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Individual Exposure to Noise and Ultrafine Particles and its Association with Heart Rate Variability

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List of abbreviations

CI	Confidence interval
dB(A)	A-weighted decibels
ECG	Electrocardiogram
EPA	Environmental Protection Agency
HF	High frequency
HR	Heart rate
HRV	Heart rate variability
KORA	Cooperative Health Research in the Region of Augsburg
L_{day}	Maximum annual A-weighted equivalent continuous sound pressure levels during the day (6 am to 6 pm)
L_{eq}	A-weighted equivalent continuous sound pressure levels
LF	Low frequency
LOD	Limit of detection
MI	Myocardial infarction
PNC	Particle number concentration
RMSSD	Root-mean square of successive differences
sd	Standard deviation
SDNN	Standard deviation of normal-to-normal intervals
UFP	Ultrafine particles
US	United States
VIF	Variance inflation factor
WHO	World Health Organisation

Specification of my contribution to the manuscripts

As an investigator of the study “Source-specific health effects of ultrafine/fine particles”, which provided the data analysed for this thesis, I developed the study documents, was part of the team that trained the study nurses and contributed to the quality assurance. In particular, I was responsible for the activity diary data. I played a significant role in the data management and in building data sets. Furthermore, I contributed to the annual progress reports and the final report of the project.

For the two manuscripts assessing noise exposure and its health effects, respectively, as the first author, I developed the specific focus of the research question, performed the statistical analyses and interpreted the results. I wrote the first complete draft of the manuscripts and finalized them based on the co-authors’ comments. For the manuscript entitled “Individual daytime noise exposure during routine activities and heart rate variability in adults: A repeated measures study” I prepared a revision based on the reviewers’ comments after discussions with my supervisors and provided point-by-point responses to the concerns raised. I submitted the manuscript entitled “Individual daytime noise exposure in different microenvironments” on February 8th 2015 and am awaiting reviewer comments.

For the other two manuscripts as a co-author, I gave relevant input on the research question and analyses of the data. I read the first draft and the revised version of the manuscripts and provided crucial comments.

Due to the different contributions to the manuscripts I will refer to “we” independent of my authorship role.

1 Summary

Cardiovascular disease is the leading cause of global mortality. Beside behavioral risk factors, environmental stressors play an important role in disease development. Epidemiological studies have shown adverse associations between chronic noise exposure and elevated blood pressure, hypertension, ischemic heart disease including myocardial infarction (MI), and mortality from MI. Moreover, particulate matter has been associated with MI, higher rates of hospitalization and mortality due to cardiac diseases. The biological mechanisms linking noise as well as air pollution to cardiovascular health are not fully understood. It is suggested that noise might influence the autonomic nervous system in terms of a stress reaction. And also air pollution, once deposited in the lung, might disturb sympathovagal balance, either directly or indirectly through inflammation and oxidative stress responses. So far, only few studies have linked personal exposures to noise and air pollution to early physiological responses.

This thesis aimed to describe the personal exposure to noise as well as particle number concentrations (PNC) as surrogate for ultrafine particles and their associations with cardiac function. For that purpose, data of a repeated measurements study conducted in Augsburg in an older population were collected. The two personal exposure analyses showed that both, personal noise levels and PNC were highly variable between and within different microenvironments and activities. Highest levels for both exposures were found in traffic environments. In the two health effects analyses, we observed immediate changes in heart rate variability (HRV) associated with increases in personal noise levels and PNC. Increases in A-weighted equivalent continuous sound pressure levels (L_{eq}) below 65 dB(A) were associated with an immediate parasympathetic withdrawal whereas increases in L_{eq} above 65 dB(A) led to concurrent increases in sympathetic activity. Results of strata analyses suggested that women were more susceptible to increases in lower noise levels as they showed stronger changes in ECG parameters. Furthermore, increases in five-minute averages of personal PNC led to rapid changes in HR and HRV. Similar associations were observed for increases in one-hour averages of stationary particles with an aerodynamic diameter below 2.5 μ m. As we observed the effects in individuals with impaired glucose tolerance or diabetes the study might partly explain the link of air pollution to diabetes exacerbation.

In conclusion, this thesis amplifies the knowledge about personal exposures to noise and PNC. As we observed adverse changes in cardiac function with personal noise exposure as well as with freshly emitted ultrafine particles and aged fine particulate matter, this thesis provides important insight into the mechanistic pathways connecting noise and air pollution to cardiovascular events.

2 Zusammenfassung

Weltweit stellen Herz-Kreislauf-Erkrankungen die häufigste Todesursache dar. Neben verhaltensbezogenen Risikofaktoren spielen Umweltstressoren eine erhebliche Rolle in der Krankheitsentwicklung. Epidemiologische Studien haben Zusammenhänge zwischen chronischer Lärmexposition und erhöhtem Blutdruck, Bluthochdruck, koronarer Herzkrankheit und Tod durch Herzinfarkt gezeigt. Darüber hinaus wurde Feinstaub mit Herzinfarkt, höheren Raten an Krankenhauseinweisungen und Mortalität aufgrund kardiovaskulärer Probleme assoziiert. Der biologische Mechanismus, der Lärm und Luftschadstoffe mit kardiovaskulären Erkrankungen verbindet, ist noch nicht gänzlich erforscht. Es wird angenommen, dass Lärm im Rahmen einer Stressreaktion das autonome Nervensystem beeinflusst. Darüber hinaus könnten Luftschadstoffe das sympathovagale Gleichgewicht stören, entweder direkt oder indirekt durch Entzündungsprozesse und oxidativen Stress. Bisher haben nur wenige Studien die persönliche Exposition gegenüber Lärm sowie Luftschadstoffen mit schnellen physiologischen Reaktionen in Beziehung gesetzt.

Diese Dissertation hatte zum Ziel, die persönliche Exposition gegenüber Lärm als auch Partikelanzahlkonzentrationen als Maß für ultrafeine Partikel zu beschreiben und deren Zusammenhang mit der Herzfunktion abzuschätzen. Dazu wurde eine Studie mit wiederholten Messungen in Augsburg mit älteren Teilnehmern durchgeführt. Die zwei Auswertungen zu persönlicher Exposition zeigten, dass beides, persönlicher Lärm als auch persönliche Partikelanzahlkonzentrationen sehr stark zwischen und innerhalb verschiedenen Umgebungen und Aktivitäten variierten. Die höchsten Werte wurden jeweils beim Aufenthalt im Verkehr gemessen. In den zwei Analysen zu den Gesundheitseffekten zeigten sich sofortige Veränderungen der Herzrate und der Herzratenvariabilität (HRV) in Zusammenhang mit persönlichem Lärm und Partikelanzahlkonzentrationen. Anstiege im Lärmlevel unter 65 dB(A) waren mit einer sofortigen verringerten parasympathischen Aktivität assoziiert, während Anstiege im Lärmlevel über 65 dB(A) direkt zu einer Steigerung der sympathischen Aktivität führten. Die Ergebnisse einer nach Geschlecht stratifizierten Analyse wiesen darauf hin, dass Frauen suszeptibler gegenüber Anstiegen in niedrigen Lärmleveln sind, da sie stärkere Veränderungen der EKG-Parameter zeigten. Bezüglich Luftschadstoffen waren Anstiege in Fünf-Minuten-Mitteln der Partikelanzahlkonzentrationen mit schnellen Veränderungen in der Herzrate und der HRV assoziiert. Ähnliche Ergebnisse zeigten sich für Anstiege in Ein-Stunden-Mitteln stationär gemessener Feinstaubwerte. Da wir diese Zusammenhänge in Personen mit gestörter Glukosetoleranz oder Diabetes beobachtet haben, erklärt die Studie möglicherweise zum Teil die Verbindung zwischen Luftschadstoffen und der Verschlechterung von Diabetes.

Diese Arbeit erweitert das Wissen über persönliche Expositionen gegenüber Lärm und ultrafeinen Partikeln. Wir konnten Assoziationen zwischen ungünstigen Veränderungen der Herzfunktion und Lärm sowie frisch emittierter ultrafeiner Partikel und gealtertem Feinstaub zeigen. Daher bietet diese Arbeit wertvolle Einsicht in die biologischen Abläufe, die Lärm und Luftschadstoffe mit kardiovaskulären Ereignissen verbinden.

3 Introduction

In 2012, around 38 million people died from noncommunicable diseases worldwide, in particular from cardiovascular diseases, cancers, diabetes and chronic lung disease¹. Beside behavioral risk factors, environmental stressors play an important role in disease development. Recently, air pollution and noise exposure were placed as the first two most dangerous environmental threats to human health in six European countries².

3.1 Cardiovascular disease and heart rate variability

Cardiovascular diseases are the leading cause of global mortality. A total of 17.5 million people died from cardiovascular diseases in 2012. Of these 7.4 million people died from ischemic heart disease and 6.7 million from stroke³.

A well-established determinant of cardiovascular health is heart rate variability (HRV). In several epidemiological studies a decreased HRV was considered as independent risk factor for adverse cardiovascular events and cardiovascular deaths⁴⁻⁷. HRV describes the difference in the time intervals between adjacent heart beats. It reflects the ability of the human body to change heart rate according to current requirements. Heart rate and HRV are mediated by the autonomic nervous system (ANS) with increased sympathetic activity and reduced parasympathetic tone leading to higher heart rate and HRV mitigation. It can easily be assessed by using electrocardiogram (ECG)⁸ recording. The standard deviation of normal-to-normal intervals (SDNN) counts as marker for overall HRV. The root-mean square of successive normal-to-normal interval differences (RMSSD) and high frequency (HF) power indicate parasympathetic modulations. Low frequency (LF) power is related to both the sympathetic and parasympathetic system⁹. Changes in the LF:HF ratio may provide information on sympathovagal balance.

3.2 Noise

Noise is ubiquitous and part of our everyday life. It is considered not only as an environmental nuisance but also has great public health impact. Almost every third person in the WHO European region is exposed to high noise levels. The WHO estimates that 61,000 years are lost due to noise-induced cardiovascular disease in the Western European population¹⁰. Studies on chronic noise exposure have suggested an association with elevated blood pressure^{11,12}, hypertension or the use of anti-hypertensive medication¹³⁻¹⁶, ischemic heart disease including myocardial infarction (MI)^{17,18}, and mortality from MI¹⁹. Such long-term studies where noise is assessed through strategic noise mapping provide the basis for the development of guideline values by the WHO. Thereby, noise sources of interest are mainly road traffic, railway

traffic, aircraft traffic and occupational noise. However, individuals are usually exposed to noise from more than one source simultaneously. Also, noise levels predicted through noise mapping do not provide valid information about personal exposure. However, there is only a small number of studies that described individual exposure from the everyday life including several sources²⁰⁻²³ and assessed its effects on human health²⁴⁻²⁷.

A possible mechanistic pathway connecting noise exposure to adverse cardiovascular health effects is described within the noise-stress model²⁸⁻³⁰. Accordingly, noise exposure can influence the ANS and the endocrine system. An activation of the sympathetic nervous system as well as the release of adrenalin, noradrenalin and cortisol may affect cardiovascular risk factors. A permanent adverse change in e.g. blood pressure, cardiac rhythm or homeostatic factors may become manifest in cardiovascular diseases. Up to now, several studies have shown associations between noise exposure and increased stress hormone levels^{28,31,32}. However, possible effects of noise exposure on the ANS have rarely been assessed in epidemiological studies.

3.3 Air pollution

An overwhelming body of evidence demonstrates adverse effects of air pollution on human health³³. Worldwide, ambient air pollution caused 3.7 million premature deaths in 2012; of these, 80% were due to ischemic heart disease and stroke³⁴. It has been shown, that ambient particles might trigger myocardial infarction^{35,36} and lead to higher rates of hospitalisation^{37,38} or mortality due to cardiac diseases^{39,40} within a few hours after exposure. Several pathways explaining cardiovascular effects of air pollution have been proposed^{33,41}. Shortly, it is hypothesised that after inhalation (1) particles deposit in the lung and lead via direct stimulation of pulmonary receptors to parasympathetic withdrawal and/or sympathetic activation, (2) deposited particles lead to oxidative stress and inflammation resulting in a systemic chain reaction due to a release of cytokines, acute-phase-reactants, and vasoactive hormones, (3) UFP and soluble constituents translocate into the circulation where they may exacerbate atherosclerosis, provoke local oxidative stress and inflammation and affect the vascular endothelium. These biological reactions may lead to cardiac arrhythmia, reduced heart rate variability, instability of atherosclerotic plaques and endothelial dysfunction^{40,42-44}. In the long run, these repeated adverse effects on the cardiovascular system might result in acute cardiovascular events like myocardial infarction.

Patients at higher cardiovascular risk because of an underlying chronic disease are assumed to be more susceptible to air pollution effects than others³³. In particular, diabetes is characterized by reduced heart rate variability and increased levels of inflammatory markers^{6,45,46}. Thus, individuals with impaired glucose metabolism presumably react stronger to air pollution exposures than healthy individuals^{47,48}.

Moreover, recent evidence presents ambient air pollution as one of the emerging risk factors of type 2 diabetes⁴⁹⁻⁵¹.

Particulate matter with an aerodynamic diameter below 10 μm (PM₁₀) and below 2.5 μm (PM_{2.5}) are the most health-damaging particles and accordingly, national ambient air quality standards were set. Ultrafine particles (UFP) with a size range of 0.01 to 0.1 μm are supposed to play an independent role as they might penetrate more deeply into the lung and might be more toxic than larger particles^{52,53}. However, UFP is not regulated by policies because epidemiological studies on UFP and their association with human health are still scarce.

In most studies, particulate matter was measured at one or more central measurement sites and only few studies examined personal exposure to air pollution. Particle mass concentrations of PM_{2.5} and PM₁₀ measured at a background station are generally regarded as representative for larger urban areas. However, UFP dominating particle number concentrations (PNC) have greater spatial variability^{54,55}. It has been shown, that vehicle exhaust particles, the major source of UFP, undergo a rapid physical transformation⁵⁶ leading to decreased UFP with increasing distance to a road^{57,58}. Thus, centrally measured UFP might not be a good surrogate for personal exposure.

3.4 Specific Aims

The main objectives of this thesis were:

- (1) To describe personal noise exposure in different microenvironments.
- (2) To describe personal exposure to ultrafine particles in different microenvironments.
- (3) To assess the short-term effects of personal noise exposure on heart rate variability in an older population.
- (4) To assess the short-term effects of personal ultrafine particles on heart rate variability in an older susceptible population.

3.5 Methods

In order to attain the main objectives we used data of a prospective panel study which was conducted in Augsburg, Germany during March 2007 and December 2008. The participants were recruited from the follow-up examination of the KORA (Cooperative Health Research in the Region of Augsburg) survey 2000⁵⁹ conducted in 2006–2008. Individuals had either diagnosed type 2 diabetes, impaired glucose tolerance or were healthy. In a baseline interview, they gave information on health status, medication use, disease status, and smoking history. Exclusion criteria were smoking during the preceding 12 months, intake of platelet aggregation inhibitors except for acetylsalicylic acid, an MI and/or interventional procedure (e.g., bypass surgery) less than six months

before study entry, and chronic inflammatory diseases. In addition, participants were excluded if they had an implanted pacemaker, atrial fibrillation, allergy to latex, or thrombosis or a shunt in an arm.

One hundred twelve individuals with a mean age of 62 years (standard deviation, sd: 11,6) participated in up to four repeated ECG recordings and personal exposure measurements, each with a mean duration of six hours. ECG recordings were performed with a 12-lead Mortara H12 digital Holter recorder (Mortara Instrument, Milwaukee, WI, USA) and were analyzed at the University of Rochester Medical Center (Rochester, NY, USA). Personal noise exposure was measured by noise dosimeters (model Spark@703 by Larson Davis, Inc., USA) as A-weighted equivalent continuous sound pressure levels (L_{eq}) reported in units of A-weighted decibels (dB(A)). In addition, long-term noise exposure was estimated for participants' residences as maximum annual L_{eq} during the day (6 am to 6 pm) for the sources road traffic, railway system and aircraft traffic. Personal measurements of PNC as indicator for UFP were conducted using a portable condensation particle counter (CPC, model 3007, TSI Inc., USA) which covered a diameter range from 10 nm to 1 μ m. Ambient measurements of PM_{2.5}, PM₁₀ and UFP (the size fraction of ultrafine particles from 10 to 100 nm) were obtained from a central monitoring station located in the urban background of Augsburg.

During the measurement periods, individuals were free to follow their daily routines. They recorded their activities and whereabouts in a diary. Written informed consent was obtained from all participants. The study protocol was approved by the German Ethics Committee of the Bayerische Landesärztekammer, Munich.

In order to describe individual exposure to noise and ultrafine particles descriptive statistics for several different microenvironments were developed. Additive mixed models with random effects were used to explain variability of individual exposure to noise and ultrafine particles as well as to assess its association with heart rate variability. For each analysis, an appropriate covariance structure was chosen to account for dependencies between repeated measurements.

3.6 Results

The first objective is attained within the manuscript entitled "Individual daytime noise exposure in different microenvironments" (*Environmental Research*, 140:479-487, 2015). We examined the variation in personal daytime noise exposure regarding different microenvironments, activities and individual characteristics. We included 109 individuals participating in 305 valid noise measurements, and almost 98,000 one-minute segments of L_{eq} were available. The following diary-based variables were considered: whereabouts (indoors at home / outdoors, at home, not in traffic / outdoors, not at home, not in traffic / in traffic), means of transportation (by foot / by bike / by motor vehicle or tram), being at work, being in a bistro, shopping, household

chores, gardening and manual work and physical activity (sleeping / resting / light exertion / moderate exertion / vigorous exertion).

Overall, noise levels were moderate to high (median=64 dB(A), range=37-105 dB(A)) with highest levels in traffic during bicycling (69 dB(A), 49-97 dB(A)) and lowest levels during resting at home (54 dB(A), 37-94 dB(A)). Personal noise exposures showed high variations for all microenvironments and personal activities except when being in traffic. This may be due to lower variation of different activities when in traffic or to high environmental noise that predominates variation in noise levels due to different activities. Women experienced significantly higher levels of L_{eq} than men (65.1 vs. 63.6 dB(A)) which may be due to a higher percentage of doing household chores (24% vs. 5%) and due to higher levels during indoor work (68.5 vs. 64.6 dB(A)) or due to higher traffic intensity of the road that was nearest to participant's residence (1,936 vs. 1,348 cars/day). To further investigate the influences on personal noise levels we performed two different models. In the main model, including all observations, nearly all whereabouts and activities explained variability in L_{eq} . The second model was restricted to observations made at participants' residences in order to additionally examine the influence of time-invariant characteristics and long-term noise exposure. Beside diary-based variables, window opening habits and distance to the major road explained some of the variability of L_{eq} . However, long-term noise explained no variability of L_{eq} which might be due to different averaging periods since long-term noise represented 12-hour means (6 am to 6 pm) whereas personal noise levels were collected during at least one hour between 7 am and 3 pm. In both models sex, age, physical activity and day of the week influenced L_{eq} . Additionally, an interquartile range (IQR) increase in personally measured PNC led to a significant, but small increase of 0.2 dB(A) in noise levels consistently in both models. Overall, the explained fraction of variability of L_{eq} was very small in both models (<1%). Presumably, the diary was too rough to capture all possible activities and whereabouts. On the other hand, the results show how difficult it is to assess the whole bench of sources of personal noise exposure.

The analyses entitled "Personal day-time exposure to ultrafine particles in different microenvironments" (*International Journal of Hygiene and Environmental Health*, 218 (2):188-195, 2015) deals with the second objective. We investigated personally measured PNC regarding different whereabouts and activities. Furthermore, we compared it to stationary measured PNC. We included 112 participants with 337 valid PNC measurements comprising almost 130,000 one-minute segments in the analyses. We considered the diary-based information on whereabouts (indoors; outdoors, but not in traffic; in traffic), mode of transport (by foot, by bike, by motor vehicle, underground parking lot), household chores (e.g. activities with dust lifting like vacuuming and with water vapor like cooking and dish washing), shopping, being in a bistro and passive smoking.

