to noise ratio) or to the inability of classical noise indicators to catch the difference in the meaning of noise exposure which is known to modify bodily responses. Eventually, since longitudinal studies are sparse and difficult to conduct in a continuously changing world with high mobility, the required latency time for the development of noise associated cardiovascular effects has not yet been established. Thus, the sampled population experience in the studies may differ in terms of the cumulative time to the effect and reflect only the different power to detect effects apart from the power provided by sample size.

This paper aims at sharing and integrating the existing knowledge from the Tyrol studies with a wider audience. Firstly, to make analyses available, which have not yet been published - or if so - not in English. Secondly, to summarize the main results observed over a 25 years time period. Thirdly, to add re-analyses based on the existing datasets which contribute to some of the still pertinent questions in cardio-vascular noise effects research. For this purpose
updated models were created to further evaluate interaction effects and to gain deeper insight into the meaning of effect modifiers over time.

Methods

Area, sample selection and recruitment

Both areas of investigation, the Unterinntal and the Wipptal, are located along the most important European North-South-access route for heavy goods over the Brenner Pass. The heavy goods traffic over the Brenner has tripled within the last 25 years and the fraction of goods moved onto the road has substantially increased (up to 2/3). The areas consist of small towns and villages with a mix of industrial, small businesses, tourist and agricultural activities. The primary noise sources are highway and railway traffic. In addition, densely trafficked main roads are of importance. These road link the villages and towns and act as access roads to the highway.

Over the years sampling strategies have been refined. In the early studies all people of representative villages of a certain age range (25-65 yrs or 25-75 yrs) were approached by interviewers. In the later studies a basic phone survey (15-20 minutes) was conducted based on a stratified, random sampling strategy. The address base was typically stratified using GIS (Geographic information system) data, based on fixed distances to the major traffic sources (railway, highway, main road), leaving a common "background area" outside major traffic activities and an area with exposure to more than one traffic source ("mixed traffic area"). From these five areas, households were randomly selected and replaced in case of non-participation. Entry selection criteria were age range, sufficient hearing and language proficiency and residency of at least one year at the current address. The participation was higher in the earlier (around 60 %) and lower in the most recent surveys (around 40 %).

Noise exposure assessment
The earlier studies (Noise Village study, TRANSIT study) based the assessment of noise exposure on a short-term measurement network with a central long-term recording unit. Then, the individual noise exposure assignment was done in 5 dBA classes based on these measurements and local correction by noise expert judgments for each home (Lercher et al 1995). No distinction was made between the contributing sources. In the Noise Village study this was a main road and a highway with toll station. In the TRANSIT study in two of the five communities also rail exposure was of equal importance.

In the lower Inn valley EHIA-studies for the “Brenner Eisenbahn Gesellschaft” (BEG studies: UIT-1, UIT-2) noise exposure (dBA, Ldn) was assessed by modeling (utilizing “Soundplan™ software) and a calibration by measurements from 31 sites according to Austrian guidelines (OAL Nr 28+30, ONORM S 5011). Based on both data sources approximate day-night levels (Ldn) were calculated for each respondent and noise source to facilitate comparison with typical dose-response data. Exposure and survey data were then linked via GIS.

In the latest study (ALPNAP study) railway noise emission was extracted from a typical day of noise immission measurements at close distance to the source. For highway traffic the yearly average load (light and heavy vehicles) was combined with an average diurnal traffic pattern. For main roads available traffic frequency data were supplemented with additional traffic counting. Noise emission by road traffic was calculated with the help of the Harmonoise source model (Jonasson 2007). In addition, micro-simulations of the traffic flow were conducted with Paramics (Quadstone®, www.paramics-online.com) to obtain optimal individual vehicle characteristics (speed and acceleration). Within the ALPNAP study for the first time two noise calculation procedures were implemented. “Bass3”, the propagation model developed by INTEC uses a three-dimensional object precise beam tracer gradually becoming a stochastic ray tracer at larger distance from the source to determine possible propagation paths. Sound propagation phenomena are included in an ISO9613-2 comparable way. The model includes up to four reflections and two sideway diffractions (de
Greve et al., 2005, de Greve et al., 2007). "Mithra-Sig" is the implementation of the French NMPB- Routes-96 procedure by the Centre Scientifique et Technique du Bâtiment, Lyon (CSTB), of the current interim engineering methods recommended by the Environmental Noise Directive END. It uses 2.5 dimensional tracing for visibility check. An extensive noise monitoring campaign was available to check the validity of these simulations. At 38 locations sound levels were recorded for over one week during winter (October to January) and during summer (June to August). In addition, the predicted sound pressure levels resulting from parabolic equation (PE)-modeling have been evaluated against these long-term measurements (van Renterghem et al., 2007). Indicators of day, evening, night exposure and $L_{den}$ were calculated for each source and the total exposure at several points on the building facade of the survey participants. In the present analyses, $L_{den}$ at the façade most exposed was utilized.