Overall, personal PNC had a mean of 20,422 particles per cm^3 and showed a wide range of 2,927 to 91,759 cm^{-3} . Highest personal PNC levels were associated with traffic

environments (mean: 26,394 cm⁻³ [sd: 29,537 cm⁻³], especially when in a car, bus or tram (27,980 cm⁻³ [30,229 cm⁻³]) as well as with indoor activities including water vapor (45,615 cm⁻³ [68,368 cm⁻³]), indoor passive smoking (65,042 cm⁻³ [88,632 cm⁻³]), and during shopping (39,250 cm⁻³ [58,156 cm⁻³]). Lowest values were associated with the outdoors (not in traffic) environment (13,636 cm⁻³ [21,589 cm⁻³]). These results show that personal PNC varies greatly between and within different microenvironments and activities, even when in traffic. When in a motor vehicle, high differences in PNC may result from various car ventilation settings and traffic conditions like traffic load, types of vehicles and road/street characteristics. For most environments and activities correlations between personal and stationary PNC were weak with coefficients ranging between 0.11 for being indoors without activity and 0.44 for times spent in traffic. For some microenvironments personal PNC was enormously higher than stationary PNC (in traffic: 50%, indoors activity with water vapor: 151%, during shopping: 139%). Therefore, stationary PNC may be a poor predictor of personal exposure. These results were also confirmed when we modeled personal PNC by applying mixed models. Most diary-based variables had a significant influence on personal PNC, while stationary PNC did not explain variability of personal PNC at all.

The third objective is achieved within the manuscript “Individual daytime noise exposure during routine activities and heart rate variability in adults: A repeated measures study” (*Environmental Health Perspectives*, 121(5):607-612, 2013). We included 110 individuals of the entire population who had 326 valid personal noise and ECG measurements comprising approximately 20,000 five-minute segments. In a preliminary analysis associations between concurrent noise exposure and all ECG parameters showed non-linear exposure-response functions. Therefore, we performed piecewise linear analyses with a cut-off point at 65 dB(A) and presented separate estimates for associations with a 5 dB(A) increase in L_{eq} for L_{eq} below 65 dB(A) and L_{eq} above 65 dB(A).

In association with increases in noise levels below 65 dB(A) we observed concurrent increases in HR (percent change of outcome mean: 1.48% [95% confidence interval (CI): 1.37, 1.60%]) and the LF:HF ratio (4.89% [3.48, 6.32%]) as well as concurrent decreases in LF power (-3.77% [-5.49, -2.02%]) and HF power (-8.56% [-10.31, -6.78%]). With a delay of at least five minutes above-named associations were smaller and partly insignificant. SDNN was positively associated with concurrent increases in L_{eq} below 65 dB(A) (5.74% [5.13, 6.36%]) but negatively associated with noise lagged by five to 15 minutes (-0.53% to -0.69%). For increases in L_{eq} above 65 dB(A), associations were less pronounced for HR and LF:HF ratio and showed opposite directions for SDNN, HF and LF power. In the analyses of the first manuscript PNC explained some variability of L_{eq} . However, in the health effects analyses estimates did not change meaningfully when we additionally included personal PNC. Because associations differed between low and high noise intensities, we assumed different underlying mechanisms. Associated with increases in lower noise levels, changes in LF

and SDNN indicated reduced sympathetic activation. But, as HF power decreased and HR and LF:HF ratio increased, a predominating parasympathetic withdrawal has likely occurred. In contrast, changes in ECG parameters associated with increases in higher noise levels point to an enhanced sympathetic modulation exceeding parasympathetic input. Analyses stratified by sex showed stronger changes in ECG parameters for women but only associated with increases at lower noise levels (p-value for interaction ≤ 0.002). At a five-minute scale there were no differences in noise levels between men and women as we observed at an one-minute scale in the first study. Thus, women seemed to be more susceptible to noise-induced parasympathetic modulations at lower levels. However, existing studies on sex-specific noise effects have reported inconsistent results^{14,16,24,60-62}. Overall, this study indicated an impaired HRV even associated with lower noise levels which might result in enhanced cardiovascular risk in the long run.

The manuscript “Elevated Particle Number Concentrations Induce Immediate Changes in Heart Rate Variability: A Panel Study in Individuals with Impaired Glucose Metabolism or Diabetes” (*Particle and Fibre Toxicology*, 12:7, 2015) attains the fourth objective. We examined the effects of personal PNC on heart rate variability in 64 participants (191 visits) with type 2 diabetes or impaired glucose tolerance. In addition, we wanted to examine the association with ambient PNC, PM_{2.5} and PM₁₀ measured at the central monitoring site. Almost 12,000 observations for five-minute analyses and about 1,200 segments for one-hour analyses were available.

In association with an increase of 16,000 cm⁻³ in personal PNC, we observed a five-minute delayed increase in heart rate (%-change of outcome mean: 0.23% [95%-CI: 0.11, 0.36%]) and a concurrent increase in SDNN (-0.56% [-1.02, -0.09%]). We found no associations between personal PNC and RMSSD suggesting that personal PNC rather influences the sympathetic activity than parasympathetic modulations. Models additionally including personal noise exposure led to stronger effects on SDNN (-1.20% [-1.82, -0.57%]) indicating confounding by personal noise levels. When we examined one-hour averages, IQR increases in ambient PM_{2.5} and PM₁₀ were associated with concurrent decreases in SDNN (-3.27% [-5.84, -0.69%] and -2.78% [-4.98, -0.59%], respectively) and RMSSD (-6.86% [-11.73; -1.72%] and -5.0% [-8.88, -0.95%], respectively). However, we did not observe any significant effects of one-hour ambient UFP on ECG parameters and associations with personal PNC nearly disappeared at a one-hour scale. Two-pollutant models showed independent effects of concurrent five-minute personal PNC and one-hour ambient PM_{2.5} on concurrent SDNN. Thus, we hypothesize that personal PNC and ambient particles address different underlying mechanisms. Increases of personal PNC exposure may influence the ANS by irritating receptors in the lung which occurs at a very short time scale within at least five minutes. Associations with PM_{2.5} may rather initiate a systemic inflammation process leading to delayed mitigation of HRV, which may become apparent at larger time scales within at least one hour. Nevertheless, the study shows that both, personal and

stationary particles were associated with very short-term changes in cardiac function in individuals with impaired glucose tolerance or diabetes.

3.7 Discussion and conclusions

This thesis increases the knowledge base about personal exposures to noise and PNC and its cardiovascular health effects. Personal exposure to noise and PNC showed high variations between and within different microenvironments. In traffic environment where levels were highest for both exposure types, noise levels showed low variations in contrast to PNC. Thus, influence of personal activity on personal noise exposure seems to be rather low in settings with higher environmental noise like in traffic which strengthens the importance and necessity of noise regulating policies.

In the health effects analyses, personal noise exposure led to a rapid mitigation of HRV within the first five minutes. On the one hand results provide evidence supporting the noise-stress-model suggesting that higher noise levels enhance cardiovascular risk by adverse sympathetic activation. This is also in line with WHO suggesting an average noise level of 65–70 dB(A) during the day as possible threshold for a higher cardiovascular risk⁶³. However, an important result of our analyses is that lower levels of personal noise exposure may have health consequences, too. Unfortunately, we were not able to investigate whether noise effects were stable when additionally adjusting for annoyance because such data were not available in our study. Noise exposure has been shown to be associated with annoyance⁶⁴ which in turn has been shown to be associated with cardiovascular disorders⁶⁵. Therefore, cardiovascular health effects of noise might differ in dependence of weighing the situation as unpleasant or not⁶⁶.

Furthermore, we found immediate associations with HR and HRV measures in association with personal PNC as well as ambient PM_{2.5}. Our study gives insight into the mechanistic pathways explaining the associations between air pollution and acute cardiovascular events by indicating a mitigation of heart rate variability. Such repeated impairments of the cardiac rhythm may in the long run lead to acute cardiovascular events. As we chose individuals with impaired glucose tolerance or diabetes the study partly provides a link between air pollution and worsening of glucose metabolism.

Moreover, our analyses amplifies the limited numbers of short-term studies on health effects of ultrafine particles, which often showed inconsistent results⁶⁷. Epidemiological studies of long-term exposures haven't even been conducted yet. Reasons might be different measurement techniques and exposure misclassification. Thus, there is a need to assess valid UFP exposure levels for the population. Nation-wide analysis of health effects of UFP may then be more reasonable and more epidemiological studies on UFP can be conducted. Their results may force stakeholders and policy makers to set up ambient UFP standards as already done for mass concentrations of larger particles.

As air pollution and noise exposure are both generated by urban traffic they might interact with or confound by each other. To date, only a few studies have considered the combined effect of air pollution and noise and most of them indicate independent effects^{19,68-71}. However, at least one study showed, that air pollution effects were confounded by high noise levels⁷². In our analysis of personal noise effects, additional adjustment for personal PNC led to similar estimates as the main analysis. In contrast, the analyses of personal PNC effects suggested confounding by personal noise levels. Therefore, further studies elucidating the combined health effects of noise and PNC are needed.

Overall, this thesis provides insight in personal exposures to noise and PNC, which were both highly variable dependent of personal activities and whereabouts. Furthermore, personal noise and personal PNC were associated with acute adverse changes in cardiac function.

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4 Individual Daytime Noise Exposure in Different Microenvironments

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Individual Daytime Noise Exposure in Different Microenvironments

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RUNNING TITLE

Noise exposure in microenvironments.

CID

The authors declare that they have no competing financial interests.

ABBREVIATIONS

CI	Confidence interval
dB(A)	A-weighted decibels
KORA	Cooperative Health Research in the Region of Augsburg
L_{day}	Maximum annual A-weighted equivalent continuous sound pressure levels during the day (6 am to 6 pm)
L_{eq}	A-weighted equivalent continuous sound pressure levels
LOD	Limit of detection
PNC	Particle number concentration
R^2	Coefficient of determination
sd	Standard deviation
VIF	Variance inflation factor
WHO	World Health Organisation

ABSTRACT

Background. Numerous studies showed that chronic noise exposure modelled through noise mapping is associated with adverse health effects. However, knowledge about real personal noise exposure, emitted by several sources, is limited.

Objectives. To explain the variation in personal daytime noise exposure regarding different microenvironments, activities and individual characteristics.

Materials and Methods. In a repeated measures study in Augsburg, Germany (March 2007-December 2008), 109 individuals participated in 305 personal noise measurements with a mean duration of 5.5 hours. Whereabouts and activities were recorded in a diary. One-minute averages of A-weighted equivalent continuous sound pressure levels (L_{eq}) were determined. We used mixed additive models to elucidate the variation of L_{eq} by diary-based information, baseline characteristics and time-invariant variables like long-term noise exposure.

Results. Overall noise levels were highly variable (median: 64 dB(A); range: 37-105 dB(A)). Highest noise levels were measured in traffic during bicycling (69 dB(A); 49-97 dB(A)) and lowest while resting at home (54 dB(A); 37-94 dB(A)). Nearly all diary-based information as well as physical activity, sex and age-group had significant influences on personal noise. In an additional analysis restricted to times spent at the residences, long-term noise exposure did not improve the model fit.

Conclusions. Personal exposures to day-time noise were moderate to high and showed high variations in different microenvironments except when being in traffic. Personal noise levels were greatly determined by personal activities but also seemed to depend on environmental noise levels.

KEY WORDS

Noise exposure, personal exposure, microenvironments, epidemiology, activity diary

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ETHICS

The study was conducted in compliance with the Helsinki Declaration. The study protocol was approved by the German Ethics Committee of the "Bayerische Landesärztekammer", Munich, Germany. Written informed consent was obtained from all individuals before entering the study.

1. INTRODUCTION

A growing body of evidence shows adverse associations between chronic noise exposure and human health. Several epidemiological studies have identified noise exposure to be a major contributor to hearing loss (Sliwinska-Kowalska and Davis 2012), sleep disturbance (Hume et al. 2012), cardiovascular disease (Davies and Kamp 2012), impairment of performance (Clark and Sorqvist 2012), altered endocrine responses (Babisch 2003), mental illness as well as annoyance (Stansfeld and Matheson 2003). Most of these associations were assessed in long-term studies, where noise was predicted through strategic noise mapping. Thereby, these studies concentrated on noise exposure from selected sources, in particular road-traffic, railway system, aircraft and occupational settings. The results of these studies provided the basis for the development of guideline values (Berglund et al. 1999; WHO 2009) and the calculation of burden of disease in terms of disability-adjusted life-years (WHO 2011, 2012). As a consequence, traffic noise was placed as the second most dangerous environmental threat to human health after air pollution in six European countries (EBoDE 2010; Hanninen et al. 2014). However, people are usually exposed to noise from more than one source simultaneously. Also, noise levels predicted through noise mapping do not provide valid information about personal exposure. To date, only a few studies measured noise continuously and were able to describe noise levels in specific microenvironments or during different activities (Boogaard et al. 2009; Clark 1991; Diaz and Pedrero 2006; Flamme et al. 2012; Neitzel et al. 2004b; Neitzel et al. 2014; Weinmann et al. 2012; Zheng et al. 1996). Most of these studies concluded that 24-hour means of individual noise exposure was high with levels exceeding the recommended limit of 70 dB(A) for prevention of hearing loss (Berglund et al. 1999). However, these 24-hour means depended on very specific activities contributing the majority of the total noise dose but accounting only for a minority of the individual's total investigated time (Diaz and Pedrero 2006; Neitzel et al. 2004b). Still, knowledge on personal noise levels in typical situations of daily life remains limited.

In Augsburg, Germany, an epidemiological study was conducted to assess the health effects of different environmental stressors on cardiovascular health (Hampel et al. 2012; Kraus et al. 2013; Schauble et al. 2012). Within this study, personal measurements of noise were performed. In a former analysis, we observed that personal noise was associated with adverse changes in heart rate variability, with higher effects at lower noise levels (Kraus et al. 2013). The objective of the present analysis was i) to describe individual daytime noise exposure in different typical micro-environmental settings and ii) to evaluate which factors are useful determinants of personal noise exposure in adults during daytime by the use of multiple regression models.

2. MATERIALS AND METHODS

2.1 Study design

As part of the Rochester Particulate Matter Center investigations, an epidemiological study was conducted in Augsburg and two adjacent rural districts Augsburg and Aichach-Friedberg, Germany, between March 19th 2007 and December 17th 2008. Augsburg is located in the south-west of Bavaria and covers 147 km². It is the third-largest city in Bavaria with a population exceeding 260,000 citizens. The two districts cover 1,851 km² and have a population of more than 368,000 citizens (Bavarian state office for statistics and data processing, as per 31.12.2008). Augsburg Airport is located seven kilometers from Augsburg's city center in north-easterly direction. Participants were recruited from the follow-up examination of the KORA (Cooperative Health Research in the Region of Augsburg) survey 2000 (Holle et al. 2005) conducted in 2006-2008. They were invited to participate in up to four personal exposure measurements ("visit") scheduled every four to six weeks on the same weekday between 7:30 am and 3 pm. In this period, participants were free to pursue their daily routines.

2.2 Activity diary

The participants were instructed to enter their activities and whereabouts and changes of these in a diary. For information on whereabouts, participants could tick whether they were indoors, outside but not in traffic (e.g. in a park), or in traffic. If in traffic, participants could tick which means of transport they were using. Start and end times of activities were recorded to the minute. Information on other activities was gathered by free text. After the return to the study center, the nurses checked the diary for readability, completeness and conclusiveness. Furthermore, we quantified the activities based on the classification of a metabolic equivalent unit (Peters et al. 2005).

2.3 Personal exposure

Personal noise measurements were collected by noise dosimeters (model Spark[®] 703 by Larson Davis, Inc., USA). The microphone was attached to the collar close to the ear. Noise exposure was measured as A-weighted equivalent continuous sound pressure levels (L_{eq}) reported in units of A-weighted decibels (dB(A)). The dosimeters had a measurement range of 40 dB to 115 dB with a detector accuracy of less than 0.7 dB. They were calibrated once a week. Values lying below the lower limit of detection (LOD) were substituted with 37 dB, values above the upper LOD with 115 dB (Radon 2007). In addition to noise, personal measurements of particle number concentrations (PNC), an indicator for ultrafine particles, were conducted using a portable condensation particle counter (CPC, model 3007, TSI Inc., USA) which covered a diameter range from 10 nm to 1 μ m. For both, L_{eq} and PNC, the sampling interval was five seconds. One-minute averages were determined if at least $2/3$ of the measured values in a 1-minute segment were available.

To ensure that exposure data can be aligned on the same timescale with the diary data, the time of the exposure devices was synchronized with a radio-controlled clock before starting the measurement. Each participant got a wrist watch that was likewise synchronized. Furthermore, the study nurses recorded start and end times of the measurement periods in a protocol.

2.4 Long-term noise exposure

Long-term noise was modelled by the company ACCON GmbH (DIN EN ISO 14001:2009 certified), an environmental and engineering consultancy for sound and vibration technology, air pollution control and environmental planning. Maximum annual A-weighted equivalent continuous sound pressure levels during the day (L_{day} , 6 am to 6 pm, unit: dB(A)) were estimated for the home address of each participant. Thereby, L_{day} was estimated separately for the sources road traffic including tram ($L_{dayRoad}$), railway system ($L_{dayRailway}$) and aircraft traffic ($L_{dayAircraft}$). Except for aircraft noise the exposure assessment differed between the city and rural districts due to differences in predictor information availability. In general, the basis year was 2009 but ranged from 2000 to 2011 if predictors were not available for 2009. For more details we refer to the Supplemental Material.

2.5 Statistical analyses

We generated descriptive statistics for 1-minute averages of personal noise levels for all observations and separately for different whereabouts, means of transport, activities, day of the week, season and baseline characteristics of the study participants. Medians of two or more than two groups were compared by using Mann-Whitney U test and Kruskal-Wallis test, respectively. Descriptive statistics for long-term noise at residential addresses were also computed.

To investigate which factors explain the variability in personal noise exposure we applied additive mixed models. We used an autoregressive covariance structure to account for correlations between repeated noise measurements and included a random effect to adjust for differences between each visit. We performed a supervised forward selection by minimizing Akaike's information criterion (Akaike 1973). For the main model, first, we took short-term and long-term time trends into account. Continuous trend variables were considered either linearly, or smoothly as penalized spline or polynomials up to 4 degrees (Greven et al. 2006). Second, we considered the following diary-based categorical variables: whereabouts, means of transportation, physical activity, household chores, being in a bistro, shopping, gardening and manual work, currently being at work. Further possible variables were personally measurements of PNC and relative humidity measured hourly at a fixed monitoring site in Augsburg as an indicator for rain. Finally, the baseline characteristics sex, social class and age were taken into account. For more details on considered variables we refer to Supplemental Material, Table S1.

In a second model, we restricted the data to 1-minute segments collected at participants' residences. Thereby, a visit was only included if the participant spent at least one hour at home. As possible variables explaining variability in personal noise exposure we considered short-term and long-term time trend equally to the main model. Second, we considered the diary-based variables whereabouts, gardening and manual work, physical activity, household chores as well as personally measured PNC and ambient relative humidity. Third, we took long-term noise exposure and the following time-invariant variables into account: area of home address, participants' window opening habits, the direction of the room that was mainly used, traffic intensity of the next/next major road and the distance to the next/next major road. Additionally, baseline characteristics were considered (Supplemental Material, Table S1).

Before model building, correlation coefficients between possible variables were calculated. In case of a high correlation (r_{Spearman} or $\tau_{\text{Kendall}} \geq |0.7|$) we included only one variable. In addition, the variance inflation factor (VIF) was used to quantify the severity of multicollinearity. Effect estimates for the selected variables are presented as absolute change of L_{eq} together with 95% confidence interval (CI).

In a further analysis, we substituted in both models the variable household chores by dichotomized variables reflecting different types of household chores: cooking, doing the laundry, doing the dishes, vacuum cleaning, and all other.

To evaluate the accuracy of the models we calculated coefficients of determination (R^2). Analyses were conducted using SAS statistical package (version 9.3; SAS Institute Inc, Cary, NC).

3. RESULTS

3.1 Personal noise exposure

Out of 112 individuals participating in the exposure measurements three participants did not provide valid measurements of noise and PNC. Therefore, the study population consisted of 109 individuals who participated in 305 valid visits between 7:30 am and 4:00 pm with a mean duration of 5.5 hours (standard deviation (sd): 53 minutes). Overall, almost 98,000 1-minute segments of personal exposure were collected.

The participants had a mean age of 62 years and two-thirds were unemployed or retired (Supplemental Material, Table S2). The participants spent 71% of the measurement period indoors, 22% in traffic and 5 % outside, but not in traffic. The overall median of all 1-minute segments of L_{eq} was 64.2 dB(A) with values ranging from 37.0 dB(A) to 104.6 dB(A). Variability between visits was very high with medians ranging between 37.4 and 84.5 dB(A).

Daily time-series of L_{eq} for all observations are shown in Figure 1A. We observed two peaks in the beginning and at the end of the measurement period and a smaller increase in noise levels from midday to 1:30 pm. These peaks correspond to the times participants were predominately in traffic (Figure 1B), e.g. when coming from or going back to the study center. As in the beginning and at the end of the measurement period the total number of observations was low, higher noise levels measured in traffic

became more apparent.