**Air pollution exposure assessment**

In the BEG-studies exposure by air pollution was assessed by a Swiss expert group (OEKOSCIENCE AG. Quellenstrasse 31, CH-8005 Zürich) with long-term experience to monitor and calibrate air pollution exposure in alpine areas with special consideration of meteorological conditions. An adapted Gaussian propagation modeling procedure was used. In the ALPNAP study annual means for NOx, NO2 and PM10 were calculated for an area 27 km (W-E) × 23 km (N-S) east of Innsbruck). For these air quality assessment about 300 flow fields were calculated with the meteorological model GRAMM (Graz Mesoscale Model, Almbauer et al. 2000; Öttl et al. 2005) for each domain. The model system uses special algorithms to account for low wind or calm conditions (Öttl et al. 2001, Öttl et al. 2005). Traffic emissions were modeled using the network emission model NEMO (Rexeis & Hausberger 2005, Rexeis & Hausberger 2009). For each flow field a dispersion simulation with the Lagrangian particle model GRAL (Öttl et al. 2003a & 2003b; Öttl et al. 2007) was calculated on horizontal resolutions of $10 \times 10m^2$ and in the vertical on 2m resolution. The model system uses special algorithms to account for low wind or calm conditions (Öttl et al.
2001; Öttl et al. 2005). Each run was weighted due to its meteorological classification and frequency. Thereafter, annual, summer and winter means were calculated by post processing and weighting the numerous dispersion calculations.

Within the ALPNAP study the simulation results were compared with 7 air quality stations located in the Inn Valley. The background values within this study were height corrected according to Seinfeld & Pandis (1997). Calculated NO2 and PM10 values for each of the participant's home were assigned by GIS.

**Questionnaire information**

The questionnaire covered socio-demographic data, housing, satisfaction with the environment, general noise annoyance, attitudes toward transportation, interference of activities, coping with noise, occupational exposures, lifestyle, reported sensitivities, health status, prevalent diseases and intake of medications. The telephone interview took about 15-20 minutes to complete. Education was measured in 5 grades (basic, skilled labour, vocational school, A-level, University degree). The last two grades were combined in the category "higher education". Noise sensitivity was asked with a 5-point Likert-type question. "High sensitivity" was defined by the two upper points on the scale (4 and 5). Health status was judged on a standard 5-grade scale (1 to 5). The three poorest grades were combined as "less than good" in the analysis. Active and emotional coping was assessed by a sum score based on 13 items (Botteldooren & Lercher, 2004). The area characteristic (urban, suburban and rural) was defined by residential pattern and community size.

**Statistical analysis**

The statistical analyses were carried out with "R" version 2.10.1 (R Development Core Team, 2009). Exposure-effect curves were calculated with extended logistic or ordinary least square regression methods using restricted cubic spline functions to accommodate for non-linear components in the fit if appropriate (Harrell, 2001). In the results section the p-values are reported for both the linear ("lin") and non-linear ("nlin") estimates. The non-parametric
regression estimate and its 95% confidence intervals (CI) are based on smoothing the binary or continuous responses – in the case of binary response taking the logit transformation of the smoothed estimates - using the contributed R packages "Design" and "Hmisc" (Harrell 2009). The criteria for the statistical consideration of interactions were relaxed since departure from additivity may be of relevance in a public health context when involved exposures and outcomes are prevalent (Greenland & Rothman 1998). It has also been demonstrated that selected studies can profit in terms of power by raising the Type I error rate from 5% to 20% to detect interactions that would otherwise remain uncovered (Marshall 2007). Selvin (1996) has advocated a Type I error rate of 20%. This error rate was applied to report relevant effect modification. Table 1 shows the major characteristics of the different studies.

Results

Exposure-response relationship without consideration of effect modification
Statistically significant straight noise-effect relationships with basic adjustment of relevant confounders (no interactions) were observed only in selected analyses with cardiovascular endpoints. In most analyses the noise-effect relation was statistically significant only in subgroups or with a predefined combination of susceptibility factors (mainly gender, age, family history of disease, behavioral risk factors). To illustrate this point firstly only the exposure response relations of all studies are described which result from regression models with adjustment for standard factors without IA-terms. Note: The graphs show predicted probabilities based on modeled – not observed data.

In both, the Noise Village study and the TRANSIT study no relevant relationship (main effect =ME) between noise and systolic blood pressure (SBP) could be observed (Figure 1) The UIT-1 study showed a slight linear relationship of hypertension with sound level mainly in the
older group (Figure 2). The UIT-2 study exhibited a relationship of SBP with noise only in men at age 60 yrs. In the ALPNAP study in both hypertension and angina models without interaction terms a slight curve leveling off is visible around 60 dBA,Lden (Figure 3). Only in the UIT-1 study (basic hypertension model) the sound level increase between 50 and 60 dBA,Lden was significant (OR = 1.38, CI = 1.03-1.86). Furthermore, distance to the main road was a significant factor (p= 0.007). The companion models considering interactions are described below under the specific moderation heading. Interactions (IA) that were not significant in classical statistical terms were labeled as relevant effect modification. In some studies we also describe the relationship with distance to a relevant source. Note - the meaning of the air pollution models did not change when interaction terms were included.