Figure 2 shows the percentages of 1-minute segments per L_{eq} overall as well as separated by whereabouts. The distribution for overall L_{eq} is right-skewed because L_{eq} follows a logarithmic scale; an increase of 3 dB(A) in L_{eq} corresponds to a doubling of sound pressure. However, an increase of 10 dB(A) in noise levels is subjectively perceived as a doubling in loudness. Noise levels for being indoors or being outside, but not in traffic covered a wide range while variability of noise levels for being in traffic was very small.

Descriptive statistics for L_{eq} divided by different subgroups are shown in Table 1. The median of L_{eq} differed significantly for every subgroup (p -value <0.05). Noise levels for being in traffic were almost 8 dB(A) higher than for being indoors at home and 6.6 dB(A) higher than for being outside at home, but not in traffic. In traffic, participants were exposed to the highest noise levels when cycling followed by using a motor vehicle or tram and walking (Table 1). Women were exposed to higher noise levels than men (Table 2). We observed this difference particularly for being indoors at home (men: 58.1 dB(A) vs. women: 61.6 dB(A), and for being outside at home (58.7 vs. 65.9 dB(A)), but not for being in traffic (67.3 vs. 67.7 dB(A)). Regarding age-group, highest noise levels were observed in 50 to 54 years old participants. This difference was highest for being indoors, but not at home (70.3 vs. 64.9 to 67.5 dB(A) for the other age-groups).

3.2 Long-term noise

Figure 3 shows the home addresses of the participants. Fifty-nine persons were living in the city of Augsburg and 50 persons in the rural area. Median values for long-term noise exposure were 52.1 dB(A) (range:34.2 to 70.0 dB(A)) for L_{day} Road, 39.2 dB(A) (19.9 to 61.4dB(A)) for L_{day} Railway and 23.9 dB(A) (0 to 38.1 dB(A)) for L_{day} Aircraft (Supplemental Material, Table S4).

3.3 Modeling personal exposure

Descriptive statistics for continuous variables based on 1-minute segments are shown in Supplemental Material, Table S3. Since the correlation between whereabouts and means of transportation was high ($\tau_{\text{Kendall}}=0.8$), we included only whereabouts which led to a higher reduction in AIC than means of transportation. Regression results for the main model are shown in Table 3. Regarding whereabouts, being in traffic contributed to the highest increase in L_{eq} compared to being indoors at home. Being in a bistro, shopping, doing household chores as well as gardening and manual work additionally led to an increase in personal noise exposure. Furthermore, physical activity and PNC explained some variability of L_{eq} . Sex and age-group as well as day of the week improved the model fit additionally.

When we restricted the dataset to times spent at the residences, 21,923 (22.4%) 1-minute segments collected by 38 persons in 101 visits were included for analysis. For these segments, descriptive statistics are shown in Supplemental Material, Tables S3, S5 and S6. Table 4 shows regression results for the restricted model. The diary-based

variables whereabouts, doing household chores and gardening and manual work as well as physical activity improved the model fit. PNC contributed to higher personal noise levels. Of time-invariant variables, distance to the nearest road, traffic intensity of the nearest major road and opening window habits were selected though estimates were not significant. Long-term noise levels did not seem to explain any variability of L_{eq} . Categorized age and sex as well as day of the week improved the model fit additionally. All VIFs were <2 indicating no multicollinearity between selected variables. The highest fraction of the variability of L_{eq} was explained by the covariance structure (Main model: $R^2=0.620$; model restricted to times spent at the residences: $R^2=0.591$). The full models each explained less than one percent in addition ($R^2=0.627$; $R^2=0.595$). When we substituted household chores with different types of household chores in the main and restricted model, estimates and coefficients of determination did not change meaningfully (data not shown).

4. DISCUSSION

4.1 Summary

This repeated measurements study conducted in the region of Augsburg collected almost 98,000 1-minute segments of personal noise exposure in different microenvironments during daytime hours. Median noise levels were moderate to high with L_{eq} ranging between 59 and 69 dB(A), but mean noise levels were higher ranging between 65 and 78 dB(A). Except for being in traffic, we observed a high variability of noise levels in different microenvironments. Beside whereabouts and physical activity, sex and age contributed most to personal noise exposure with women and younger people experiencing higher noise levels.

4.2 Whereabouts

Means of personal noise levels were much higher than medians. Due to the logarithmic scale of L_{eq} , single events or special activities with very high noise levels had a great influence on the overall noise dose, which was also shown by other studies (Diaz and Pedrero 2006; Neitzel et al. 2004b). Thus, the median is much more representative to describe the general noise level of a microenvironment and is used for the following paragraphs if not indicated different.

Highest noise levels were found for being in traffic. Thereby, noise levels were higher during cycling compared to using a motor vehicle as participants were exposed to traffic noise directly. An explanation for lower noise levels during walking might be that individuals preferred routes with less traffic when going by foot. Lowest noise levels were observed at participants' homes. Individuals did their household chores implying high noise levels of e.g. 66.2 dB(A) for cooking and vacuum cleaning, but also spent time with sleeping and resting implying low noise levels. Noise levels measured during resting were even lower than during sleep. Participants who were resting but not asleep

presumably rather cared for quietness and e.g. closed their windows. Furthermore, low levels of personal noise for being outside at participants' homes indicated that the environmental noise for residences was quite low.

Except for being in traffic all whereabouts covered a wide range of noise levels. On the one hand, this is due to the broad range of different activities performed by our participants while in traffic the differences in activities are generally low. On the other hand, personal activities might have a great influence on personal noise exposure in microenvironments with low levels of environmental noise like being indoors. In contrast, microenvironments with higher environmental noise levels like traffic might outweigh noise levels from personal activities and therefore greatly influence personal noise exposure. Zheng and colleagues compared personal noise measurements with daily measurements outside dwellings. Personal noise levels were higher and showed more variation during the day than environmental noise levels. The authors concluded that personal noise exposure was related to the environment as well as to personal daily activities (Zheng et al. 1996). In a field study in families of urban schoolchildren, indoor noise exposure increased with the presence or activity of the inhabitants at home but was also associated with outdoor noise levels (Pujol et al. 2014). These studies and our results confirm the strategy of policy makers in regulating environmental noise levels where individuals' options to reduce personal noise exposure by themselves are limited.

4.3 Sex and age

In our study, women were exposed to higher noise levels than men in particular indoors as well as outside at home, but not in traffic. Regarding being indoors, women did household chores during 24% of the measurement time compared to only 5% for men. Furthermore, women were exposed to considerably higher noise levels during indoor work (68.5 vs. 64.6 dB(A)). As we do not have any information about participants' occupations we can only speculate that women's jobs were characterized by higher noise levels than men's jobs. Why women were exposed to higher noise levels when being outside at home is difficult to elucidate as the descriptions of activities were similar between both sexes. Most of the time spent outside was on a balcony, a terrace or in a garden. Women's homes were closer to nearby roads compared to men's homes (mean: 19.4 vs. 25.3 meters, p -value<0.01) and traffic intensity of the nearest road was higher for women (mean: 1,936 vs. 1,348 cars/day, p -value<0.01). Nevertheless, for long-term noise from road traffic we observed no differences between both sexes. In an American study, Flamme and colleagues examined typical noise levels present in daily life in people aged 20 to 64 years. In contrast to our results, the authors found, based on the mean, greater sound exposures for men than for women for the upper half of the exposure distribution (Flamme et al. 2012). Zheng and colleagues studied personal noise levels in mainly employed residents of Beijing, China (Zheng et al. 1996). In line with our results, they observed higher L_{eq} values for females, in specific 2 dB higher than those for males during the day.

Regarding age, we found highest noise levels for persons aged 50-54 years. This age-

group had the highest percentage of employed participants (64%) followed by the age-group 55-59 years (51% employed). Noise levels at work were almost 3 dB(A) higher than in non-work situations and 66.7% of working time was spent indoors, when the observed difference in noise levels between age-groups was highest.

4.4 PNC

Beside diary-based variables and baseline characteristics, individual measurements of PNC explained some of the variability of L_{eq} in both, the main model and the model restricted to times spent at the residences. This result fits with our previous analysis on ultrafine particles performed in the same population. We observed that higher indoor PNC was associated with activities like cooking. Furthermore, being in a bistro and in traffic led to higher PNC levels, which are also microenvironments associated with higher noise levels (Gu et al. 2014).

4.5 Time-invariant variables

In our analysis, long-term noise exposure did not explain any variability of personal noise exposure. This might be due to the different averaging periods since long-term levels of noise represented 12-hour means (6 am to 6 pm), whereas personal noise levels were collected during at least one hour. Otherwise, results indicated that open or tilted windows were associated with lower noise levels at home compared to a closed window though estimates were not significant in the restricted model. One can assume that persons living in a louder environment tend to close the window. However, window opening habits should not affect personal noise levels of people living in a quiet area. Indeed, $L_{dayRoad}$ was significantly lower for participants with a habit of opening or tilting the window ($L_{dayRoad}=52.0$ (SD=51.1)) than for participants with generally closed windows (54.2 (52.8); p-value of Tukey's Studentized Range test <.0001). This confirms that outdoor sources of noise might influence personal indoor noise which is in line with Pujol et al. (Pujol et al. 2014) and strengthens the importance of noise regulation policies.

4.6 Strengths and limitations

Strengths in our study are the repeated personal measurements with a mean duration of 5.5 hours together with information on microenvironments and activities. Participants pursued their daily routines covering a wide range of typical situation of general daytime activities. However, we collected data for a period of less than six hours during morning and midday which impeded comparisons with WHO guideline values referring to 24 hour averages, the night (6 pm to 6 am) or the day (6 am to 6 pm). Moreover, as participants were forced to be in traffic when traveling to or leaving the study center in the morning and the afternoon, time spent in traffic was likely overrepresented. Another limitation refers to the small fraction of explained variance of L_{eq} that presumably was due to high variability within diary-based variables. On the one

hand, the activity diary might have been too crude and did not cover every noise source. On the other hand this analysis shows how difficult it is to assess the whole bench of sources of personal noise exposure. Neitzel et al. (Neitzel et al. 2004a) already reported in an analysis on personal activity logs and noise measurements in construction apprentices that noise levels associated with non-occupational activities were highly influenced by the details of that activity which makes any estimate of non-occupational noise exposure inevitably rough. Additionally, measurements of noise levels and diary data were temporally aligned based on the times recorded by each device, the study protocols and the participants. In cases of ambiguities, we classified 1-minute segments as unclear. However, a potential for misclassification with regard to the whereabouts might still have been left.

At last, basis years for long-term noise concentrations matched only partly our study period. However, we assume that noise from road and railway traffic and aircraft did not change essentially between 2007 and 2011.

5. CONCLUSION

The study documented that personal exposures to day-time noise were moderate to high and showed high variations except when being in traffic. Personal noise levels were mainly determined by personal activities but also depended on environmental noise levels. In settings where environmental noise is high, like being in traffic, influence of personal activity on personal noise exposure seems to be rather low which strengthens the importance and necessity of noise regulating policies.

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Figure legend

Figure 1. Time-series of A. personal noise exposure for all observations (moving averages for every 5 minutes) and B. number counts overall and separated by whereabouts.

Abbreviations: dB(A), A-weighted decibels; L_{eq} , A-weighted equivalent continuous sound pressure levels

Figure 2. Percent of 1-minute segments per L_{eq} , overall and separated by whereabouts. The dotted line represents the overall median, the short-dashed line represents the overall mean.

Abbreviations: L_{eq} , A-weighted equivalent continuous sound pressure levels; N, number of 1-minute segments; dB(A), A-weighted decibels; IQR, interquartile range.

Figure 3. Position of study center, airport and participants' residences. Coordinates of residences were blurred.

Abbreviations: dB(A), A-weighted decibels; L_{day} , maximum annual A-weighted equivalent continuous sound pressure levels during the day (6am to 6pm).

Table 1. Descriptive statistics for 1-minute averages of personal noise exposure (L_{eq} [dB(A)]) overall and separated by diary-based variables.

		N	mean (sd)	median	p25-p75	p-value
Overall		97,757	74.1 (82.7)	64.2	56.1-70.4	
Being at the study center	No	90,538	74.3 (82.9)	64.1	55.7-70.3	<.0001 ^c
	Yes	7,219	70.8 (75.3)	65.6	59.8-70.6	
Whereabouts	Indoors	69,393	73.4 (82.9)	62.5	53.7-69.7	<.0001 ^d
	- at home	42,045	71.2 (82.1)	59.6	51.0-67.6	
	- not at home	27,348	75.5 (83.6)	66.0	58.7-72.2	
	Outside, not in traffic	5,092	76.4 (82.9)	61.7	53.8-69.7	
	- at home	3,430	76.8 (83.5)	60.8	53.4-69.4	
	- not at home	1,662	75.3 (80.9)	63.3	55.0-70.3	
	In traffic	21,297	75.3 (82.3)	67.4	63.3-71.8	
Unclear ^a	1,975	73.7 (82.5)	65.3	59.4-70.1		
Means of transportation in traffic	By foot	8,179	74.0 (79.8)	66.9	62.3-71.7	<.0001 ^d
	By bike	694	78.3 (85.7)	69.2	64.5-73.5	
	By bus/tram/car/moped	12,456	75.7 (82.8)	67.7	63.8-71.7	
Being at work	No	75,834	72.7 (81.7)	63.5	55.3-69.7	<.0001 ^c
	Yes	22,923	76.9 (84.5)	66.3	58.6-72.8	
Being in a bistro	No	95,921	74.1 (82.8)	64.1	55.9-70.3	<.0001 ^c
	Yes	1,836	72.5 (75.6)	67.3	62.7-72.0	
Shopping	No	95,935	74.1 (82.8)	64.1	55.9-70.4	<.0001 ^c
	Yes	1,822	73.1 (77.6)	66.2	61.4-70.9	
Household chores ^b	No	33,903	70.9 (82.5)	58.6	50.0-66.8	<.0001 ^c
	Yes	8,142	72.2 (78.1)	63.5	55.7-70.2	
Type of household chores ^c	Doing the laundry	1,240	69.1 (74.0)	59.4	54.6-66.4	<.0001 ^d
	Doing the dishes	659	69.1 (73.4)	63.6	54.3-68.9	
	Cooking	2,506	72.1 (78.5)	66.2	60.5-70.9	
	Vacuum cleaning	1,669	74.6 (78.9)	66.2	57.3-73.8	
	Other	2,714	71.8 (78.0)	60.3	52.4-68.1	
Gardening and manual work	No	96,269	74.1 (82.8)	64.2	56.0-70.3	<.0001 ^c
	Yes	1,488	75.0 (78.9)	66.2	60.2-75.7	
Physical activity	Sleeping during the day	370	64.5 (68.5)	59.4	50.5-63.2	<.0001 ^d
	Resting	1,261	66.8 (78.4)	53.7	46.4-61.3	
	Very light/light exertion	90,519	74.2 (82.9)	64.3	56.2-70.4	
	Moderate exertion	3,666	72.8 (80.3)	64.3	56.4-72.0	
	Vigorous exertion	687	69.9 (74.6)	63.0	57.1-67.8	
	Unclear	1,254	71.5 (78.4)	65.7	59.8-70.2	

^aWhereabouts were unclear if a diary entry contained more than one information on the whereabouts/activity.

^bHousehold chores when being indoors at home.

^cSome observations are belonging to more than one group.

^d p -value for differences between medians of subgroups determined with ^cMann-Whitney U test or ^dKruskal-Wallis test.

Abbreviations: dB(A), A-weighted decibels; L_{eq} , A-weighted equivalent continuous sound pressure levels; max, maximum; min, minimum; N, number of 1-minute segments; p25, 25. percentile; p75, 75. percentile; sd, standard deviation.

Table 2. Descriptive statistics for 1-minute averages of personal noise exposure (L_{eq} [dB(A)]) overall and separated by trend variables and participants' characteristics.

		N	mean (sd)	median	p25-p75	p-value
Overall		97,757	74.1 (82.7)	64.2	56.1-70.4	
Day of the week	Monday	13,630	75.9 (83.1)	65.7	58.2-71.8	<.0001 ^d
	Tuesday	23,738	75.1 (84.8)	64.9	57.5-71.4	
	Wednesday	17,880	75.1 (82.1)	65.3	57.3-71.2	
	Thursday	22,713	71.4 (77.5)	62.6	54.3-69.0	
	Friday	19,796	71.8 (79.8)	63.0	53.4-69.0	
Season ^a	Spring	21,072	71.9 (78.4)	63.7	56.2-69.7	<.0001 ^d
	Summer	29,035	73.4 (83.1)	64.2	56.0-70.4	
	Autumn	30,401	74.3 (81.3)	64.1	55.8-70.3	
	Winter	17,249	76.2 (84.8)	65.0	56.4-71.2	
Sex	Female	35,981	75.0 (81.9)	65.1	57.7-71.4	<.0001 ^c
	Male	61,776	73.4 (83.1)	63.6	54.9-69.8	
Social class ^b	<10 points (lowest)	19,071	74.1 (84.1)	64.5	57.1-70.5	<.0001 ^d
	10-12 points	12,524	74.2 (82.2)	62.9	55.8-68.9	
	13-15 points	22,876	72.5 (79.0)	64.7	57.0-70.6	
	16-19 points	22,242	75.3 (82.8)	63.9	55.1-69.9	
	>19 points (highest)	21,044	74.0 (83.2)	64.5	54.7-71.4	
Age-group [years]	<50	17,053	75.9 (84.7)	65.5	58.4-71.1	<.0001 ^d
	50-54	8,329	78.7 (84.2)	67.4	58.7-75.2	
	55-59	12,168	73.6 (79.0)	64.9	56.8-71.9	
	60-64	10,758	71.3 (76.9)	63.2	55.4-69.1	
	60-69	20,818	71.8 (83.5)	62.6	53.9-69.1	
	70-74	16,064	72.4 (79.8)	63.6	56.1-69.4	
	≥75	12,567	71.9 (79.1)	63.5	54.6-70.1	

^aSpring: March to May, summer: June to August, autumn: September to November, winter: December to February.

^bBy Helmert et al. (1990).

^c p -value for differences between medians of subgroups determined with Mann-Whitney U test or

^dKruskall-Wallis test.

Abbreviations: dB(A), A-weighted decibels; L_{eq} , A-weighted equivalent continuous sound pressure levels; max, maximum; min, minimum; N, number of 1-minute segments; p25, 25. percentile; p75, 75. percentile; sd, standard deviation.

Table 3. Regression results of the main model based on time-varying activities in all indoor and outdoor environments.

Variables	Coding	Absolut change of L_{eq} [dB(A)]	CI-	CI+
Whereabouts	Indoors, at home	<i>Reference</i>		
	Indoors, not at home	4.37*	3.96	4.78
	Outside, not in traffic, at home	0.62	-0.12	1.36
	Outside, not in traffic, not at home	3.63*	2.61	4.66
	In traffic	5.94*	5.59	6.30
	Unclear	4.78*	3.69	5.87
Being in a bistro	No	<i>Reference</i>		
	Yes	1.99*	0.99	3.00
Shopping	No	<i>Reference</i>		
	Yes	0.85*	-0.11	1.82
Household chores	No	<i>Reference</i>		
	Yes	2.03*	1.54	2.52
Gardening and manual work	No	<i>Reference</i>		
	Yes	2.89*	1.81	3.98
Physical activity	Sleeping during the day	<i>Reference</i>		
	Resting	-1.60	-3.87	0.66
	Very light / light exertion	3.63*	1.55	5.72
	Moderate exertion	4.28*	2.09	6.47
	Vigorous exertion	5.15*	2.83	7.47
Unclear	3.30*	0.83	5.77	
Particle number concentration ^a	-	0.23*	0.19	0.27
Sex	Female	<i>Reference</i>		
	Male	-1.51*	-2.60	-0.43
Age-group [years]	<50	<i>Reference</i>		
	50-54	2.44*	0.35	4.53
	55-59	-0.60	-2.42	1.22
	60-64	-1.97*	-3.86	-0.08
	65-69	-1.90*	-3.48	-0.33
	70-74	-0.12	-1.84	1.59
≥75	-1.12	-2.95	0.72	
Day of the week	Monday	<i>Reference</i>		
	Tuesday	-1.16	-2.87	0.54
	Wednesday	-1.67	-3.37	0.04
	Thursday	-3.57*	-5.26	-1.88
	Friday	-3.31*	-5.02	-1.60
Half-hourly trend (polynom 3)	-	See Supplemental Material. Figure S1		

^a Absolut change of L_{eq} was calculated per increase of IQR = 15,053 particles/cm³.