Exposure-effect relationship with effect modification
a) Noise annoyance
It has been argued that subjective reports of actual perceived exposure may be a better exposure indicator than noise itself. Due to the established noise-stress-CVD hypothesis of action it would also seem reasonable to find noise-CVD associations particularly among those who showed a particular disturbance or interference by noise either during day (impairment of concentration or performance) or during nighttime (impairment of sleep). Only a few studies have tested these hypotheses (Babisch et al. 1995, Selander et al. 2009). Overall, our data did not reveal any significant support to the simple hypothesis that higher noise annoyance is associated with a higher cardiovascular disease outcome. To the contrary, from our early work on in the Noise Village study we consistently observed the opposite in our SBP or hypertension relationships with traffic noise. Reporting higher annoyance (very much versus not at all) was significantly linked with lower SBP (-5.83, CI = - 8.99 to -2.68) mmHg, adjusting age, sex, bmi, education, cholesterol, family history, window behavior) in the TRANSIT study (Lercher et al. 1993). Likewise in the Noise Village study, the prevalence of hypertension was higher (Figure 4) in those reporting less interference by noise in their daily life (IA noise*interference p=0.06).
We explained this finding - which was unexpected at a first glance - with the much higher adaptive efforts that higher annoyed subjects invested to reduce noise exposure compared with less annoyed subjects (Lercher et al. 1996a). This supports a protective effect of certain active behavioral coping strategies – induced by higher annoyance. In the later studies, however, these associations of both coping activities and annoyance with blood pressure were weaker or no longer statistically significant. It remains to speculate whether the health gains of active coping fade away over time when the troubling noise exposure situation persists. Alternatively, it may be that annoyance reporting habits changed over time or coping became more common. Thus, the power to detect health gains of protective behavior diminished over time.

b) Bedroom location

In the Tyrol studies we did not consistently observe improved exposure effect relationships by either introducing bedroom location or an indicator of sleep disturbance as independent factors into the regression models. However, some models did improve. E.g. participants with bedrooms facing towards a quiet yard (Figure 5) did show a clear trend towards a reduction in hypertension diagnoses in the ALPNAP-study ($OR=0.78$, $CI = 0.59-1.05$). In the UIT-2 study a relevant interaction (IA) with bedroom location ($IA: p=0.18$, $ME_{bedroom}: OR=2.01(1.09, 3.78)$) was observed when the distance to the main road was considered as a additional source parameter ($ME_{distance}: p=0.02$) in a non-significant rail noise model. The interaction of bedroom location in the highway model was similar but statistically not relevant ($IA: p=0.31$) and also the single main effect (ME) of bedroom location was less precise ($ME_{bedroom}: OR=1.77$, $CI = 0.72, 4.39$), $ME_{distance}: p=0.08$, Figure 6). In addition, the presence of night disturbance by rail did exhibit a further main effect in both the rail ($OR= 2.24$, $CI = 1.21-4.17$) and the highway model ($OR=1.98$, $CI = 1.08-3.62$).
c) Length of exposure

Duration of living at the current home may be another candidate variable representing a more homogeneous group with longer latency times for potential health effects. Bluhm et al. (2007) observed a stronger association between noise and hypertension in subjects with a longer period of residence (>10 yrs). We found no significant effect of longer duration on the overall noise-disease association in the ALPNAP-study in the regression model. Duration of living is, however, tightly associated with older age (IA: p=0.12) and house type (≥ 20 yrs in single homes 52% versus 21% in apartment blocks). Thus it is difficult to disentangle, especially when a large proportion of the sample has such a record of longer living (66 %) or single housing (56 %). However, when an extreme comparison was made with a strong family history of hypertension in the model adjustments, duration of living for ≥30 years at the present address was significantly associated with hypertension (OR=1.68, CI = 1.07-2.66)) against <8 years of living. The comparison of living for ≥30 years versus < 30 years in the UIT-1 study revealed quite clear results supporting that length of exposure was an important variable (Figure 7). In these analyses distance to the road was considered as exposure and heart problems as an outcome. When distance was replaced by the overall sound level, duration of living at the current home was significant (p= 0.04). However no sign of effect modification by noise level was evident.

d) Age

**Hypertension:** The re-analyses of the Tyrol health studies revealed substantial evidence for effect modification by age and gender on the relationship between noise and indicators of hypertension. Already in the small noise village study we observed supporting evidence for a noise effect only in those at a higher age compared with participants at a lower age with both dichotomous and continuous blood pressure outcomes. The interaction with noise level was statistically significant (IA: p=0.01 lin, p=0.02 nonlin). In the TRANSIT study, the age-noise level interaction on treated hypertension was significant only in men (IAtreat: p=0.03) (Figure 8). In the UIT-1 study (IA: p=0.02 lin, p=0.03 nonlin) and the ALPNAP-study (IAdiagnosis:...
p=0.003 lin, p=0.005 nonlin, $I_{A_{treat}}$: p=0.013 lin, p=0.006 nonlin) also the overall effect modification by age was highly significant with respect to any measurement of hypertension.

**Heart disease:** In the Transit-study we found a non-significant but relevant age-noise level interaction on the prevalence of angina pectoris indicating that the relationship with noise showed up only in elderly people at higher noise levels (Figure 9). This view was also supported in the results of the UIT-1 study when distance to the road was considered as exposure ($I_A$: p=0.26 lin). The analyses from the ALPNAP-study did not support these earlier findings. Rather, it was found that age was less important when other risk factors (e.g. hypertension) were considered that are accompanied with older age.

e) Gender

**Blood pressure and hypertension:** In the Noise Village study the effect of the interaction of noise with age on systolic blood pressure was more pronounced in men (Figure 10). In the TRANSIT study this kind of effect modification could be replicated with respect to the prevalence of hypertension (p=0.22lin). Also with a separate gender sub-regression the pattern was confirmed ($I_{A_{age}}$: men: p=0.06, women: n.s). Likewise, a separate age sub-regression (three categories) on continuous blood pressure mimicked this pattern without reaching significance ($I_{A_{sex-age}}$: p=0.33). Also in the UIT-2 study interaction patterns due to gender ($I_{A_{sex}}$: p = 0.18lin, 0.398nonlin) occurred when adjustment for known hypertension was included. In the ALPNAP-study the effect modification due to age was stronger - the noise-sex interaction, however, was of minor importance. In summary, we observed a stronger not always significant effect of the noise level in men compared to women. In addition effect modification due to age was present and enhanced often the overall effect.

**Heart disease:** Neither in the Transit nor the ALPNAP study we found an indication of a relevant effect modification due to gender on the relationship between the noise level and...
heart disease (IA: p=0.6). In both studies the prevalence of angina pectoris was slightly higher among men across noise levels.

f) Education

Education was associated with both dichotomous and continuous blood pressure outcomes in the Noise Village study. The interaction of education with the noise level was evident in both sexes – but only relevant in the older age group (>45 yrs) (IA: p=0.20). The power (N=174) was limited to test interactions. In the Transit and the UIT-1 studies education was not significant overall due to social differences between the studied communities. In the UIT-2 study there was a significant main effect of education on systolic blood pressure (lower SBP in subjects with higher education compared to lower education: mean adjusted difference: -3.90, CI = -7.79 to -0.01 mmHg) – but no relevant signs of interaction with noise level were found. In the ALPNAP study, this trend was reversed – but there hypertension diagnosis or treatment was the outcome. This may be due to differences in the detection and treatment of hypertension in general practice.

g) Family history

The TRANSIT study revealed some interaction of family history with noise level on SBP (IA: p=0.11) in men, also in the presence of an additional effect modification by age (IA: p=0.06 lin p=0.14 nonlin). A similar non-significant result was obtained in the UIT 2 study with respect to systolic blood pressure. In fact the effect modification due to family history was caused by the interaction of sex with noise level. In the ALPNAP study we could test for possible interactions of family history with noise level by a more detailed question (no=0, one parent=1, two parents=2). Two noise propagation models were tested. With the MITHRA propagation model the interaction with noise level was relevantly moderated by the degree of family history (IA: p=0.11 lin) with an additional non-linear component (Figure 11). Sex did not modify the associations any further but age did to a highly significant extent (IA: p=0.013 lin, p=0.006 nlin). Similar results were obtained when the ISO-implementation by INTEC was
used for noise propagation. The effect modification due to family history (IA: p=0.16 lin) was obvious but not accompanied by a relevant effect modification due to age. Further strong indications of interaction with family history were found with respect to other CV-outcomes when keeping age and sex constant or when including further risk factors.

h) Hypertension

In the TRANSIT study (Figure 12) we observed a highly significant impact of known hypertension on the prevalence of angina pectoris (p=<.0001). However, no relevant interaction with noise level was evident. Similar results were obtained in the ALPNAP study (Heimann et al. 2007) with respect to angina pectoris. Subjects with preexisting hypertension did exhibit a steeper increase in prevalence between noise levels of 50 and 60 dBA (OR=2.23, CI = 1.10-4.52) but no statistically relevant effect modification of hypertension on the relationship between noise and angina pectoris was observed.

i) Depression

In the TRANSIT study a borderline significant association between the prevalence of depression and the prevalence of angina pectoris was found. No interaction with noise level was present. While there was no association with blood pressure or hypertension in the ALPNAP study we also found a significant difference between people who suffered from depression and the probability of an angina pectoris diagnosis (OR=2.06, CI = 1.08 - 3.94). There was, likewise, no relevant interaction with the noise level.

j) Air pollution:

**Hypertension.** Support comes neither from the BEG studies nor from the ALPNAP study (not shown) for a significant positive effect of NO₂ or PM₁₀ on blood pressure or hypertension. Rather opposite trends were observed. In addition no relevant signs of interaction could be found.
**Angina pectoris:** Like in the case of hypertension air pollution did also not affect the noise angina pectoris relation in the ALPNAP study. The observed inverse association is fully determined by the noise level.

k) Health status

From a prospective study Babisch et al., (2003) reported a stronger relation between annoyance and IHD in middle aged men with no prior disease at entry point. A similar effect modification ($p=0.16$) was observed in the presence of a strong noise*age interaction ($p=0.02$) in the UIT-1 study with respect to hypertension (Figure 13). Only in those subjects with good or very good health status a significant exposure effect relation was observed regarding hypertension diagnosis or treatment. Also with respect to three health status categories in the ALPNAP study only for those with very good health status a relation with noise level was found in men (IA: $p=0.18$) but not in women. The ALPNAP study could not confirm such an effect modification of health status on the association between noise level and angina pectoris – although health status was a relevant predictor of disease when persons with excellent versus poor health status were compared (OR=0.50, CI = 0.24-1.01).

I) Combination of risk factors

**Hypertension:** Using the final model (adjusted for the other factors) of the ALPNAP study simulations were carried out to demonstrate the relevant effect modification of the most important risk factors (age, family history, health status) on the relationship between the noise level and hypertension when the factors are varied in terms of extreme group comparisons (Figure 14).