* p -value <0.05

Abbreviations: CI-, lower confidence interval; CI+, upper confidence interval; dB(A), A-weighted decibels; IQR, interquartile range; L_{eq} , A-weighted equivalent continuous sound pressure levels.

Table 4. Regression results of the model restricted to times spent at the residences based on time-varying activities and time-invariant variables.

Variables	Coding	Absolut change of L_{eq} [dB(A)]	CI-	CI+
Whereabout	Indoors	<i>Reference</i>		
	Outside	0.85	-0.22	1.92
Houshold chores	No	<i>Reference</i>		
	Yes	2.60*	1.77	3.43
Gardening and manual work	No	<i>Reference</i>		
	Yes	4.28*	2.54	6.02
Physical activity	Sleeping during the day	<i>Reference</i>		
	Resting	0.34	-3.20	3.88
	Very light / light exertion	3.52*	0.60	6.45
	Moderate exertion	3.15*	0.03	6.27
	Vigorous exertion	3.98	-0.11	8.07
Particle number concentration ^a	-	0.21*	0.14	0.29
Distance to the nearest road ^b	-	-0.23	-1.09	0.63
Traffic intensity of the nearest major road ^c	-	-0.25	-0.64	0.14
Habits of opening window	Closed	<i>Reference</i>		
	Open or tilted	-1.43	-4.77	1.92
	Depending on temperature	-1.15	-3.99	1.70
	Unknown	0.32	-6.71	7.35
Sex	Female	<i>Reference</i>		
	Male	-1.91	-4.33	0.52
Age-group [years] ^d	<50	<i>Reference</i>		
	50-54	0.96	-3.08	4.99
	55-59	-3.32	-7.66	1.01
	60-64	-4.25*	-8.44	-0.07
	65-69	-2.37	-6.09	1.35
	70-74	1.15	-3.07	5.38
Day of the week	Monday	<i>Reference</i>		
	Tuesday	-4.11*	-7.57	-0.66
	Wednesday	-2.22	-7.98	3.55
	Thursday	-5.98*	-9.72	-2.24
	Friday	-7.27*	-10.74	-3.81
Hourly Trend (4 th order polynomial)	-	See Supplemental Material. Figure S2A		
Daily Trend (4 th order polynomial)	-	See Supplemental Material. Figure S2B		

^aAbsolut change of L_{eq} was calculated per increase of IQR = 11,810 particles/cm³.

^bAbsolut change of L_{eq} was calculated per increase of IQR = 10.3 meters.

^cAbsolut change of L_{eq} was calculated per increase of IQR = 5,293 cars/day.

^dIndividuals ≥ 75 years of age were not included in Model 2 as they did not spent at least one hour at home

* p -value <0.05

Abbreviations: CI-, lower confidence interval; CI+, upper confidence interval; dB(A), A-weighted decibels; IQR, interquartile range; L_{eq} , A-weighted equivalent continuous sound pressure levels.

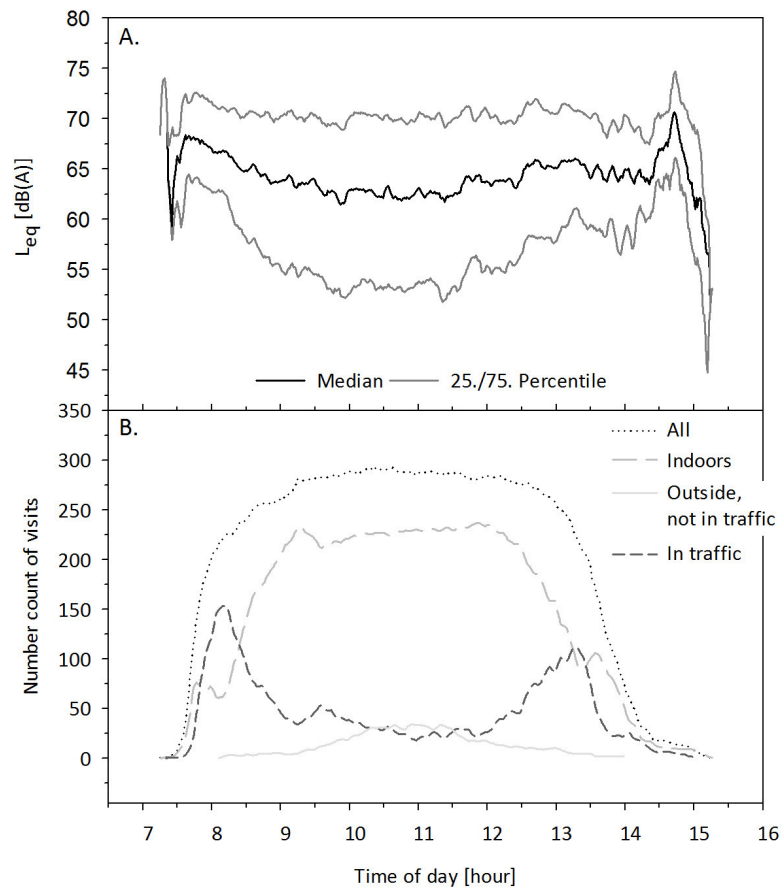


Figure 1. Time-series of A. personal noise exposure for all observations (moving averages for every 5 minutes) and B. number counts overall and separated by whereabouts.

Abbreviations: dB(A), A-weighted decibels; L_{eq} , A-weighted equivalent continuous sound pressure levels

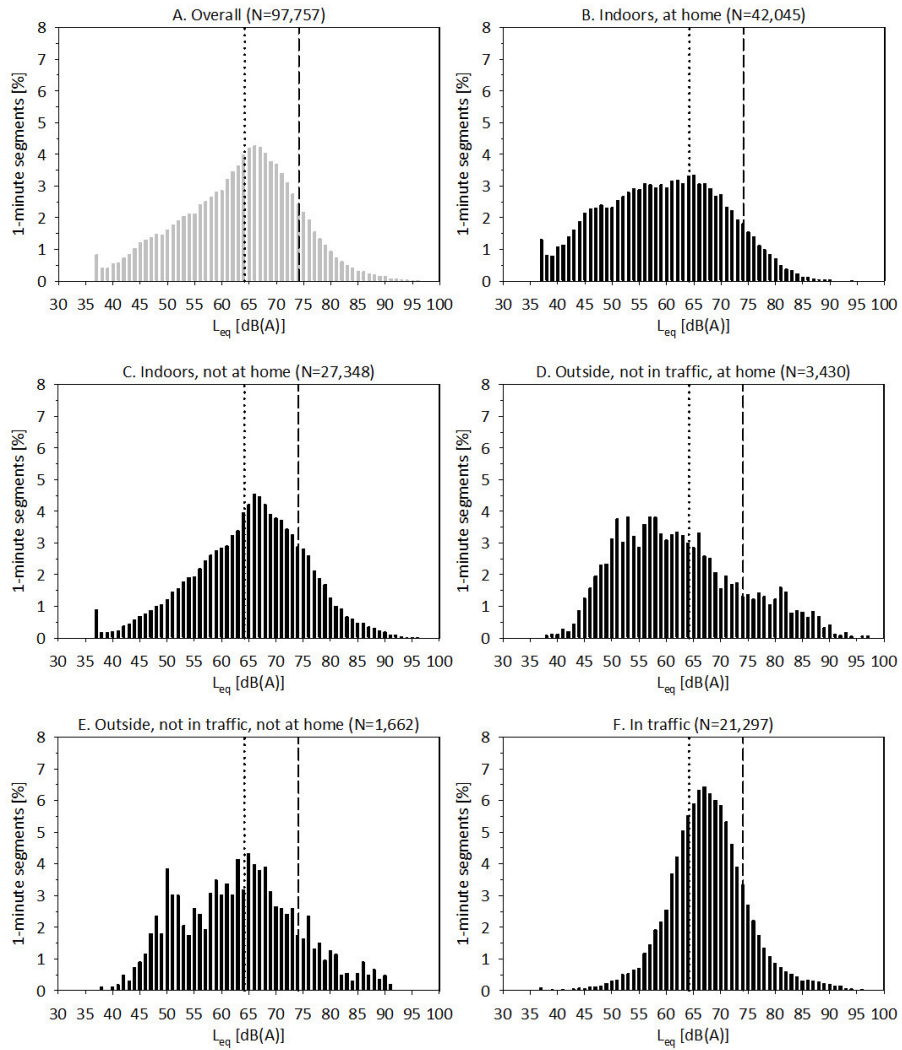


Figure 2. Percent of 1-minute segments per L_{eq} , overall and separated by whereabouts. The dotted line represents the overall median, the short-dashed line represents the overall mean.

Abbreviations: L_{eq} , A-weighted equivalent continuous sound pressure levels; N, number of 1-minute segments; dB(A), A-weighted decibels; IQR, interquartile range.

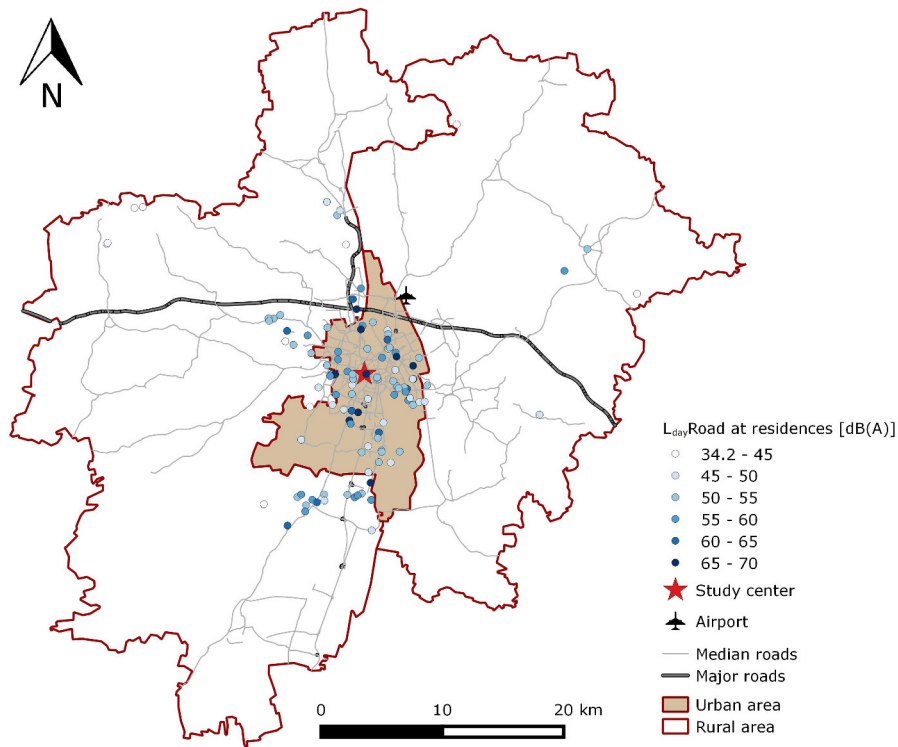


Figure 3. Position of study center, airport and participants' residences. Coordinates of residences were blurred.

Abbreviations: dB(A), A-weighted decibels; L_{day} , maximum annual A-weighted equivalent continuous sound pressure levels during the day (6am to 6pm).

SUPPLEMENTAL MATERIAL

Individual Daytime Noise Exposure in Different Microenvironments

Ute Kraus, Susanne Breitner, Regina Hampel, Kathrin Wolf, Josef Cyrus, Uta Geruschkat, Jianwei Gu, Katja Radon, Annette Peters, Alexandra Schneider

Detailed description of calculating long-term noise exposure.

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|-----------|---|
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Reference

Detailed description of calculating long-term noise exposure

For city dwellers, calculation of long-term noise exposure from road traffic and the railway system was available for 2009 and based on the noise- and air pollution information system (“Lärm- und Luftschadstoff Informationssystem”, LLIS, <http://www.laermkarten.de/augsburg/>) for the city of Augsburg. LLIS was developed by ACCON themselves in the year 2000 using the software CadnaA (Computer Aided noise Abatement; DataKustik GmbH, Greifenberg, Germany). LLIS provides a digital three-dimensional ground model of Augsburg which comprises around 150 km² considering all breaking edges and bridge constructions. Furthermore, all noise abatement walls at public roads with an overall length of 37 km were included in the calculation. Information on ground plan, occupancy, height and reflection characteristics of around 87,000 buildings were taken into account. The road network had an overall length of 750 km in 2009. Roads were described through width, type, road surface and traffic volume including frequency of heavy goods vehicles over 2.8 metric tons. Emissions from the light-rail system comprising a total length of 115 km were also integrated. Information on the railway system derived from the Federal Railway Authority and included the traffic volume, track speed and track ballasts. Noise levels were calculated four meters above the ground. If the home address did not correspond to a building available in LLIS the address was assigned to the nearest building.

For rural inhabitants, ACCON referred to a network of roads and railways generated using georeferenced pictures from google earth and open-street map data. The digital model included roads with a total length of 1,300 km. Data on speed limits and daily traffic counts originates from different dates between the years 2000 and 2011. Data were derived from the Bavarian Ministry of the Interior, Building and Transport, the digital street map of Augsburg, several traffic censuses and surveys. If data on traffic counts were not available like for small towns they were estimated. The railway system included a track length of 200 km. Information on its traffic volume were derived from DB Netz AG, Regionalbereich Süd.

The calculation of L_{day} Aircraft was the same for all participants. The city airport of Augsburg provided data from 2009 including all flight routes and numbers of aircraft movements.

Table S1. Description or coding of potential variables explaining the variability in personal noise exposure.

Variable		Description / Coding
Short-term time trends	Half-hourly trend	<i>Continuous</i>
	Hourly trend	<i>Continuous</i>
	Part of the day	Before midday / after midday
	Day of the week	Monday to Friday
Long-term time trends	Daily trend	<i>Continuous</i>
	Month	January to December
	Season	Spring: March to May; Summer: June to August; Autumn: September to November; Winter: December to February
Diary-based variables	Whereabouts (Main model)	Indoors, at home / indoors, not at home / outside, not in traffic, at home / outside, not in traffic, not at home / in traffic / unclear
	Whereabouts (Restricted to times spent at the residences)	Indoors, at home / outside, at home
	Means of transportation	By foot / by bike / by bus, car, tram, motor cycle
	Physical activity	Sleeping during the day / resting / very light to light exertion / moderate exertion / vigorous exertion / unclear
	Household chores	Yes / no
	Being in a bistro	Yes / no
	Shopping	Yes / no
	Gardening and manual work	Yes / no
Currently being at work	Yes / no	
Other continuous variables	Personally measured particle number concentrations	<i>Continuous</i> ; unit: particles/cm ³
	Ambient relative humidity	<i>Continuous</i> ; unit: %
Time-invariant variables	L_{day} Road	<i>Continuous</i> ; unit: dB(A)
	L_{day} Railway	<i>Continuous</i> ; unit: dB(A)
	L_{day} Aircraft	<i>Continuous</i> ; unit: dB(A)
	Distance to the nearest road ^a	<i>Continuous</i> ; unit: meters
	Distance to the nearest major road ^a	<i>Continuous</i> ; unit: meters
	Traffic intensity of the nearest road ^a	<i>Continuous</i> ; unit: cars/day
	Traffic intensity of the nearest major road ^a	<i>Continuous</i> ; unit: cars/day; a major road was defined as road with a traffic volume ≥ 5000 cars/day

Table S1 *continued*.

Variable	Description / Coding	
Window opening habits	Closed / open or tilted / depending on temperature / unknown	
Direction of the mainly used room	Towards garden / main road / minor road / courtyard	
Area of home address	Urban / rural	
Baseline characteristics	Sex	Women / men
	Social class ^b	<10 points (lowest class)
		10-12 points
		13-15 points
		16-19 points
>19 points (highest class)		
Age	<i>Continuous</i> ; unit: years	
Age-group	<50; 50-54; 55-59;60-64;65-69;70-74;≥75 years	

^aInformation was estimated based on a local road network (Basic Digital Landscape Model) for road traffic with linked road types and traffic counts obtained from the Bavarian State Office for Survey and Geoinformation.

^bBased on Helmert et al. (1990)

Abbreviations: dB(A), A-weighted decibels; L_{day} , maximum annual A-weighted equivalent continuous sound pressure level during the day (6am to 6pm).

Table S2. Baseline characteristics of the study population (N=109).

Variable	mean (sd)	
Age [yrs]	61.6 (11.6)	
Body mass index [kg/m ²]	28.6 (5.3)	
	N (%)	
Male	69 (63.3)	
Social class ^a :	<10 points (lowest class)	21 (19.3)
	10-12 points	17 (15.6)
	13-15 points	26 (23.9)
	16-19 points	22 (20.2)
	>19 points (highest class)	23 (21.1)
Employed	40 (36.7)	

^aBased on Helmert et al. (1990).

^bType 2 diabetes (classified based on a self-reported diagnosis by a physician, medication use, or based on an oral glucose tolerance test) or impaired glucose tolerance (classified based on an oral glucose tolerance test)

^cEver physician diagnosed.

Abbreviation: N, number count; sd, standard deviation.

Table S3. Descriptive statistics for 1-minute segments of continuous variables.

	mean	(sd)	IQR
Main model (N=97,757)			
PNC [particles/cm ³]	20,870	(34,971)	15,053
Relative humidity ^a [%]	73.7	(17.5)	29.3
Age [years]	61.7	(11.4)	18.0
Model restricted to times spent at the residences (N=21,923)			
Distance to the nearest road [m]	20.5	(11.8)	10.3
Distance to the nearest major road ^b [m]	286.9	(238.8)	170.4
Traffic intensity of the nearest road [cars/day]	806.6	(1012.9)	0 ^c
Traffic intensity of the nearest major road [cars/day]	12,150	(11,937)	5,293
PNC [particles/cm ³]	21,681	(41,879)	11,810
Relative humidity ^a [%]	73.6	(17.1)	28.4
Age [years]	61.8	(8.2)	12.0

^aAmbient measurements, 1-hour averages

^bA major road was defined as road with a traffic volume ≥ 5000 cars/day.

^cBecause the 25. percentile, median and 75. Percentile had each the value 500 the IQR was null.

Abbreviations: IQR, interquartile range; N, number count; PNC, particle number concentration; sd, standard deviation.

Table S4. Descriptive statistics for annual averages of long-term noise (L_{day} , [dB(A)]).

	N	mean (sd)	median	p25-p75	p-value
L_{day} Road	109	59.1 (62.4)	52.1	49.8-57.4	
Urban area	59	59.7 (63.1)	51.9	49.9-57.5	0.86
Rural area	50	58.3 (60.8)	53.2	49.0-57.3	
L_{day} Railway	86	49.3 (53.2)	39.2	30.6-47.0	
Urban area	50	49.3 (53.5)	39.5	30.6-46.7	0.84
Rural area	36	49.4 (52.6)	39.2	30.4-47.0	
L_{day} Aircraft	85	31.8 (35.7)	23.9	17.5-29.7	
Urban area	52	28.5 (31.7)	20.8	15.3-28.1	0.0034
Rural area	33	34.4 (37.4)	27.6	22.3-34.8	

Abbreviations: dB(A), A-weighted decibels; L_{day} , maximum annual A-weighted equivalent continuous sound pressure levels during the day (6am to 6pm); N, number count; p25, 25. percentile; p75, 75. percentile; sd, standard deviation.

p-value for differences between urban and rural area determined with Mann-Whitney U test.

Table S5. Descriptive statistics for annual averages of long-term noise (L_{day} , [dB(A)]) used for the model restricted to times spent at the residences.

	N	mean (sd)	median	p25-p75
Per individuals				
L_{day} Road	38	54.6 (55.9)	52.3	49.8-55.3
L_{day} Railway	38	50.3 (54.3)	38.9	29.3-47.9
L_{day} Aircraft	38	30.5 (34.1)	20.5	15.3-29.2
Per 1-minute segments				
L_{day} Road	21,923	54.7 (56.2)	52.0	48.3-55.2
L_{day} Railway	21,923	49.6 (53.7)	38.8	29.3-47.9
L_{day} Aircraft	21,923	28.8 (33.0)	20.3	14.0-27.9

Abbreviations: dB(A), A-weighted decibels; L_{day} , maximum annual A-weighted equivalent continuous sound pressure levels during the day (6am to 6pm); N, number count; p25, 25. percentile; p75, 75. percentile; sd, standard deviation.

Table S6. Descriptive statistics for 1-minute averages of personal noise exposure, overall and separated by possible categorical variables used for the model restricted to times spent at the residences.