**Heart disease:** Likewise we calculated the effect of two significant risk factors in the ALPNAP-study, namely, hypertension and depression on the probability of angina pectoris due to the noise exposure (highway) for subjects aged 40 and 60 yrs, respectively (Figure 15). A strong effect modifying impact of the prevalence of these two diseases on the
association between the noise level and the probability of developing angina pectoris is evident. However, the wide confidence intervals indicate the limitation when combinations with small subgroups are investigated.

m) Noise sensitivity

**Hypertension:** With respect to hypertension in none of the studies carried out in Tyrol positive relations with noise sensitivity were observed. To the contrary, consistently noise sensitivity was non-significantly or even inversely associated with blood pressure readings or self reported hypertension or treatment. On the other hand weather sensitivity (a general indicator of vegetative reactions) was a stronger predictor (p=0.01) in the UIT-1 study – but also no relevant interaction with noise level was evident (Figure 16). The finding of higher weather sensitivity related to hypertension could not be fully replicated with systolic blood pressure as an outcome in the UIT-2 study. Instead, an underlying relevant sex-noise interaction (p=0.17) was evident, showing a noise effect only in men. Noise sensitivity was again not a relevant parameter. However, vibration sensitivity also exhibited an inverse relation with blood pressure - but there was no effect modification of vibration sensitivity on the relationship between the noise level and blood pressure in the UIT-2 study. The smaller sample size in this study (N=514) was the reason why only borderline significance was achieved (weather: p=0.09, vibration: p=0.05).

**Heart disease:** Different results were obtained for heart disease. In the TRANSIT study, angina pectoris showed a non-significant association with noise sensitivity (p=0.11) but there was neither any interaction with sex (IA: p=0.98) nor with the noise level (IA: p=0.72). In the UIT-1 study noise sensitivity was not a significant predictor either. Instead weather sensitivity exhibited a strong effect modifying impact (IA: p=0.11) on the relationship between distance to the highway and the prevalence of angina pectoris (Figure 17). In the ALPNAP study a different pattern was found (Figure 18). There a strong interaction of sensitivity with sex (IA: p=0.01) was found on the non-linear relationship between the sound level (highway) and the
prevalence of angina pectoris (IA: p=0.16). The sex-sensitivity-interaction showed a deviating pattern: although sensitive males showed consistently the highest disease rates with varying noise level, sensitive females exhibited the lowest rates of angina pectoris. Note – the confidence intervals are wide.

**Discussion**

*Exposure modifiers*

The results from literature and the results of our studies over time suggest that there are important modifiers that may partly be responsible for the large variations found in the noise health effects research. Bluhm et al. (2007) suggested exposure misclassification as a main culprit. Specifically, their findings of stronger associations in persons with a longer length of exposure (years of residence) at the same address, having triple-glazed windows, bedroom windows not directly facing a road or living in single houses do support this suggestion of potential over- and underestimation of true exposure. Caution is warranted, since the effect modification due to the length of exposure may be actually caused by older age which is typically confounded with it.

On the other hand a longer duration of time spent living at the same address may also indicate a certain time of exposure required to exert an effect (Bluhm et al. 2007). Therefore, studies with an insufficient proportion of people living longer at the same address (>10 yrs) may lack the power to detect noise effects. In the Bluhm et al. study this proportion was high (44.5%). In the ALPNAP-study 50 % lived at least 16 yrs and 25% at least 30 yrs at the same address. From meta-analysis of annoyance studies (Fields 1993) we know that confounding with age is a serious problem. In the Bluhm et al. study the age range went up to 80 yrs, which is an unusually high age range with inclusion of a large proportion of elderly people very likely to have lived longer at the same address.
We have seen protective effects (closing windows during night) as an additional modifier of exposure over and above the fact of having tightly fitted windows (Lercher 1996). Tightly fitted windows or closing windows during daytime alone did not show up as significant variables.

Selander et al. (2009) found an elevated association between road traffic noise and myocardial infarction in participants reporting noise annoyance mostly in their bedrooms. These findings can be interpreted in different causal pathway directions. First, bedroom exposure is a better exposure indicator in general by reducing exposure misclassification, since most participants (nightshift workers as an exception) are actually in bed while daytime exposure can vary substantially due to activity pattern and work exposure. Second, bedroom exposure is a causally relevant exposure since sleep is affected and impaired sleep is a known risk factor for myocardial infarction in men and women (Schwartz et al., 1999; Greenland et al.; 2003, Leineweber et al., 2003; Meisinger et al 2007).

Our studies support bedroom location or night disturbance as a potential moderator especially when additional noise sources contribute to the overall noise exposure. The effect seems, however, to depend also on the kind of source combination (rail-highway-main road). Therefore, bedroom location should be considered in the analysis design - but high variation is possible due to the actual feature of the specific source combinations.

Effect modification: Socio-demographic factors

a) Gender and age

Several studies observed differences in the effect of noise on cardiovascular outcomes by gender (Herbold et al., 1989; Belojevic et al., 2002; Babisch et al 2005; Willich et al., 2005; Bjork et al., 2006; Bluhm et al., 2007; Jarup et al., 2008; Barregard et al., 2009). Unfortunately, the found associations are not uniform – thus casting doubt on their reliability and validity. Similar to what has been argued in air pollution studies - that effects only found
in women may be related to their longer duration of exposure at daytime – thus asserting this issue is related to exposure assessment rather than implying a different vulnerability.

However, there is evidence of a gender difference of psycho-physiological reactions towards stress. Generally, males are more susceptible to cardiovascular disease (Stoney et al. 1987) and women show greater resistance to stress between puberty and menopause (Kajantie & Phillips 2006; Kajantie 2008).

In accordance with these findings the Tyrol studies do not provide support for a stronger effect in women. Instead, more often men did exhibit stronger effects in interactions with noise exposure and older age. When no effect modification by gender was observed, disparities in health care may be at work, like in hypertension treatment or angina pectoris diagnosis (Vaccarino 2006; Johnstone et al., 2007; Gu et al., 2008; Bittner 2008; Hemingway et al., 2008). The extra-large studies of de Kluizenaar et al. 2007 and Bodin et al. 2009 used their power to test whether certain age ranges do exhibit stronger associations between noise and cardiovascular outcomes. The findings of these studies suggested the middle age ranges (40-60 yrs) to be associated with hypertension but not to other ages. Because the findings reported so far concerned middle-aged people the explanations were targeted to explain this finding. In view of the results from the Tyrol studies, where the elderly consistently were more affected, other explanations are necessary and equally plausible. Since noise is viewed as subtle but a chronic stressor, longer latency periods may be necessary to observe effects. In a recent, large semi-ecological medication study in the same study area we reported most significant findings for the age group above seventy years (Rüdisser et al., 2008).

The observed moderating effects of age or gender should be reviewed with caution, especially, when only category specific effects are reported and no exposure-effect relation is presented. Opposite to the argument of Bodin et al. (2009) it can be stated that cohort analyses have shown that some classical cardiovascular risk factors loose their importance
to predict cardiovascular mortality due to the survivor effect and age itself gains in importance (Grundy et al., 2001). It may therefore be that stress related risks gain importance the longer they can exhibit their subtle chronic effect. Eventually, the support for a positive association between noise annoyance and cardiovascular health is weak. At least in the Tyrol studies more often the opposite effect was observed.

b) Education

The results show that when measured blood pressure was considered, lower education was consistently associated with higher blood pressure and higher prevalence of hypertension based on standard cut-off points. When reported hypertension was used, persons with a higher education exhibited a higher prevalence. This suggests a differential effect of health care on education. However, no significant effect modification with noise level was observed in any of the studies.

Effect modification: vulnerability factors

a) Family history

Family history of hypertension is an established major risk factor for the development of hypertension (Stamler et al., 1979; Burke et al., 1998; Wang et al., 2008). In all studies (not available in UIT-1) family history was a significant contributor to either continuous or dichotomized blood pressure outcomes or treatment. Significant or public health relevant effect modification was observed with age and also with noise level. This supports the idea of higher vulnerability of people with a family history to noise exposure with a certain latency time. Since more than one third of the adult population in the ALPNAP study (41%) showed some degree of family history (one parent) effect modification should be evaluated in all noise - hypertension studies.

b) Hypertension

High blood pressure is a proven risk factor for cardiovascular diseases (Yusuf et al., 2001).
Selander et al. (2009) found a stronger association between road traffic noise and myocardial infarction in those with hypertension. Earlier or recent hypertension was also a significant contributor to angina pectoris in the ALPNAP and the TERW-89 study. The moderation with noise level did not become significant.

c) Depression
Depression is a known risk marker for cardiovascular diseases (Yusuf et al., 2001). Most studies have found depression to be significantly associated with mortality and/or cardiac morbidity—although the mechanisms underlying this relationship remain unclear (Suls & Bunde 2005; Carney et al., 2005). Since dysregulation of the autonomic nervous system is a plausible pathway to disease (Carney et al., 2002) chronic exposure to noise is a possible candidate for effect modification. Both in the TRANSIT and the ALPNAP study depressive symptoms or depression diagnosis were significant contributors in an angina pectoris regression model. Although some interaction between the noise level and the state of depression was visible in the figures the power was too low to gain significance. However, presence of both depression and hypertension showed a higher prevalence of angina at higher noise levels. We are not aware of other studies having evaluated depression as possible moderator of the noise angina relationship.

d) Health status
Health status is a general and reliable predictor of future morbidity and mortality (Idler et al., 1997; Lekander et al., 2004; Chen et al., 2007; Singh-Mantoux et al., 2007). In all studies (not available in Noise village and TERW-89) health status made a significant contribution to the cardiovascular outcomes studied. Consistently, persons with a poor health status showed higher starting levels of morbidity but typically also stronger slopes in the exposure response analysis. However, due to the generally lower disease levels sometimes only people with an excellent or good health status exhibited a significant increase of either hypertension or angina pectoris with increasing noise level in a dose response fashion. Therefore, effect
modification was not always significant at classical error rates \((p < 0.05)\) but still relevant in terms of potential public health significance \((p < 0.20)\). We are only aware of one study (Babisch et al., 2003) having applied a similar approach by using disease status as possible moderator of the noise exposure disease relationship.