		N	mean (sd)	median	p25-p75	p-value
L_{eq} [dB(A)]		21,923	72.3 (83.4)	60.2	51.9-68.1	
Whereabout	Indoors	20,194	72.2 (83.5)	60.1	51.6-68.0	<.0001 ^b
	Outdoors	1,729	73.6 (79.1)	61.0	54.4-68.2	
Household chores	No	17,582	72.3 (83.8)	59.5	51.0-67.6	<.0001 ^b
	Yes	4,341	72.3 (78.7)	62.7	55.2-69.5	
Type of household chores ^a	Doing the laundry	986	68.4 (73.7)	58.3	53.6-64.8	<.0001 ^c
	Doing the dishes	255	69.8 (72.4)	66.0	61.2-70.4	
	Cooking	1,305	72.2 (79.2)	66.1	60.8-70.7	
	Vacuum cleaning	752	74.6 (79.6)	64.0	55.2-73.3	
	Other	1,401	72.6 (78.8)	60.5	52.1-68.1	
Gardening & manual work	No	21,144	72.0 (83.5)	59.9	51.0-67.7	<.0001 ^b
	Yes	779	77.0 (80.0)	72.3	61.2-78.0	
Physical activity	Sleeping	325	64.5 (68.5)	60.0	51.5-63.2	<.0001 ^c
	Reclining	388	67.3 (71.7)	55.5	44.9-66.5	
	Very light to light exertion	19,011	72.4 (83.7)	60.2	51.6-67.9	
	Moderate exertion	1,970	70.9 (74.4)	59.5	53.6-69.9	
	Vigorous exertion	229	76.7 (77.0)	76.5	64.3-78.3	
Habits of opening windows	Closed	2,957	69.8 (74.0)	63.1	55.5-68.7	<.0001 ^c
	Open or left ajar	7,524	72.5 (79.2)	58.9	50.7-67.0	
	Depending on temperature	11,063	72.4 (84.8)	60.1	51.6-68.1	
	„I don't know“	379	75.9 (79.6)	69.7	55.9-75.6	
Direction of window towards...	Garden	7,616	70 (75.6)	60.2	51.0-67.3	<.0001 ^c
	Main road	1,967	72.4 (81.0)	56.2	49.7-64.5	
	Minor road	10,676	72.8 (84.8)	61.1	53.1-69.3	
	Courtyard	1,664	75.4 (81.6)	59.1	51.8-67.2	

Table S6 *continued*.

		N	mean (sd)	median	p25-p75	p-value
Day of week	Monday	1,952	74.3 (81.1)	64.0	57.0-72.1	<.0001 ^c
	Tuesday	7,155	73.4 (85.7)	60.5	52.7-68.3	
	Wednesday	883	71.8 (74.8)	65.2	58.4-71.2	
	Thursday	7,547	70.4 (76.4)	58.7	50.8-67.0	
	Friday	4,386	71.7 (78.8)	58.7	48.6-67.1	
Season	Spring	3,364	71.7 (77.4)	62.1	54.4-69.0	<.0001 ^c
	Summer	7,635	72.9 (85.5)	59.9	51.8-68.2	
	Autumn	7,033	72.3 (80.2)	59.5	50.2-67.4	
	Winter	3,891	71.1 (78.1)	60.4	52.3-68.2	
Sex	Male	12,700	72.8 (84.5)	58.8	50.5-67.1	<.0001 ^b
	Female	9,223	71.4 (78.2)	61.9	53.9-69.1	
Social class (by Helmert)	<10 points (lowest class)	6,104	74.1 (86.1)	60.7	53.3-68.7	<.0001 ^c
	10-12 points	2,364	73.4 (80.1)	60.1	54.3-66.6	
	13-15 points	6,419	71.6 (77.5)	61.9	53.1-69.4	
	16-19 points	2,359	70.2 (75.6)	56.6	47.1-65.8	
	>19 points (highest class)	4,677	69.9 (75.5)	58.3	49.8-67.1	
Age [years]	<50	1,951	71.7 (75.6)	64.2	56.4-70.6	<.0001 ^c
	50-55	3,102	74.4 (80.6)	65.0	55.4-73.0	
	55-60	2,223	68.6 (73.5)	56.4	49.7-64.1	
	60-65	3,000	69.7(75.4)	58.3	51.6-65.3	
	65-70	7,420	71.9(85.6)	57.6	49.4-66.0	
	>70	4,227	73.6(79.6)	62.7	54.7-69.5	
Area	Rural	6,184	70 (76.9)	64.2	56.4-70.6	<.0001 ^b
	Urban	15,739	72.9 (84.1)	65.0	55.4-73.0	

^a Some observations are belonging to more than one group.

p-value for differences between subgroups determined with ^bMann-Whitney U test or ^cKruskall-Wallis test.

Abbreviations: N, number count; p25, 25. percentile; p75, 75. percentile; sd, standard deviation.

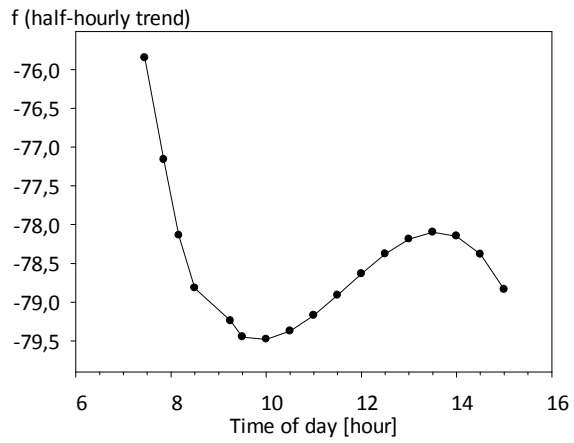


Figure S1. Third order polynomial half-hourly trend line for the main model.

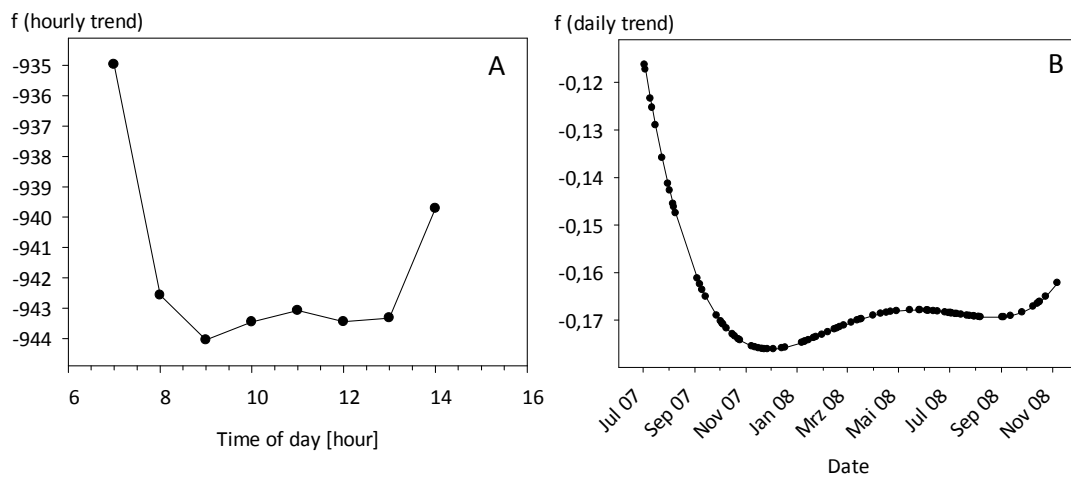


Figure S2. Fourth order polynomial hourly (A) and daily (B) trend line for the model restricted to times spent at the residences

Reference

Helmert U, Shea S, herman B, Greiser E. 1990. Relationship of social class characteristics and risk factors for coronary heart disease in West Germany. Public Health 104:399-416.

5 Personal day-time exposure to ultrafine particles in different microenvironments

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Personal day-time exposure to ultrafine particles in different microenvironments



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ABSTRACT

In order to assess the personal exposure to ultrafine particles (UFP) during individual day-time activities and to investigate the impact of different microenvironments on exposure, we measured personal exposure to particle number concentrations (PNC), a surrogate for UFP, among 112 non-smoking participants in Augsburg, Germany over a nearly two-year period from March 2007 to December 2008. We obtained 337 personal PNC measurements from 112 participants together with dairies of their activities and locations. The measurements lasted on average 5.5 h and contained on average 330 observations. In addition, ambient PNC were measured at an urban background stationary monitoring site. Personal PNC were highly variable between measurements (IQR of mean: 11 780–24 650 cm⁻³) and also within a single measurement. Outdoor personal PNC in traffic environments were about two times higher than in non-traffic environments. Higher indoor personal PNC were associated with activities like cooking, being in a bistro or exposure to passive smoking. Overall, personal and stationary PNC were weakly to moderately correlated ($r < 0.41$). Personal PNC were much higher than stationary PNC in traffic (ratio: 1.5), when shopping (ratio: 2.4), and indoors with water vapor (ratio: 2.5). Additive mixed models were applied to predict personal PNC by participants' activities and locations. Traffic microenvironments were significant determinants for outdoor personal PNC. Being in a bistro, passive smoking, and cooking contributed significantly to an increased indoor personal PNC.

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Introduction

Epidemiological studies have suggested that ultrafine particles (UFP, particles with diameter smaller than 100 nanometers) are associated with pulmonary and cardiovascular diseases (Andersen et al., 2010; Delfino et al., 2005; Ibalid-Mulli et al., 2002; Ruckerl et al., 2011). UFP dominate particle number concentrations (PNC) but contribute very little to particle mass concentrations (PMC). UFP have been found to have health effects of similar magnitude of larger particles, but the effects are suggested to be independent of effects of larger particles (Pekkanen et al., 2002; Stolzel et al., 2007).

UFP show greater spatial variability (Cyrys et al., 2008; Puustinen et al., 2007) than particle mass, which are generally well correlated within an urban area (Cyrys et al., 1998; DeGaetano and Doherty, 2004; Gu et al., 2013; Wilson et al., 2005). Major sources of ambient UFP include vehicles which emit a large amount of particles in the ultrafine mode. Vehicle exhaust (containing both gas vapor and UFP) goes through a rapid physical transformation including dispersion, coagulation and condensation right after being emitted (Kumar et al., 2011). Number concentrations show a decreasing gradient within a few hundred meters downwind of a road/freeway (Sturm et al., 2003; Zhu et al., 2002). Therefore, exposure to UFP can differ greatly between urban microenvironments. Many studies have measured the exposure to air pollution while commuting including car driving, public transport and cycling, as reviewed by Knibbs et al. (2011). These studies indicated that in spite of the limited time spent on commuting, it contributed to a significant amount of the total daily exposure (Berghmans et al., 2009; Dons et al., 2012; Kaur and Nieuwenhuijsen, 2009; Knibbs et al.,

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2011). High UFP concentrations were also found to be related to activities like cooking, smoking, dining in a restaurant (Wallace and Ott, 2011) and vacuum cleaning (Knibbs et al., 2012). Weichenthal et al. (2006) found electric oven use, indoor relative humidity and smoking to be major determinants of mean indoor UFP exposure. When no indoor sources were present, the indoor/outdoor concentrations were found to be well correlated (Cyrus et al., 2004; Diapouli et al., 2007). However, parameters like outdoor concentration, ventilation condition and particle size distribution can affect the indoor exposure (Cyrus et al., 2004; Rim et al., 2013; Zhu et al., 2005). Therefore, assessment of personal exposure to UFP should consider a variety of microenvironments and respective sources.

Individual's exposure to UFP is also closely associated with time-activity patterns, i.e., where and how he/she spends the time. To accurately quantify the personal exposure to UFP, one needs to take both concentrations variability between microenvironments and individual's time-activity pattern into account. However, the direct measurement of personal exposure to UFP and the assessment of the association with microenvironments as well as time-activity patterns have been limited up to now (Buonanno et al., 2012; Cattaneo et al., 2009).

Epidemiological studies on short-term health effects of UFP often relied on data measured from the central monitoring station, which is considered to represent the average population exposure. Due to the highly variable nature of UFP, the relationship between personal exposure and ambient concentrations should be evaluated in depth (HEI, 2013). Such personal measurement will also provide a more accurate estimate on exposure for subsequent epidemiological panel studies.

As part of the Rochester Particulate Matter Center investigations, an epidemiological study focusing on the health effects of UFP was conducted in the city of Augsburg as well as the administrative districts of Augsburg and Aichach-Friedberg, Germany, between March 19th 2007 and December 17th 2008 (Kraus et al., 2013; Rückel et al., 2014). In the framework of this study, we measured personal exposure to UFP among 112 participants, as well as UFP levels at a fixed monitoring station located at the urban background of Augsburg. Each participant also filled in time-activity diaries which provided an excellent opportunity for an exposure study.

The aim of the analysis is to assess the personal exposure to UFP during individual day-time activities and to investigate the impact of different microenvironments i.e. locations or human activities on personal UFP concentrations.

Methods

Study overview

In this study, we measured personal exposure to UFP among 112 participants within a period of nearly two years between March 19th 2007 and December 17th 2008. Each participant was invited to participate in the exposure measurements scheduled every four to six weeks on the same weekday. The measurement was conducted on average 21.1% in the spring, 32.3% in summer, 28.5% in autumn and 18.1% in winter. Participants were recruited from the follow-up examination of the KORA (Cooperative Health Research in the Region of Augsburg) survey (Holle et al., 2005) and were between 32 and 82 years old, with a mean age of 61.7 years. Out of 71 male and 41 female participants, 41 were employed. They were equipped with a bag containing portable devices and were asked to keep a diary for recording their activities and whereabouts whenever their activities or locations changed. All measurements started in the morning at the KORA study center located in the city center of Augsburg. Each measurement lasted about 5 to 6 h. During

this time, the participants were able to follow either their normal daily routines or to choose any other activities they liked within the Augsburg area. At the end of the measurement, the participants went back to the KORA study center where the study nurses reviewed the diary with the participants and downloaded the data from the instruments.

Measurements

We measured personal exposures to PNC with three portable, real-time Condensation Particle Counters (CPC, model 3007, TSI Inc., Shoreview, MN, USA). It measures PNC in the size range of 10 nm to 1 µm in diameter. The zero point was checked on CPC 3007 before and after each measurement by applying a High Efficiency Particulate Air (HEPA) filter. Personally measured PNC were all obtained in 5-second resolution. One-minute averages were calculated if at least two thirds of the values in a 1-minute segment were available. CPC 3007 is sensitive to tilt as the optical chamber may be flooded by the 2-Propanol and the instrument may shut down and stop collecting data. There were 45 measurements with personal PNC data totally missing mainly due to tilt of CPC 3007. These measurements were not included in the study.

In addition, PNC was measured simultaneously with CPC 3025 (TSI Inc, USA, measuring particles 3–2000 nm) at an urban background measurement station. The monitoring site is located at an urban background setting south of the city centre of Augsburg with the nearest busy street about 100 m away. Details regarding the location of the measurement site can be found in Birmili et al. (2010) and Pitz et al. (2008). As shown by Cyrus et al. (2008) this measurement station could be considered representative for urban background PNC in Augsburg, where most of the study participants are living. Stationary PNC was measured in 1-minute resolution.

The CPC 3007s were serviced before the start of the study and during the measurement period by the manufacturer. Inter-comparisons between all portable CPCs and a quality assured Twin Differential Mobility Particle Sizer (TDMPs, measuring particles 3–800 nm) at the measurement station were conducted at regular intervals. Stationary PNC data were also corrected by the TDMPs, which allows a direct comparison between personal and stationary PNC. A detailed description of the comparisons is provided in the Supplementary material.

Air temperature and relative humidity were recorded by data loggers (model Tinytalk 2, Gemini Data Loggers Ltd., Chichester, UK) on a 5-second resolution. One-minute averages were calculated if at least two thirds of the values in a 1-minute segment were available.

Data preparation

A structured/open-ended participant diary (paper-and-pencil diary) was used to collect information on the activities, locations, and transport modes that the participants were using during the measurement period. We were also interested in whether the participants were in a smoking environment or were physically active. Whenever their location or activity changed, the participants were asked to indicate it in the diary. The diary was reviewed by the nurses right after each measurement. In the following data management process, different categorical variables were built. Besides describing whereabouts, transport modes, household duties and passive smoking, a variable named "activity pattern" was created to examine the exposure to UFP under some common daily activities. It comprises the following nine categories: (1) indoors, no exact activity (the participant did not clearly indicate their activities); (2) indoors, with dust lifting activities (e.g., making the bed and dusting); (3) indoors, with water vapor (related to activities producing water vapor such as ironing, coffee making, and cooking etc.); (4) indoors, without dust lifting; (5) shopping (e.g., in the supermarket

or at the cafeteria); (6) outdoors, not in traffic; (7) in traffic: car, bus or train; (8) in traffic: on foot or by bike; and (9) in underground parking lot.

We identified some inconsistencies between PNC peaks and diary activities: for example, we observed extreme high PNC peaks in the indoor environment although participants indicated no activities at all. Such events (1.5% of all data) were considered to contain invalid diary codes, but the measured personal PNC were assumed to be correct. Thus, we included these events for evaluating the average personal exposure of each participant (UFP exposure: individual measurement and case study section) while in following sections (UFP exposure descriptive analysis section to Modeling personal PNC section) – when analyzing the relationship between exposure and diary based information – these data were excluded.

Statistical modeling

We used additive mixed models to predict 1-minute resolution personal PNC by various daily activities and whereabouts. A random intercept for each measurement was applied to account for the differences between PNC measurements. We included first order auto correlation (AR1) of $\log(\text{personal PNC})$ to account for the dependencies of consequent PNC measurements in the modeling. We modeled outdoor and indoor personal PNC separately, as activities and potential major sources of UFP were largely different between the two microenvironments. For both models, a forward selection was performed to select the optimized model by minimizing the model's Akaike's information criterion (AIC) (Akaike, 1973). For outdoor PNC, we included the activity pattern as independent variable. The outdoor activity pattern is a categorical variable and contains four factors: (1) outdoor, not in traffic; (2) in traffic: car, bus or train; (3) in traffic: on foot or by bike; and (4) in underground parking lot. For indoor model, we used indoor activities as independent variables including (whether or not) being in a bistro, passive smoking, cooking, resting, washing, sleeping, being in the basement, being in the bathroom and vacuuming. These variables are categorical variables (yes/no). In addition, for both models we considered stationary PNC as a possible predictor. Because the distribution of both personal and stationary PNC was highly skewed they were log-transformed to fulfill a Gaussian distribution of the errors. Furthermore, we took time of day, month of the year, relative humidity and air temperature represented by smooth functions into account.

The model procedure was carried out in R (version 2.15.3) using the "mgcv" package (<http://cran.r-project.org/web/packages/mgcv/mgcv.pdf>).

Results

UFP exposure: Individual measurement and case study

Overall, 337 effective and valid PNC measurements of 112 participants were obtained (129 757-minute observations). The individual measurements lasted 5.5 h on average and roughly covered the time between 7:30 am and 2:30 pm. Personal exposure to PNC averaged over each measurement showed a wide range of 2927 to 91 759 particles per cm^3 (cm^{-3}) with an overall average of 20 422 cm^{-3} .

Fig. 1 shows the box plots of personal and stationary PNC averaged by each measurement in four seasons. Stationary PNC was lower in summer and higher in other seasons, especially in winter. Personal PNC showed higher variability within each season, and less variability between seasons.

Fig. 2 shows the exemplary time-series of personal PNC measured by one participant, his/her activities as well as the stationary

PNC measured at the same time at the fixed monitoring station, on January 10, 2008 (Fig. 2a) and February 7, 2008 (Fig. 2b), respectively, to illustrate the typical patterning of personal PNC and diary activities.

On January 10, 2008, only three major activities were recorded and the participant spent most of the time in the office. The personal PNC showed simpler trends with higher values in the beginning and at the end of the measurement when walking from/to the study center. Personal PNC remained at lower levels when working in the office. Note that, in this case, personal PNC in the office is comparable with stationary PNC.

Fig. 2b shows another measurement for the same participant. The personal PNC fluctuated greatly during the 6 h of measurement. Very high PNC peaks were observed between 7:30 and 8:30 am when driving, and personal PNC varied greatly (mean \pm SD, 34 323 \pm 19 720 cm^{-3}). Personal PNC were much smoother during shopping between 8:30 and 9:40 am and two supermarkets showed different mean PNC levels (11 584 vs. 4062 cm^{-3}). No physical activities were recorded between 9:40 and 11:00 am, when personal PNC were steady and remained at low levels of 2823 \pm 291 cm^{-3} . The measured personal PNC at the neighbors were 7811 \pm 974 cm^{-3} , which was higher than in the participant's own home. Between 11:42 am and 12:34 pm, when vacuuming, personal PNC had an average of 15 842 \pm 14 079 cm^{-3} with rapid fluctuations. Average personal PNC of this measurement were 14 744 \pm 14 170 cm^{-3} and equivalent stationary PNC were 12 007 \pm 5568 cm^{-3} . A difference of 23% in averaged levels was observed ($p < 0.05$ for Mann-Whitney test), however, personal PNC had much higher variability.