e) Noise sensitivity

Noise sensitivity is known be associated with higher symptom rates and medication consumption (Stansfeld 1992; Lercher et al., 1996a) and is also a predictor of noise annoyance. Recently, work based on data from the Finnish Twin Cohort study reported an association of noise sensitivity with hypertension after adjustment for noise exposure and other factors in a multivariate model (Heinonen-Guzejev et al., 2004). In a further study a relation between self-reported noise exposure and cardiovascular mortality was observed in noise sensitive women – but not among men (Heinonen-Guzejev et al., 2007). On the other hand, we observed consistently a negative relationship between noise sensitivity and hypertension as a health endpoint. This is fully in contrast to the results of the Finnish studies (overview in Heinonen 2009) showing several associations of noise sensitivity with hypertension and heart disease (morbidity and mortality) in noise exposed female subjects. Overall, there was a non-significant trend in noise sensitive subjects to show a higher prevalence of angina pectoris at higher noise exposure – but due to a significant interaction \((sex*sensitivity, p=0.01)\) this was not true in women. Thus there is no good evidence for a relation of noise sensitivity in women from this study. The power to detect weaker associations was low in the ALPNAP study. But also the pooled Caerphilly and Speedwell analyses (only men) did not observe a significant association \((OR=0.9)\) with noise sensitivity in a larger sample (Babisch et al., 1999). Note, the Finnish studies differ methodologically since both noise exposure and noise sensitivity was obtained subjectively. Such a procedure is vulnerable to the known subjective bias from stress research (Kasl 1984, Lazarus 1993).
**Measures of hypertension**

In the noise literature the clear diagnosis of hypertension (from medical sources or patient remembered doctor diagnoses) is used in the analyses. Women are expected to show a lower prevalence of hypertension till the end of the fifth decade (Hajjar & Kotchen 2003). Since medication use or type was not confirmed in our studies misclassification may be introduced by missing other medications that may lower blood pressure. Furthermore, true awareness and control rates cannot be determined with the kind of data available. The literature reports awareness rate around 70%. Treatment and control rates are found around 60% and 30%, respectively, with lower rates in the elderly (Hajjar & Kotchen 2003; Cutler et al., 2008). The experience with other surrogate measures of hypertension in our studies showed following characteristics:

- Blood pressure readings were less often significantly related to noise levels
- Dichotomizing blood pressure readings at higher cut-off levels (160/95mmHg) were more likely significantly associated with noise exposure
- Treated hypertension was not a better indicator than doctor diagnosis or known hypertension.
- When using treated hypertension we did not observe a gender difference in prevalence. This gender difference was consistently present using remembered diagnosis or personal readings of blood pressure – indicating a lower prevalence of treatment among men than women. These findings are confirmed by large population surveys – but it seems that the male population is catching up (Cutler et al., 2008).

**Time effects and latency to the effect**

Since these are series of cross-sectional studies over time it is difficult to comment on time factors. However, there are some findings which contribute to the current scarce knowledge:

1. In the studies where we had two timeframes in the retrospective question available (e.g. “hypertension diagnosis ever” and “hypertension diagnosis during past 12 months”) the
precise time framing “past 12 months” did exhibit a stronger relation with noise than the more
loose time framing “ever”. This finding may be explained by the concurrent measurement of
exposure and outcome and thus reflect higher precision in both. Alternatively, it could also
give hints for time windows where a certain proportion of the study population may exhibit
noise related effects.

2. Consistently, we found persons at a higher age (>60 yrs) showed a firmer relation with
noise than at a lower age (~ 40 yrs). This relation was typically enhanced in the presence of
an additional risk factor for the outcome under investigation (especially family history of
hypertension). These findings suggest longer latency times and the need of other risk factors
to be present in order to develop noise related effects. The findings from our semi-ecological
study, where significant relations with noise (antihypertensive prescriptions) were only found
at an older age (>70 yrs), indirectly support longer latency times in general (Rüdisser et al.
2008).

3. Duration of living may not be a good approximation of the length of exposure since it was
strongly associated with age, housing factors and education in our studies. From the social
science literature it is long known and recently confirmed that people moving around less are
better off in the light of various health outcomes and health related behaviour (Metzner et al
1982; Larson et al. 2005; Norman et al. 2005; Jelleyman & Spencer 2008). At least in our
studies we observed no significant difference in subset analyses with 10, 20 or 30 years of
living at the same address. Although utilizing length of residence as a continuous variable
with adjustments of age, housing, education and health status did show a weak increase in
the odds for hypertension development when the contrast in duration was stretched (<8 yrs
versus >30 yrs). Although, it is not clear whether this indeed represents an independent
finding – it supports also longer latency times similar to the conclusions from the Speedwell
and Caerphilly studies (>15 yrs).
Both noise and air pollution is often emitted by the same source, namely motorized traffic and depending on propagation conditions a wide range of correlations is reported (Allen et al., 2009). Such conditions open the possibility of confounding and make it difficult to disentangle associated effects statistically (Schwela et al., 2005). A large number of studies have shown stable associations of ambient air pollution with morbidity and mortality of cardio-pulmonary disease (Pope & Dockery 2006, Krewski & Rainham 2007, Brook 2008). A smaller number of studies have reported associations with blood pressure or hypertension (Ibald-Mulli et al., 2001; Zanobetti et al., 2004). Since noise exposure is also associated with CHD and hypertension (Babisch 2008) and only a few recent studies have actually considered both pollutants in the regression models (Heiman et al., 2007; de Kluizenaar 2007; Beelen et al., 2008; Selander et al., 2009) it remains an open question what contribution is made by which pollutant to which health outcome.