UFP exposure descriptive analysis

Table 1 gives a summary of personal PNC for different whereabouts and transport modes. In this study, the participants spent 69% of their time indoors, 23% in traffic environment, and 5% outdoors. Highest exposure to PNC was found within traffic environment, followed by indoor environment, and outdoors but in the non-traffic environment. In our study when participants were in traffic, they were mostly exposed as car driver (44%) and pedestrian (38%). The other microenvironments include being in public transport as a passenger (15%) and riding a bicycle (3%). Median personal PNC in different transport modes were high, ranging from 16 506 to 19 974 cm^{-3} . There were walking activities (94 h) in the non-traffic environment. Significantly lower PNC were observed when walking in the non-traffic environment than in traffic ($p < 0.01$).

Different PNC were observed between activities. Low personal PNC were found being outdoors but not in traffic, being indoors with no exact activity, and being indoors with and without dust lifting. Activities including shopping, indoors with water vapor, being in traffic or in an underground parking lot were related to high personal PNC.

When in indoor environment, participants spent 13% of time doing household duties, such as cooking, vacuum cleaning and washing. PNC were elevated when doing household duties compared with non-household duties ($p < 0.01$). Higher PNC were also found when cooking and washing. Personal PNC under passive smoking indoors were highly increased compared with smoke-free environment.

Time-series of UFP exposure

Fig. 3 shows the frequencies of the diary information including whereabouts, transport modes and household duties, respectively, and personal and stationary PNC averaged by time of day. Measurements were mainly between 8:00 am and 2:00 pm (Fig. 3a).

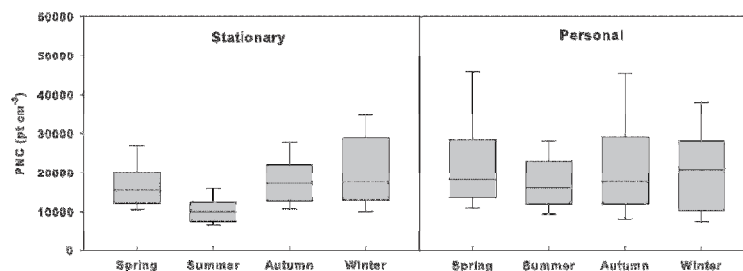


Fig. 1. Box plots of stationary and personal PNC averaged by each measurement in four seasons (spring: March–May; summer: June–August; autumn: September–November; winter: December–February). The lines in the boxes are median values. Lower and upper whiskers indicate the 5 and 95 percentile, respectively.

Participants were more frequently in the traffic environment in the morning (around 8:00 am) and the afternoon (around 1:00 pm). Within traffic environment (Fig. 3b), car driving, taking public transport, going by bike and walking in traffic all showed peaks in the morning and afternoon. For indoor environment, household duties (Fig. 3c) showed high frequencies between 10:00 am and noon, among which, cooking activities peaked between 11:00 am and 12:00 pm, washing activities showed higher frequencies around 11:00 am while vacuuming activities spread quite evenly from 9:30 am to 12:00 pm.

Fig. 3d shows the averaged time series of personal and stationary PNC. Stationary PNC showed a more steady decrease from morning until midday than personal PNC. In contrast, two peaks in personal PNC time-series were observed with one in the morning and the other around noon until afternoon.

Relationship between personal and stationary PNC

The relationship between personal and stationary PNC includes the difference in absolute concentration and their temporal

correlation. Table 2 summarizes the average personal and stationary PNC values, as well as relative differences and ratios between them. In most cases/microenvironments, personal and stationary PNC were weakly correlated for both 1-minute data and data averaged by measurement. The average values are shown separately by whereabouts and activity pattern. For all microenvironments combined, personal PNC were 17% higher than stationary PNC. Considering specific microenvironments, personal PNC in traffic were 50% higher than stationary PNC, 10% higher for being indoors and 7% higher for being outdoors but not in traffic. Indoors with no exact activities and indoors without dust lifting showed marginal differences of -3% between personal and stationary PNC. Traffic-related activities showed larger differences between personal and stationary PNC. The largest differences were observed for indoor activities with water vapor (151%) and shopping (139%).

Modeling personal PNC

For both models, stationary PNC was tested and in both cases great increases in AIC values were observed, indicating the

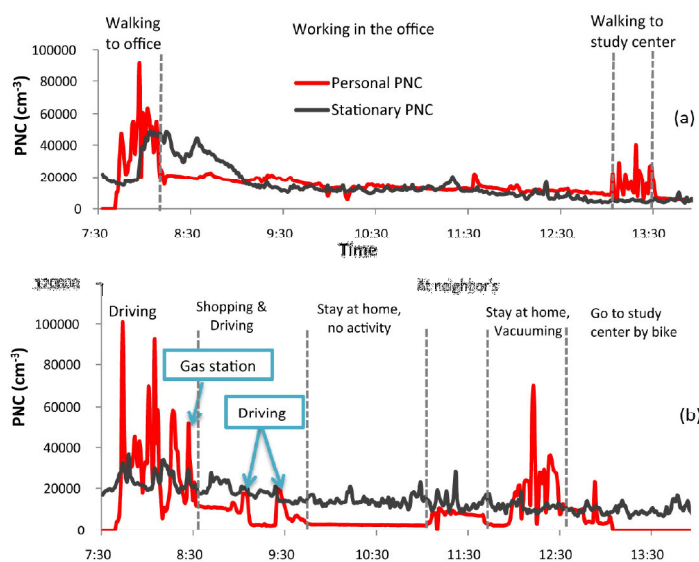


Fig. 2. Personal PNC, major activities and whereabouts as well as the stationary PNC. Time-series were measured by the same participant on (a) January 10, 2008 and (b) February 7, 2008, respectively.

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Table 1
Descriptive statistics of 1-minute personal exposure to UFP by whereabouts, transports and other activities.

Diary information		PNC (cm^{-3})							
		N (h)	Mean	SD ^a	Min	25p ^b	Median	75p ^b	Max
Whereabouts	Indoors	1214	17 220	31 475	509	5210	8821	15 759	593 728
	Outdoors, not in traffic	94	13 636	21 589	1046	6619	9086	12 763	465 054
	Outdoors, in traffic	412	26 394	29 537	570	9605	18 058	32 908	494 463
Transport modes	Unclear	36	15 708	15 994	1357	6952	10 111	18 683	223 051
	Car driving	181	28 425	31 869	714	9212	18 677	36 756	494 463
	Public transport	62	26 688	24 825	1954	11 853	19 974	33 221	433 379
	Bicycle riding	12	35 844	58 754	2223	10 396	19 075	34 560	343 871
	On foot, in traffic	157	23 209	24 308	570	9176	16 506	28 682	434 719
Activity pattern	On foot, not in traffic	94	13 621	21 605	1046	6604	9075	12 742	465 054
	Unclear	20	16 225	17 698	1550	6530	9440	20 380	223 051
	Indoors, no exact activities	157	14 591	29 571	622	4939	7881	13 266	593 728
	Indoors, with dust lifting	47	18 681	35 860	762	4851	8728	15 435	518 513
	Indoors, with water vapor	45	45 615	68 368	2202	7830	17 933	50 654	561 148
	Indoors, without dust lifting	846	15 151	24 598	509	5169	8716	14 918	541 060
	Shopping	36	39 250	58 156	1284	9497	18 733	38 243	311 336
	Outdoors, not in traffic	94	13 636	21 589	1046	6619	9086	12 763	465 054
	In traffic: car, bus or train	244	27 980	30 229	714	9883	19 100	35 759	494 463
	In traffic: on foot or by bike	149	23 817	29 081	570	9146	16 212	28 455	434 719
	Underground parking lot	19	26 310	21 728	1858	10 756	20 373	34 775	184 893
Household duties ^c	Unclear	119	16 910	30 494	944	5298	8463	16 337	426 593
	Yes	153	22 533	41 715	532	5379	9854	19 683	561 148
Household duties ^b	No	1603	18 827	29 301	509	5973	10 240	19 744	593 728
	Cooking	50	39 279	64 524	2320	8167	17 108	41 062	561 148
	Vacuuming	29	13 063	14 079	762	5268	9340	15 508	121 392
	Washing	22	29 665	41 554	762	6248	13 125	31 558	214 012
Passive smoking	Everything else	62	13 844	23 342	532	4648	7 327	12 750	342 545
	Yes, indoors	13	65 042	88 632	1041	10 911	25 597	61 508	374 428
	Yes, outdoors	12	19 689	22 445	3296	6097	10 298	25 114	165 069
	No, indoors	1170	16 690	29 891	509	5186	8741	15 466	593 728
No, outdoors	496	23 727	28 168	570	8 555	14 953	29 034	494 463	

^a SD: standard deviation.

^b 25p and 75p: 25 and 75 percentiles, respectively.

^c Codes only apply to indoor environment, and one observation may contain more than one household duties.

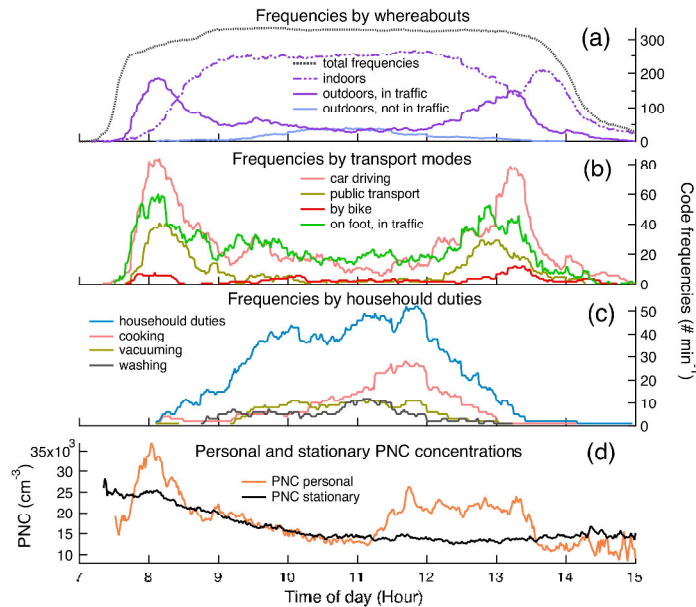


Fig. 3. Averaged time-series of the frequencies of major diary information: (a) whereabouts, (b) transport modes and (c) household duties, as well as (d) personal and stationary particle number concentrations.

Table 2
Average personal and stationary PNC, the ratios, and Spearman's rank correlations.

Diary information	Personal PNC ^a	Stationary PNC ^a	Ratio (<i>p/s</i>)	<i>r</i> ₁ ^b	<i>r</i> ₂ ^b
All microenvironments combined	19 100	16 320	1.17	0.20	0.29
Whereabouts					
Indoors	17 220	15 676	1.10	0.16	0.21
Outdoors not in traffic	13 636	12 706	1.07	0.36	0.34
Outdoors in traffic	26 394	17 628	1.50	0.32	0.44
Activity pattern					
Indoors no exact activities	14 591	15 056	0.97	0.09	0.11
Indoors with dust lifting	18 681	14 592	1.28	0.41	0.33
Indoors with water vapor	45 615	18 185	2.51	0.16	0.19
Indoors without dust lifting	45 151	15 611	0.97	0.14	0.19
Shopping	39 230	16 396	2.39	0.19	0.20
Outdoors not in traffic	13 636	12 706	1.07	0.37	0.36
In traffic: car bus or train	27 980	18 052	1.55	0.30	0.35
In traffic: on foot or by bike	23 817	16 992	1.40	0.36	0.49
Underground parking lot	26 310	16 891	1.56	0.23	0.19
Not clear	16 910	15 853	1.07	0.17	0.21

^a In cm⁻³.^b *r*₁ and *r*₂ are coefficients of Spearman's rank correlation between personal and stationary PNC for 1-minute data, and data averaged by measurement, respectively.**Table 3**
Model results for outdoor personal PNC.

Variables	Estimate	CI ^{-a}	CI ^{+a}	<i>p</i> Value
Intercept	13 996	13 122	14 962	<0.001
	Relative change of the mean (%)			
	Reference			
Activity pattern				
Outdoor, not in traffic				
In traffic: bus, car or train	24%	18%	31%	<0.001
In traffic: on foot or by bike	18%	12%	25%	<0.001
In underground parking lot	23%	14%	32%	<0.001

^a CI⁻, CI⁺: lower and upper confidence interval.

inclusion of stationary PNC is not preferred. Stationary PNC was found significant in outdoor model ($p < 0.001$), but insignificant in indoor model ($p = 0.9$). We thus report for both models the results without stationary PNC.

Modeling outdoor personal PNC

Based on the forward selection procedure, time of day and month of year were included as smooth functions. Table 3 gives the model results for outdoor personal PNC. The model had an intercept of 4.146 (equivalent to 13 996 cm⁻³). Regarding the activity pattern, all three microenvironments in traffic contributed significantly to personal PNC compared with non-traffic environments (with a factor of 1.24, 1.18 and 1.23, respectively). The model can explain 13.3% of the variance of log(outdoor personal PNC).

Modeling indoor personal PNC

In the modeling for indoor personal PNC, time of day and month of year were included as smooth functions. Nine independent variables were finally included in the model, which were being in a bistro, passive smoking, being in the bathroom, sleeping, washing, cooking, resting, vacuuming and being in the basement. The model had an intercept of 3.951 (equivalent to 9 528 cm⁻³). As shown in Table 4, being in a bistro, passive smoking and cooking contributed to an increase of personal PNC (with a factor of 1.77, 1.44 and 1.06, respectively), while the other variables contributed to a decrease of personal PNC (with a factor in the range of 0.85–0.96). The model explained 6.1% of the variance of log(indoor personal PNC).

Discussion

In this study we evaluated the short-term variation of average personal exposure to PNC in different microenvironments. It is visible that high temporal variability characterizes personal exposure to UFP. Averaged personal PNC varied between different measurements and within one measurement. The large variation of PNC levels was observed between microenvironments. Personal PNC

fluctuated greatly within traffic related microenvironments. Large differences when driving may result from car ventilation settings (Hudda et al., 2012), traffic conditions (congested condition, busy or empty road and the emissions of nearby cars) and road/street characteristics (Dons et al., 2013; Scungio et al., 2013). In contrast, PNC were very steady when indoors without any activities. In addition, we observed different PNC levels between the same type of locations/activities, for example between two different supermarkets, and between indoor at home and indoor in the office. Such differences can be caused by indoor particle sources, and by different infiltration of particles from the outdoors (e.g. type of building, ventilation conditions). This should be considered when developing the

Table 4
Model results for indoor personal PNC.

Variables ^a	Estimate	CI ^{-b}	CI ^{+b}	<i>p</i> Value
Intercept	9528	8933	10 162	<0.001
	Relative change of the mean (%)			
Being in a bistro				
No				
Yes	77%	69%	85%	<0.001
Passive smoking				
No				
Yes	44%	35%	53%	<0.001
Being in the bathroom				
No				
Yes	-11%	-14%	-8%	<0.001
Sleeping				
No				
Yes	-15%	-21%	-8%	<0.001
Washing				
No				
Yes	-13%	-17%	-8%	<0.001
Cooking				
No				
Yes	6%	2%	10%	<0.001
Resting				
No				
Yes	-4%	-9%	-2%	<0.01
Vacuuming				
No				
Yes	-8%	-12%	-3%	<0.01
Being in the basement				
No				
Yes	-5%	-9%	-1%	<0.05

^a Variables are listed in the order of inclusion in the model.^b CI⁻, CI⁺: lower and upper 95% confidence interval.

exposure assessment for UFP based on microenvironments/time-activity pattern.

We found personal PNC with dust lifting activities not significantly different ($p=0.80$) from those without dust lifting activities, indicating that these activities contributed little to UFP emission. PNC during vacuuming were lower compared with other household duties, which indicates that vacuuming is not a significant indoor UFP source indoors in this study. Vacuuming has been reported as an indoor source of UFP (Knibbs et al., 2012), but the amount of generated particles is highly variable depending on the types of vacuum cleaner used and ventilation condition, which are unknown in this study.

We observed different levels of PNC in different microenvironments which were recorded by means of diary codes. It is important to mention that the diary codes were built not only considering the factors that might influence the PNC (like traffic and indoor activities), but also the simplicity and feasibility for the participants to handle with. Because of that it is possible that for some specific microenvironments no codes were available or the codes were not precise enough. In addition, such diaries have further limitations including posing challenge for participants (especially the old) and leading to missing data or errors in the diary. The imprecise time-activity diary information could introduce bias in estimation of PNC in each specific microenvironment. In panel studies estimating the individual (personal) exposure by using time-weighted pollutant concentrations in each microenvironment without measurements such imprecise information leads to uncertainty and bias to risk estimates. To address the limitations of diaries the use of GPS logger for collecting personal time-location information was recommended recently (Breen et al., 2014). It reduces the errors arising from manual recording and coding. Furthermore, collecting of time-activity information within one specific microenvironment might allow better understanding of the PNC variability within that microenvironment.

In this study, participants were asked to come to the study center in the early morning and come back in the afternoon. Thus, they would inevitably go through traffic environments during these day-times. This design was chosen mostly due to the limitation of CPC instrument, which can measure only about 6 h each time. This common behavior pattern for all study participants resulted in two PNC peak periods; the first one in the beginning and the second one at the end of each measurement (Fig. 3a and b). The elevated PNC were measured during the traveling from the study center in the morning and to the study center in the afternoon (mostly in traffic environment). This pattern is similar with pattern of people who commute to work. Note that we don't intend to measure the representative exposure of the population; rather, we aim to study the relationship between personal exposure to PNC and different activities in different microenvironments. A broad peak of personal PNC was observed at midday and in the afternoon. The midday peak can be explained by indoor activities such as cooking, which was associated with very high PNC as shown in Table 1.

When studying the relationship between personal and stationary PNC, the overall difference between the mean values was 17% (personal PNC: $19\,100\text{ cm}^{-3}$, stationary PNC: $16\,320\text{ cm}^{-3}$), indicating that using the stationary PNC as a surrogate of averaged exposure of a group of population will not yield a large bias. However, for an individual, the personal PNC can differ greatly from the stationary PNC, and the differences were highly associated with the locations and activities of participants.

Multivariable statistical models aimed at determining influences of the personal PNC. The models explained only a small fraction of the variance in personal PNC. The obtained r^2 values were 0.13 and 0.06 for outdoor and indoor models, respectively. The unexplained variance can be attributed to the variance of PNC within same microenvironment/activity, between participants, as

well as to the errors of the measurement, missing data and errors in recording the activities in the diary.

To summarize, we measured personal PNC among 112 participants (covering 337 days) and studied the relationship between personal PNC and different microenvironments, activities, as well as stationary PNC. PNC changed greatly and rapidly with the changing of microenvironments and participants' activities. Mean exposure among participants varied also greatly due to different microenvironments/choices of activities. High personal PNC were associated with traffic, as well as indoor activities including cooking, passive smoking and being in a bistro, which has also been confirmed by additive mixed models. The models showed that traffic microenvironments increased the personal PNC by a factor of 1.18–1.24, compared with non-traffic environments; while being in a bistro, passive smoking and cooking increased personal PNC by a factor of 1.77, 1.44 and 1.04, respectively. Stationary PNC correlated weakly to moderately with personal PNC. The overall average of personal and stationary PNC for all participants were similar (17% difference), however, there were much larger differences when in traffic and under some indoor activities.

Conclusions

Personal exposures to UFPs were the highest in outdoor traffic environment, followed by indoor environments and were the lowest in outdoor not in traffic environment. Indoor activities associated with elevated exposures included passive smoking and cooking activities. Exposure levels in shopping and when water vapor is present were also higher than stationary urban background levels. UFP exposures vary substantially in microenvironments and by activities and therefore stationary outdoor monitoring is a poor predictor of actual personal exposures.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ijheh.2014.10.002>.

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6 Individual daytime noise exposure during routine activities and heart rate variability in adults: A repeated measures study

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Individual Daytime Noise Exposure during Routine Activities and Heart Rate Variability in Adults: A Repeated Measures Study

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BACKGROUND: Epidemiological studies have demonstrated associations between noise exposure and cardiovascular events. However, there have been few studies of possible underlying mechanisms.

OBJECTIVES: We examined the association between individual daytime noise exposure and heart rate variability (HRV).

METHODS: In a prospective panel study in Augsburg, Germany (March 2007–December 2008), 110 individuals participated in 326 electrocardiogram recordings with a mean duration of 6 hr. Five-minute averages of heart rate (HR) and HRV parameters were determined. Individual noise exposure was measured as A-weighted equivalent continuous sound pressure levels (L_{eq}). Effects were estimated using additive mixed models adjusted for long- and short-term time trends and physical activity. Due to nonlinear exposure–response functions, we performed piecewise linear analyses with a cut-off point at 65 dB(A).

RESULTS: Concurrent increases of 5dB(A) in $L_{eq} < 65$ dB(A) were associated with increases in HR (percent change of mean value: 1.48%; 95% CI: 1.37, 1.60%) and the ratio of low-frequency (LF) to high-frequency (HF) power (4.89%; 95% CI: 3.48, 6.32%), and with decreases in LF (–3.77%; 95% CI: –5.49, –2.02%) and HF (–8.56%; 95% CI: –10.31, –6.78%) power. Standard deviation of normal-to-normal intervals (SDNN) was positively associated with concurrent noise < 65 dB(A) (5.74%; 95% CI: 5.13, 6.36) but negatively associated with noise lagged by 5–15 min (–0.53% to –0.69%). Associations with cardiac function were less pronounced for noise ≥ 65 dB(A), with some in opposite directions from associations with noise < 65 dB(A). Concurrent associations were modified by sex and age.

CONCLUSIONS: Individual daytime noise exposure was associated with immediate changes in HRV, suggesting a possible mechanism linking noise to cardiovascular risk. Noise at lower levels may have health consequences beyond those resulting from “fight-or-flight” responses to high levels of noise.

KEY WORDS: autonomic nervous system, epidemiology, heart rate variability, noise exposure, short-term changes. *Environ Health Perspect* 121:607–612 (2013). <http://dx.doi.org/10.1289/ehp.1205606> [Online 19 March 2013]

Epidemiological studies indicate that noise exposure is associated with adverse cardiovascular health effects (Babisch 2006; Ising and Kruppa 2004; Tonci et al. 2010). More precisely, studies on chronic noise exposure have suggested an association with elevated blood pressure (Chang et al. 2003; Fogari et al. 2001), hypertension or the use of anti-hypertensive medication (Bartregard et al. 2009; Bluhm et al. 2007; de Kluienaar et al. 2007; Jarup et al. 2008), ischemic heart disease including myocardial infarction (MI) (Babisch et al. 2005; Selander et al. 2009), and mortality from MI (Huss et al. 2010). Studies of short-term cardiovascular effects have reported elevated blood pressure levels and increased heart rate (HR) in association with noise exposure (Chang et al. 2009; Haralabidis et al. 2008; Lusk et al. 2004). Most previous studies have focused on effects of higher noise intensities that were generated by specific sources, particularly aircraft, road traffic, and occupational noise and noise produced in laboratory settings. Information about effects of individual noise exposure

during everyday life, which may include a wide range of noise intensities, is very limited.

Underlying mechanisms linking noise to enhanced cardiovascular risk are rarely explored in epidemiological studies. A potential mechanistic pathway is that noise exposure serves as a stressor that increases the sympathetic tone of the autonomic nervous system, either directly or indirectly via hormone release, resulting in a “fight-or-flight” reaction (Babisch 2003; Babisch et al. 2001; Henry 1992; Ising et al. 2003). An effect of noise on the autonomic nervous system may be assessed through time- and frequency-domain analysis of heart rate variability (HRV) (Malik 1996). Decreased HRV is considered a risk factor for adverse cardiovascular events (Buccellati et al. 2009; Gerritsen et al. 2001). For instance, a reduction in the standard deviation of normal-to-normal intervals (SDNN) is a better predictor of death due to progressive heart failure than are other conventional clinical measurements (Nolan et al. 1998). However, there have been relatively few studies of the association between noise exposure and HRV, and results have

been inconsistent. Two experimental studies that examined the effects of white noise, which contains every frequency within the range of human hearing in equal amounts, found increased low frequency (LF) power but no changes in high frequency (HF) power in association with short-duration white noise, consistent with an effect mediated by an increase in sympathetic tone (Björ et al. 2007; Lee et al. 2010). In contrast, authors of a recent field study reported a decrease in respiratory sinus arrhythmia associated with indoor traffic noise exposure during sleep, consistent with an effect mediated by a reduction in parasympathetic tone (Graham et al. 2009).

The objective of the present epidemiological study was to provide further insight into the biological mechanism of cardiovascular health effects associated with noise by investigating the acute effects of routine daytime noise exposure on HR and HRV parameters in individuals.

Methods

Study design. As part of the Rochester Particulate Matter Center investigations, a prospective panel study was conducted in Augsburg, Germany, between 19 March 2007 and 17 December 2008. Participants were

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recruited from the follow up examination of the KORA (Cooperative Health Research in the Region of Augsburg) survey 2000 (Holle et al. 2005), which was conducted in 2006–2008. In a baseline interview, participants gave information on health status, medication use, disease status, and smoking history. Because of several other objectives of the study, general exclusion criteria were smoking during the preceding 12 months, intake of platelet aggregation inhibitors except for acetylsalicylic acid, an MI and/or interventional procedure (e.g., bypass surgery) < 6 months before study entry, and chronic inflammatory diseases such as Crohn's disease, colitis ulcerosa, or rheumatoid arthritis. In addition, participants were excluded from the present analysis if they had an implanted pacemaker, atrial fibrillation, allergy to latex, or thrombosis or a shunt in an arm.

Participants were invited to complete up to four repeated electrocardiogram (ECG) recordings and individual exposure measurements. The examinations were scheduled every 4–6 weeks on the same weekday between 0730 and 1500 hours. During the measurement periods, participants were free to pursue their daily routines. Participants recorded all of their activities and whereabouts in a diary, and were asked to note whenever they felt annoyed by noise. For detailed information on the diary, see Supplemental Material, p. 2 (<http://dx.doi.org/10.1289/ehp.1205606>). A variable indicating physical activity was derived by quantifying each diary entry on the basis of a metabolic equivalent unit (Peters et al. 2005). The categories were 1) sleeping, 2) reclining, 3) very light to light exertion (e.g., eating, reading, cooking, slow walking, car driving), 4) moderate exertion, with deep breathing (e.g., biking, light gardening, vacuum cleaning), 5) vigorous exertion, with panting (e.g., jogging, heavy gardening, climbing stairs), and 6) heavy exertion, with gasping (running, shoveling heavy snow).

Written informed consent was obtained from all participants. The study protocol was approved by the German Ethics Committee of the Bayerische Landesärztekammer, Munich, Germany.

ECG monitoring and HRV parameters. To assess cardiac rhythm, participants were equipped with a 12-lead Mortara H12 digital Holter recorder (Mortara Instrument, Milwaukee, WI, USA). ECG recordings were analyzed at the University of Rochester Medical Center (Rochester, NY, USA), and ECG parameters were computed according to Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology recommendations (Malik 1996). In addition to HR we evaluated the time domain HRV parameters SDNN and RMSSD (root-mean square of successive differences), and the frequency-domain HRV

parameters LF power (0.04–0.15 Hz, normalized units), HF power (0.15–0.40 Hz, normalized units), and the LF:HF ratio. Five-minute averages of HR and time-domain HRV parameters were determined for every 5-min interval with at least 200 beats recorded, and 5-min averages of frequency-domain parameters were determined for intervals with at least 300 beats recorded. Only individuals with at least one ECG recording with a duration of > 2 hr were included in analyses.

Individual exposure. Measurements were made using a noise dosimeter (Spark[®] model 703; Larson Davis Inc., Depew, NY, USA) with the microphone attached to the participant's collar close to the ear. These instruments were successfully applied in a previous study (Weinmann et al. 2012). Noise exposure was measured as A-weighted equivalent continuous sound pressure levels (L_{eq}) reported in units of A-weighted decibels [dB(A)]. The A-weighted system is an expression of the relative loudness of sounds as perceived by the human ear. The dosimeters were calibrated once a week and had a measurement range of 40–115 dB with a detector accuracy of < 0.7 dB error. Measurements below the lower limit of detection (LOD) were assigned a value of 37 dB, and those above the upper LOD were assigned a value of 115 dB (Radon 2007). In addition to noise, particle number concentrations (PNC)—an indicator for ultrafine particles—were measured using a portable condensation particle counter (model 3007; TSI Inc., Shoreview, MN, USA) that covered a diameter range from 10 nm to 1 μ m. For both, L_{eq} and PNC, 5-min averages were temporally aligned to the 5-min averages of the outcome data and were determined if at least two-thirds of the values in a 5-min segment were available.

Statistical analyses. To assess acute effects of individual noise exposure on ECG parameters, we applied additive mixed models with a random participant effect to adjust for differences in individual levels of cardiac rhythm between all participants. To account for correlations between repeated ECG measures within the same individual, we used a compound symmetry covariance structure and included the lagged outcome in the model. Except for HR, all outcome variables were log-transformed to produce normally distributed residuals. We analyzed each ECG parameter in separate models adjusted for a set of confounders that minimized Akaike's information criterion (Akaike 1973). Long-term and daily time trend were forced into all models, along with physical activity. Trend variables were modeled as untransformed linear variables or, using penalized splines or polynomials (up to 4 degrees) to allow for nonlinear exposure response functions, to optimize model fit (Grevén et al. 2006). Weekday and season were evaluated as

potential confounders but were not included in final models because they did not improve model fit. Additionally, all HRV parameter models were adjusted for HR. In addition to including concurrent L_{eq} in the final models, all models included variables indicating L_{eq} lagged in 5-min intervals up to 15 min (0–5, 5–10, and 10–15 min). Covariates included in the final models for each outcome are listed in Supplemental Material, Table S1 (<http://dx.doi.org/10.1289/ehp.1205606>).

To assess the potential for overcontrolling by HR, we also evaluated associations between HRV parameters and L_{eq} without adjusting for HR. Results were consistent for all parameters except RMSSD, which showed associations with L_{eq} that were in opposite directions depending on adjustment (data not shown). Therefore, we considered the association to be unstable and do not report results for RMSSD here.

A preliminary analysis showed nonlinear exposure–response functions for associations between concurrent noise and all ECG parameters [see Supplemental Material, Figure S1 (<http://dx.doi.org/10.1289/ehp.1205606>)]. Therefore, we modeled noise exposure as a piecewise linear term with a cut-off point at 65 dB(A), and present separate estimates for associations with a 5-dB(A) increase in L_{eq} for $L_{eq} < 65$ dB(A) and $L_{eq} \geq 65$ dB(A). Furthermore, we assessed whether associations were modified by sex or age (< 65 years vs. ≥ 65 years) by performing stratified analyses. For sensitivity analyses, we excluded all participants with hearing impairment and with intake of beta-adrenergic receptor blockers (beta-blockers). Moreover, we additionally adjusted our models for the diary-based information on the whereabouts of the participants as a proxy indicator of the noise source. In a further analysis, we included PNC exposures with the same lags as L_{eq} in the models to examine potential confounding by ultrafine particle exposures. Effect estimates are presented as percent changes in the mean values of each outcome together with 95% CIs. Data were analyzed with SAS statistical package (version 9.2; SAS Institute Inc., Cary, NC, USA).

Results

Study population. Overall, 110 individuals participated in 385 visits including ECG and individual exposure measurements. Baseline characteristics of the 110 individuals are described in Table 1. Fifty-nine measurements were not valid because of missing data due to technical problems or bad signal quality of the ECG recordings. Thus, 326 valid measurements with a mean duration of 6 hr were available for analyses, comprising approximately 20,000 5-min segments. Women were on average younger than men, but disease status and medication use was comparable between

women and men [see Supplemental Material, Table S2 (<http://dx.doi.org/10.1289/ehp.1205606>)]. Persons < 65 years of age were less likely to report a metabolic disorder or hypertension, reported less medication use, and were more likely to be employed than persons > 65 years (see Supplemental Material, Table S3).

Diary. Overall, the participants made 4,165 diary entries with on average 12.8 entries per visit. However, only 4,148 diary entries were included in the analyses because for 17 entries physical activity could not be assigned clearly to one category. Participants spent more than half of the time indoors and showed very low variation in physical activity [see Supplemental Material, Table S4 (<http://dx.doi.org/10.1289/ehp.1205606>)]. More than 90% of the time physical activity was classified as very light or light. Because of the small numbers in the lowest and highest categories, we combined categories 1 and 2 as well as 4, 5, and 6, respectively. Twenty-six participants reported 43 episodes of annoyance by noise over a total of 34 visits. However, we did not evaluate annoyance further because data on the time, duration, and intensity of annoyance were often incomplete.

Table 1. Baseline characteristics of the study population ($n = 110$).

Variable	n (mean \pm SD or %)
Age (years)	110 (61.3 \pm 11.7)
Body mass index (kg/m ²)	110 (28.6 \pm 5.3)
Male	69 (62.7)
Smoking history	
Never smoker	59 (53.6)
Ex-smoker	51 (46.4)
Metabolic disorder (T2D, IGT) ^a	64 (58.2)
Self-reported history ^b	
MI	6 (5.5)
Angina pectoris	6 (5.5)
Coronary heart disease	7 (6.4)
Hypertension	61 (55.5)
Use of medication ^c	
Agents acting on renin-angiotensin system	40 (36.4)
Beta blocker	28 (25.5)
Calcium channel blockers	11 (10.0)
Antidiabetics	18 (16.4)
Diuretics	36 (32.7)
Nitrates	1 (0.9)
Statins	19 (17.3)
Antihypertensive drugs	54 (49.1)
Hearing impairment ^d	15 (13.6)
If yes:	
Physician diagnosed	12 (10.9)
Wearing hearing aid	2 (1.8)
Employed (%)	41 (37.3)

Abbreviations: IGT, impaired glucose tolerance; T2D, type 2 diabetes.

^aParticipants with T2D were classified based on a self-reported diagnosis by a physician, medication use, or a fasting glucose level > 125 mg/dL or a 2-hr glucose level > 200 mg/dL in an oral glucose tolerance test (OGTT). IGT was classified based on 2-hr OGTT glucose levels \geq 140 mg/dL but < 200 mg/dL. ^bEver physician diagnosed. ^cAt least once during the study period (19 March 2007 to 17 December 2008). ^dNot validated.

ECG parameters and exposure. Descriptive statistics of noise, PNC, and ECG parameters are shown in Table 2. Mean level of personal noise exposure [75.1 dB(A)] was quite high. However, as expected, there existed very much variation from this average [SD = 83.0 dB(A)] resulting from combining such a huge number of observations collected in several different situations. HF power and the LF:HF ratio showed the highest correlation of the outcomes ($r = -0.59$), with weaker correlations (-0.02 to 0.41) between other pairs of ECG parameters [see Supplemental Material, Table S5 (<http://dx.doi.org/10.1289/ehp.1205606>)]. The correlation between L_{eq} and PNC was $r = 0.15$. Women and men were on average exposed to similar noise levels [75.8 dB(A) in women vs. 74.6 dB(A) in men, $p = 0.34$]. Women had higher values of HR and HF power than men, but no differences were seen for the other ECG parameters (data not shown). Compared to the older age group, individuals < 65 years were exposed to higher levels of L_{eq} [76.9 dB(A) vs. 72.0 dB(A), $p = 0.01$] and had higher ECG parameter values except for HF power (data not shown).

Association of noise and ECG parameters. The estimated percent changes in the mean values of each outcome associated with a 5-dB(A) increase in L_{eq} are shown in Figure 1 [for numeric data, see also Supplemental Material, Table S6 (<http://dx.doi.org/10.1289/ehp.1205606>)]. HR and the LF:HF ratio increased in association with noise exposure above and below 65 dB(A), with stronger associations estimated for concurrent increases in $L_{eq} < 65$ dB(A) (HR: 1.48%; 95% CI: 1.37, 1.60% and 0.18%; 95% CI: 0.05, 0.31%, respectively; LF:HF ratio: 4.89%; 95% CI: 3.48, 6.32 and 1.38%; 95% CI: 0.03, 2.75%, respectively). A 5-dB(A) increase in $L_{eq} < 65$ dB(A) was associated with an immediate increase in SDNN (5.74%; 95% CI: 5.13, 6.36%) followed by decreases for lagged exposures that were significant when lagged 5–10 min (-0.67% ; 95% CI: -1.26 , -0.12%) and 10–15 min (-0.67% ; 95% CI: -1.26 , -0.13%). An increase in $L_{eq} \geq 65$ dB(A) was associated with a small reduction in concurrent SDNN (-0.67% ; 95% CI: -1.30 , -0.04%), but was

not associated with lagged SDNN. LF and HF power decreased with concurrent noise < 65 dB(A) (-3.77% ; 95% CI: -5.49 , -2.02% and -8.56% ; 95% CI: -10.31 , -6.78 , respectively), but lagged noise was positively associated with LF power (2.14% to 2.24%). In contrast, 5-dB(A) increases in $L_{eq} > 65$ dB(A) were associated with increased LF and HF power that were statistically significant for concurrent noise (4.42%; 95% CI: 2.59, 6.32% and 2.89%; 95% CI: 0.95, 4.87%, respectively) and lagged noise at 0–5 min (3.69%; 95% CI: 1.86, 5.56% and 3.45%; 95% CI: 1.50, 5.44%, respectively).

Stratified analyses focused on immediate effects, because we found strongest associations with concurrent noise in the main analyses. Associations with a 5-dB(A) increase in concurrent noise < 65 dB(A) were stronger in women than men for HR, HF power, and the LF:HF ratio (p for interaction ≤ 0.002), but there were no significant differences between men and women for associations with noise ≥ 65 dB(A) (Table 3). Associations with concurrent noise < 65 dB(A) were stronger among those ≥ 65 years of age for SDNN and the LF:HF ratio, whereas associations with increases in $L_{eq} \geq 65$ dB(A) were stronger in those < 65 years, with significant differences between the age groups for HR, LF power, and the LF:HF ratio (Table 4).

Sensitivity analyses. Associations were comparable after exclusion of 15 hearing-impaired participants, except for a slightly weaker association between SDNN and concurrent $L_{eq} < 65$ dB(A) overall (5.20%; 95% CI: 4.55, 5.85%) and among men (but not women) in stratified analyses (4.51%; 95% CI: 3.74, 5.29%). Associations were also comparable after we excluded 30 persons (88 valid visits) who reported beta-blocker intake, except for stronger overall associations between increases in $L_{eq} < 65$ dB(A) and concurrent HR and HF power and the LF:HF ratio lagged 0–5 min (HR: 1.60; 95% CI: 1.46, 1.75%; HF power: -2.36 ; 95% CI: -4.46 , -0.22% ; LF:HF ratio: 1.82%; 95% CI: 0.311, 3.36%). Adjusting for the whereabouts of the participants (as a proxy indicator of noise source) had little influence on associations, except for weaker associations between HR

Table 2. Descriptive statistics of 5-min averages of L_{eq} , PNC, and ECG measures.

Variable	n	All (Mean \pm SD)	$L_{eq} < 65$ dB(A)		$L_{eq} \geq 65$ dB(A)		p -Value ^a
			n	(Mean \pm SD)	n	(Mean \pm SD)	
L_{eq} [dB(A)]	21,419	(75.1 \pm 83.0)	8,818	(80.4 \pm 59.7)	12,601	(77.3 \pm 84.1)	< 0.0001
PNC (n)	17,388	(21,236 \pm 34,039)	7,423	(17,358 \pm 28,054)	9,965	(24,131 \pm 37,836)	< 0.0001
HR (beats/min)	21,419	(78.4 \pm 14.7)	8,818	(75.1 \pm 14.1)	12,601	(80.8 \pm 14.7)	< 0.0001
SDNN (msec)	21,415	(51.6 \pm 28.9)	8,816	(51.0 \pm 27.4)	12,599	(52.0 \pm 28.4)	< 0.0001
LF power (nu)	18,722	(44.4 \pm 28.0)	7,331	(45.8 \pm 27.1)	11,391	(43.4 \pm 28.5)	< 0.0001
HF power (nu)	18,722	(15.3 \pm 15.2)	7,331	(16.6 \pm 15.9)	11,391	(14.3 \pm 14.6)	< 0.0001
LF:HF ratio (nu)	18,722	(5.3 \pm 4.9)	7,331	(5.1 \pm 4.8)	11,391	(5.4 \pm 4.9)	0.0002

nu, normalized units.

^a p -Value of fixed effect for noise indicator in an univariate mixed model to test the differences in associations according to $L_{eq} < 65$ dB(A) and $L_{eq} \geq 65$ dB(A).

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and increases in $L_{eq} < 65$ dB(A) overall (e.g., concurrent: 1.32%; 95% CI: 1.21, 1.44%) and in stratified analyses (data not shown). Furthermore, we assessed whether associations differed when adjusted for individual exposure to PNC based on data from 290 visits with valid PNC measurements, but associations were similar overall and in stratified analyses, indicating no confounding by exposure to ultrafine particles (data not shown).