In both the UIT studies and the ALPNAP study high quality air and noise pollution propagation data were available for individual assignment. In none of the investigated health endpoints (angina, blood pressure/hypertension) a relevant or consistent relation with the studied range of air pollutants (NO$_2$, PM$_{10}$) nor relevant moderation could be established. The large population based Oslo Health Study (N=18,770) was also unable to find a relation between indicators of air pollution exposure and blood pressure (Madsen & Nafstad 2006). Since we had two noise assignments options in the ALPNAP study of which the ISO-assignments showed very low correlations with NO$_2$ (r=0.12) and PM$_{10}$ (r=0.09) confounding is highly unlikely to be of importance in this study. Although the MITHRA-assignments showed higher correlations (NO$_2$: r=0.48 and PM$_{10}$: r=0.39) the statistical importance of both the air pollutants and the noise variables did not change. In the BEG studies the highway noise to air correlations were stronger (NO$_2$: r=0.63 and PM$_{10}$: r=0.61).
Methodological issues

a) Interaction assessment and non-linearity

The investigation of moderation of the noise health relationship by public health relevant factors is a necessary requirement for the better understanding of the processes that determine the person-environment-health relationship (Lercher 1996b, Evans & Lepore 1997, Evans 2001, Bodin et al., 2009). The single reporting of average risk effects or associations from an entire population can often conceal the substantial variation that may occur in important subgroups (the elderly, women, persons with positive family history of cardiovascular diseases including high blood pressure). This deviation from average risk can be even more pronounced when risk combinations are considered (see Figure 53). If significant interactions are present the meaning of main effects becomes questionable. Unfortunately, most studies do not have the power to evaluate effect modification and interaction tests in general lack power (Greenland 1993, Marshall 2007). The relaxation of the significance criteria can sometimes help (Selvin 1994, Marshall 2007). The use of p-values as sole criterion is discouraged (Matthews & Altman 1996). However, caution is needed since additional mediation or residual confounding may distort the results or make it hard to interpret (Pearce & Greenland 2004). Therefore, only biological plausible effect modification (based on prior knowledge) should be tested and a step by step procedure is advised - followed by detailed sensitivity analyses to safeguard the conclusions. Eventually, there is a strong need to examine non-linear components in the exposure-response analyses. Substantial over- and underestimations may result without consideration.

b) Noise propagation modeling

Typically, engineering methods and the resulting noise maps are validated against long-term noise measurements in “simple” open area propagation conditions and not in complex residential settings where most people actually live. The availability of having two (in the case of highway noise three) noise propagation methods in the ALPNAP study opened the unique opportunity to evaluate the modeling in the framework of the actual noise – health
relations. Thus the effects of noise modeling techniques on the estimation of noise associated health impacts could be directly assessed. While sometimes only marginal differences were noted even with complex effect modification, in other cases (e.g. angina pectoris) only with one method a significant exposure-response relationship was established but not with the second method. This leaves behind a substantial amount of uncertainty. Therefore, a move from mere exposure modeling to exposure effect modeling is required to minimize bias in public health risk assessment of the effects of sound on humans.

Conclusions

Because noise is not a strong risk factor per se the specific context of the exposure, health predispositions and the adaptability to this person-environment configuration determines whether effects occur. Specifically, the coping opportunities are of importance. If active coping (closing windows, bedroom on quiet site) is not feasible noise persists as a chronic stressor and with advancing age the effects may surface. Since the effects of age and gender observed in noise effects research can only be prevented by reducing the intensity and the duration of exposure overall - residential areas should be considered as sensitive areas and noise should not exceed 55 dBA. This is in accordance with the results of the most recent studies (Bluhm et al. 2007, Barregard et al. 2009, Selander et al. 2009). Finally, from the reported studies we could not find support for a relevant role of air pollution. Both neither with diagnoses of hypertension nor with heart disease statistical significance did come in reach and no signs for a relevant moderation of the noise health relation by air pollution could be observed in the Tyrol studies.

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<table>
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<th>Study</th>
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Figure 1: Systolic blood pressure: Exposure-response for highway sound exposure by age and sex. Adjusted for bmi, education, smoking, alcohol, sleep problems, window behaviour, work satisfaction [Noise Village study, 1984]
Figure 2: Hypertension diagnosis/treatment: Exposure-response for overall sound exposure (road & rail traffic) by age and sex. Adjusted for health status, weather and noise sensitivity, work noise and vibration, distance to highway and rail – [UIT-1 study, 1998]
Figure 3: Angina pectoris: Exposure-response for highway sound exposure by age. Adjusted for bmi, family history, known hypertension, education, health status, depression, smoking, occupation, coping, anger, PM10 - [ALPNAP study, 2006 (MITHRA)]
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Figure 9: Angina pectoris: Exposure-response for overall sound exposure (road & rail traffic) by age. Adjusted for sex, bmi, family history, cholesterol, education, health, smoking, fat intake, exercise, nightshift, community – [TRANSIT study, 1989]
Figure 10: Systolic blood pressure: Exposure-response for highway sound exposure by age and sex. Adjusted for bmi, education, occupational noise, noise annoyance, IA sound level* age, level*sex, level*annoyance, level*occ. noise – [Noise Village study, 1984]
Figure 11: Hypertension treatment: Exposure-response for highway sound exposure at age 60 yrs by family history. Adjusted for age, sex, bmi, education, health status, duration of living, house type, IA sound level*age, level*history, level*health status, age*duration of living – [ALPNAP study, 2006 (sound propagation: MITHRA)]
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Figure 15: Angina pectoris: Exposure-response for highway sound exposure at age 60 yrs with hypertension and depression by sex. Adjusted for bmi, family history, education, smoking, sensitivity, coping, anger, NO2-level, IA sound level*age, level*anger, level*hypertension, level*smoking, sex*sensitivity – [ALPNAP study, 2006 (MITHRA)]
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