Discussion

Summary of results. We investigated associations between 5-min averages of individual noise exposure from everyday life and HR and HRV. Associations differed for L_{eq} below and above 65 dB(A), but overall results support immediate effects of noise. HR and the LF:HF ratio were increased in association with concurrent noise exposure, with stronger associations for a 5-dB(A) increase in $L_{eq} < 65$ dB(A). SDNN increased in association with concurrent increases in noise < 65 dB(A) but decreased in association with lagged exposure, whereas noise ≥ 65 dB(A)

was associated with concurrent reductions in SDNN only. LF and HF power decreased in association with concurrent noise < 65 dB(A), but decreased in association with concurrent noise and noise 0–5 min prior with increased levels of $L_{eq} \geq 65$ dB(A). Associations also were modified by sex and age.

Noise exposure and autonomic function.

The activity of the autonomic nervous system is reflected in HR and HRV, with higher levels of sympathetic input and lower levels of parasympathetic tone leading to increased HR and reduced HRV. The time-domain parameter SDNN reflects all periodic components of the variability of the HR. The contribution of sympathetic and parasympathetic activity can be separated, to some degree, by performing spectral analysis. It is generally accepted that HF power is mediated by the parasympathetic nervous system (Malik 1996), whereas the interpretation of LF power is controversial. In previous literature, LF power is often described solely as marker for sympathetic activity; however, LF power rather seems to be related to both the sympathetic and parasympathetic

system (Stein and Kleiger 1999). Changes in the LF:HF ratio may provide information about the balance between sympathetic and parasympathetic modulations.

The observed immediate increase in HR and the LF:HF ratio associated with increases in $L_{eq} < 65$ dB(A) is consistent with parasympathetic withdrawal and/or elevated sympathetic tone, though the concurrent decrease in both HF and LF power is more consistent with a reduction in parasympathetic activity specifically. Subsequent increases in LF power after a delay of at least 10 min may indicate recovery of the autonomic nervous system. However, the immediate increase in SDNN followed by a decrease within 5 min is difficult to explain. In short-term recordings, not only LF and HF power but also very low frequency (VLF; ≤ 0.04 Hz) power can be determined as spectral components of HRV. The physiological correlates of VLF power are not well understood (Malik 1996). However, an additional analysis of the effect of noise exposure on VLF power indicated an immediate increase associated with a 5-dB(A) increase in noise < 65 dB(A) (14.6%; 95% CI: 12.6, 16.7%), but no delayed associations (data not shown). This suggests that the immediate increase in SDNN may have been the result of an increase in VLF power that was more pronounced than the concurrent decreases in LF and HF power. Furthermore, we speculate that this overreaction of the autonomic nervous system was regulated and returned to normal at least with a delay of 5 min.

Positive associations between HF power and increases in $L_{eq} \geq 65$ dB(A) indicate an increase in parasympathetic activity. However, we also observed a small concurrent increase in HR that suggests an accompanying increase in sympathetic activity exceeding the parasympathetic modulation. Accordingly, the immediate elevation in the LF:HF ratio, which was only marginally significant, and the strong immediate increase in LF power also suggest increased sympathetic activity resulting in reduced HRV. This conclusion is further supported by the concurrent reduction in SDNN.

Because associations differed between low and high noise intensities, we assume different underlying mechanisms. Under participation of the limbic system and the hypothalamus, noise exposure is hypothesized to influence the autonomic nervous system either directly or indirectly through stress-induced hormone release (Babisch 2003; Babisch et al. 2001; Ising et al. 2003). As in the general noise stress model (Henry 1992), a “fight-or-flight” response is activated by stressful situations, leading to the release of norepinephrine and other hormones that activate the synaptic transmission of sympathetic signals to the cardiac muscle fibers, in addition to increasing HR directly. Thus, changes in HRV associated

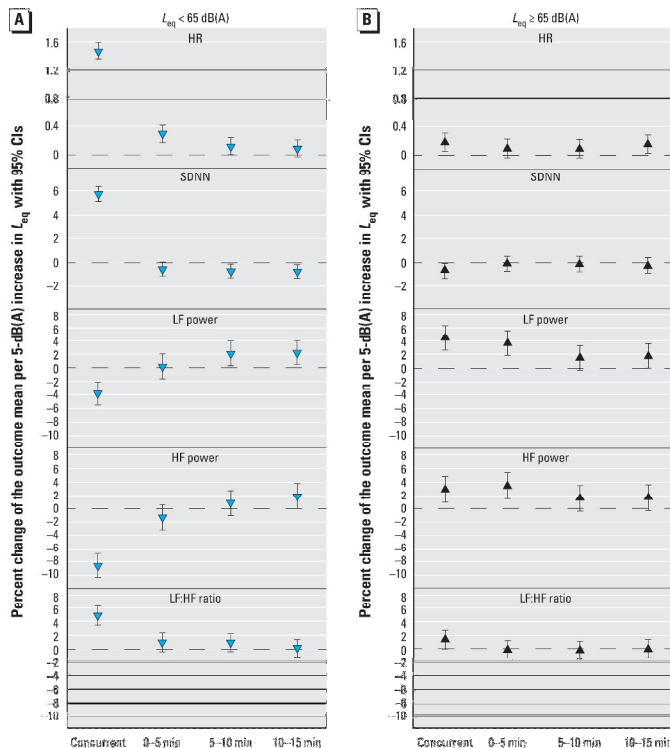


Figure 1. Adjusted associations between ECG measures and a 5-dB(A) increase in 5-min averages of noise exposure < 65 dB(A) (A) and ≥ 65 dB(A) (B). See Supplemental Material, Table S6 (<http://dx.doi.org/10.1289/ehp.1209606>) for numeric data.

with increases in lower noise intensities might be attributable mainly to parasympathetic withdrawal. In contrast, increases in higher noise intensities, which may be more stressful than comparable increases at lower levels of L_{eq} , may lead to a transient reduction in HRV due to enhanced sympathetic activation and additional release of stress hormones. In the long run, any impairment in HRV may result in increased cardiovascular risk (Buccellietti et al. 2009; Geritsen et al. 2001).

Previous studies of the effects of acute noise exposure on HRV are very limited and were mostly conducted in laboratory settings. Recently, Lee et al. (2010) exposed 16 healthy individuals to white noise of different intensities. In contrast with our findings, HR and HF power showed no changes in response to noise intensities ranging from background levels to 80 dB(A). LF power and the LF:HF ratio increased in response to white noise at 50 dB(A) or higher relative to mean values during exposure to background noise, and the LF:HF ratio tended to be higher during exposure to 70 and 80 dB(A) compared with 50 and 60 dB(A). Hence, at higher noise intensities increases in sympathetic activity may have been more pronounced than decreases in parasympathetic tone. Another laboratory study investigated the effects of white noise of 85 dB(A) on HRV in 20 young adults. The authors found an increase in total spectral power, a measure for total HRV, as well as an increase in LF power after 5–10 min of exposure, but no changes in HF power or HR (Björ et al. 2007). Nevertheless, laboratory studies do not reflect real-life conditions, which may explain the differences in results compared to epidemiological studies. A recent field study assessed the relation of night noise on respiratory sinus arrhythmia, which reflects HF power, as well as on pre-ejection period, a measure for sympathetic activity. The authors concluded that increased indoor traffic noise exposure levels during nighttime, which were < 30 dB(A), were associated with cardiac parasympathetic withdrawal, but not with changes in sympathetic tone (Grabam et al. 2009). Even though these findings are consistent with our results, sleep is a state of reduced sympathetic activity and pronounced parasympathetic influence compared with waking hours, which complicates comparisons. Other epidemiological studies that estimated effects of short-term noise exposure on autonomic function reported positive associations with blood pressure and HR, suggesting an increase in sympathetic tone (Chang et al. 2003, 2009; Fogari et al. 2001; Haralabidis et al. 2008; Lusk et al. 2004). To our knowledge, only one previous study investigated possible effects of individual noise exposure during everyday life. Chang et al. (2009) conducted a study in 60 young adults who carried noise dosimeters and ambulatory blood pressure monitoring

devices for 24 hr. A 5-dB(A) increase in environmental daytime noise with an average L_{eq} of 61.3 dB(A) was significantly associated with systolic (1.15 mmHg; 95% CI: 0.86, 1.43 mmHg) and diastolic (1.16 mmHg; 95% CI: 0.93, 1.38 mmHg) blood pressure (Chang et al. 2009).

Stratified analyses. Our study showed that sex significantly modified associations with increased noise < 65 dB(A), suggesting that women were more susceptible to increased noise exposure within the lower L_{eq} range than men. Because women were on average younger than men, these differences may have been confounded by age. However, stratified analyses by age group did not support this hypothesis. Existing studies on sex-specific effects have reported inconsistent results, with some reporting stronger associations in women (Bluhm et al. 2007; Chang et al. 2009; Heinonen-Guzejev et al. 2007; Willich et al. 2006), whereas others observed evidence of noise effects only in men (Babisch 2005; Barregard et al. 2009; Jarup et al. 2008), and at least two studies did not find sex differences at all (de Kluizenaar et al. 2007; Rosenlund et al. 2001). The inconsistencies may reflect differences among study populations, for example, regarding age and disease status, study designs, and measures of exposure.

Analyses stratified by age group suggested stronger effects of increases in noise

< 65 dB(A) among those ≥ 65 years of age than in younger individuals. Hypertension was more common in the older age group, which may have increased susceptibility to effects of noise exposure on HRV. However, significant associations with increases in noise ≥ 65 dB(A) were only observed in those < 65 years.

Strengths and limitations. Participants had up to four repeated measurements with a mean duration of 6 hr. Calculating 5-min averages of L_{eq} and ECG parameters made a large number of repeated within-subject data available. By including a random effect for each person in the regression models, we were able to adjust for interindividual differences in ECG parameters and time-invariant characteristics such as sex and age. An additional strength is that we measured individual noise exposure, which may have substantially reduced exposure misclassification relative to previous studies that estimated noise exposure based on noise mapping. Another advantage of our study is that we performed a sensitivity analysis by additional adjustment for individually measured PNC. Traffic is a shared source of noise and air pollution and provides potential for confounding. Changes in HRV were already reported in association with PNC in diabetic participants of the same study population (Peters et al. 2010). However, adjusting for PNC had little or no influence on effect estimates for noise, consistent with previous

Table 3. Adjusted immediate associations between 5-min averages of noise exposure and ECG measures by sex (percent change (95% CI)).

ECG measures	Male	Female	p-Value ^a
< 65 dB(A)			
HR	1.37 (1.24, 1.51)	1.74 (1.52, 1.96)	< 0.0001
SDNN	5.44 (4.71, 6.18)	6.36 (5.24, 7.48)	0.091
LF power	-3.40 (-5.48, -1.26)	-3.82 (-6.91, -0.63)	0.39
HF power	-6.56 (-9.73, -3.33)	-12.11 (-15.00, -9.11)	0.0017
LF:HF ratio	2.93 (1.21, 4.69)	8.88 (6.42, 11.40)	< 0.0001
≥ 65 dB(A)			
HR	0.14 (-0.02, 0.30)	0.21 (0.00, 0.42)	0.27
SDNN	-0.80 (-1.61, -0.01)	-0.54 (-1.52, 0.45)	0.34
LF power	3.38 (1.05, 5.77)	6.09 (3.10, 9.16)	0.083
HF power	2.69 (0.20, 5.24)	3.66 (0.59, 6.84)	0.32
LF:HF ratio	0.61 (-1.15, 2.59)	2.13 (0.04, 4.26)	0.14

^ap-Value for interaction calculated using a method proposed by Altman and Bland (2002).

Table 4. Adjusted immediate associations between 5-min averages of noise exposure and ECG measures by age group (percent change (95% CI)).

ECG measures	< 65 years	≥ 65 years	p-Value ^a
< 65 dB(A)			
HR	1.39 (1.21, 1.57)	1.61 (1.46, 1.75)	0.20
SDNN	4.87 (4.01, 5.74)	5.93 (5.06, 6.81)	0.047
LF power	-4.50 (-6.80, -2.15)	-1.84 (-4.45, 0.85)	0.069
HF power	-8.10 (-10.45, -5.69)	-8.97 (-11.57, -6.29)	0.32
LF:HF ratio	3.91 (2.07, 5.77)	6.99 (4.77, 9.25)	0.019
≥ 65 dB(A)			
HR	0.27 (0.10, 0.44)	-0.02 (-0.21, 0.17)	0.0098
SDNN	-0.82 (-1.58, -0.06)	-0.28 (-1.32, 0.78)	0.20
LF power	6.33 (4.04, 8.68)	0.61 (-2.35, 3.71)	0.0019
HF power	3.63 (1.16, 5.67)	1.63 (-1.63, 5.00)	0.18
LF:HF ratio	2.82 (0.93, 4.26)	-0.82 (-3.13, 1.53)	0.0093

^ap-Value for interaction calculated using a method proposed by Altman and Bland (2002).

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studies (Beelen et al. 2009; Fuks et al. 2011). A further strength is that we examined high and low noise levels separately. The selection of 65 dB(A) as cut-off point was data driven. However, we consider the cut-off point as reasonable because the World Health Organization concluded that an average noise level of 65–70 dB(A) during the day is a possible threshold for a higher cardiovascular risk (Berglund et al. 1999).

Nevertheless, some limitations must be considered, including the potential for residual confounding. Depending on source and behavioral context, individuals may evaluate noise as annoying or even pleasant resulting in different physiological reactions. Nevertheless, we were not able to account for subjective annoyance because diary data were imprecise. A further limitation is that we were able to consider only PNC as potential confounder. Other pollutants were measured at a central monitoring site at a much lower time resolution. Therefore, they did not match our individual 5-min–based outcome data. Furthermore, ECG parameters strongly depend on movements and exercise of study participants. Even low-intensity exercise can increase HR and may produce higher noise intensities due to heavier respiration and rubbing of clothes. For this reason, it is essential to adjust for physical activity. Indeed, our variable reflecting physical activity was associated with all of the outcomes included in the analyses [see Supplemental Material, Table S7 (<http://dx.doi.org/10.1289/ehp.1205606>)]. However, our information on physical activity was based on self-report instead of actigraphy. Therefore, we adjusted for HR when estimating associations with HRV parameters. With regard to HR as response variable, it is not clear whether the adjustment for self-reported physical activity was sufficient; therefore, associations might be overestimated. Another limitation is that measurements of ECG parameters, noise, and PNC were temporally aligned based on the times recorded by each device and the study protocols. In case of inconsistencies in times, we confirmed with the study nurses and corrected the times wherever possible. Finally, the study population consisted mainly of elderly people and a lot of exclusions were made. Thus, generalizability to other populations might be restricted.

Conclusions

Our study suggests acute changes in cardiac function in association with individual day time noise exposure possibly mediated by a sympathovagal imbalance. Our results suggest that different biological pathways can be activated depending on noise intensity, and that noise at lower levels may have health consequences beyond those commonly attributed to “fight-or-flight” responses to high levels of noise.

CORRECTION

In the original manuscript published online, the values in Tables 3 and 4 had some rounding errors. They have been corrected here.

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SUPPLEMENTAL MATERIAL

Individual Daytime Noise Exposure During Routine Activities and Heart Rate Variability in Adults: A Repeated Measures Study

Kraus U, Schneider A, Breitner S, Hampel R, R ckerl R, Pitz M, Geruschkat U, Belcredi P, Radon K, Peters A

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Detailed description of the diary and physical activity

During the measurement period between 7:30 a.m. and 3 p.m. participants were free to go where ever they liked and to pursue their daily routines. All their activities and whereabouts were recorded in a diary. In doing so, participants always made a diary entry when they changed their whereabouts or activity. Times were recorded precisely to the minute. A diary entry included a free text description of the activity. Furthermore, participants had to tick whether they were indoors, outside and not in traffic (e.g. in a park), or in traffic. Additionally, persons were asked to note when they felt annoyed by noise and to rate this annoyance on a scale with five levels ranging from “minor” to “extreme”. After returning to the study center the nurses checked the diary for readability, completeness and conclusiveness. Every ambiguity was directly solved in discussion together with the participant. Dichotomous variables for the whereabouts were built.

To ensure that diary data can be aligned on the same timescale with exposure and outcome data, each participant got a wrist watch that was regularly synchronized with a radio controlled clock. The clocks of the exposure devices were likewise synchronized before starting the measurement. Furthermore, the study nurses recorded start and end times of the measurement periods in a protocol. Before combining the data times were compared with the times that were recorded by the study nurses.

TABLE S1. *Final confounder models for each ECG parameter.*

ECG parameter	Confounder model
HR	lagged HR, long-term time trend (linear), daily time trend based on every five minutes (smooth), physical activity (categorical)
SDNN	lagged SDNN, long-term time trend (polynomial, 2nd order), daily time trend based on every 30 minutes (polynomial, 4th order), physical activity (categorical), HR
LF power	lagged LF power, long-term time trend (linear), daily time trend based on every 15 minutes (polynomial, 4th order), physical activity (categorical), HR
HF power	lagged HF power, long-term time trend (linear), daily time trend based on every 15 minutes (polynomial, 4th order), physical activity (categorical), HR
LF/HF ratio	lagged LF/HF ratio, long-term time trend (polynomial 3rd order), daily time trend based on every 5 minutes (smooth), physical activity (categorical), HR

Abbreviations: HF, high frequency; HR, heart rate; LF, low frequency; SDNN, standard deviation of normal-to-normal intervals

TABLE S2. Baseline characteristics of the study population by sex.

Characteristic	Men	Women	P
	N (% or mean \pm SD)	N (% or mean \pm SD)	
Age [yrs]	69 (63.7 \pm 11.1)	41 (58.1 \pm 11.9)	0.016 ^e
Body mass index [kg/m ²]	69 (28.8 \pm 4.7)	41 (28.2 \pm 6.4)	0.59 ^e
Smoking history			
Never smoker	45 (65.2)	14 (34.1)	0.0016 ^f
Ex smoker	24 (34.8)	27 (65.9)	
Metabolic disorder (T2D ^a or IGT ^a)	42 (60.9)	22 (53.7)	0.46 ^f
Self-reported history ^b			
Myocardial infarction	6 (8.7)	0 (0.0)	0.08 ^g
Angina pectoris	2 (2.9)	4 (9.8)	0.19 ^g
Coronary heart disease	6 (8.7)	1 (2.4)	0.25 ^g
Hypertension	42 (60.9)	19 (46.3)	0.14 ^f
Use of medication ^c			
Agents acting on renin-angiotensin-system	27 (39.1)	13 (31.7)	0.43 ^f
Beta blocker	21 (30.4)	7 (17.1)	0.12 ^f
Calcium channel blockers	8 (11.6)	3 (7.32)	0.53 ^g
Antidiabetics	14 (20.3)	4 (9.8)	0.15 ^f
Diuretics	24 (34.8)	12 (29.3)	0.55 ^f
Nitrates	1 (1.5)	0 (0.0)	1.00 ^g
Statins	16 (23.2)	3 (7.3)	0.033 ^f
Antihypertensive drugs	38 (55.1)	16 (39.0)	0.10 ^f
Hearing impairment ^d (%)	12 (17.4)	3 (7.3)	0.14 ^f
If yes: Physician diagnosed	9 (13.0)	3 (7.3)	1.00 ^g
Wearing hearing aid	2 (2.9)	0 (7.3)	1.00 ^g
Employed (%)	24 (34.8)	17 (41.5)	0.48 ^f

^aParticipants with T2D were classified based on self-report of a diagnosis by a physician, self-reported medication use, or a fasting glucose level >125mg/dl or 2h glucose level \geq 200mg/dl in an oral glucose tolerance test (OGTT). IGT was specified as having 2h OGTT glucose levels \geq 140mg/dl but <200mg/dl.

^bEver physician diagnosed.

^cAt least once during the study period (Mar 17th 2007 to Dec 17th 2008).

^dNot validated.

P-values determined with ^eStudent's *t*-test, ^fchi-square test or ^gFisher's exact test.

Abbreviations: T2D, type 2 diabetes; IGT, impaired glucose tolerance; SD, standard deviation.

TABLE S3. *Baseline characteristics of the study population by age-group.*

Characteristic	< 65 years	≥ 65 years	P
	N (% or mean ± SD)	N (% or mean ± SD)	
Age [yrs]	55 (52.1 ± 8.6)	55 (58.1 ± 11.9)	<.0001 ^d
Body mass index [kg/m ²]	55 (28.3 ± 6.3)	55 (28.9 ± 4.3)	0.55 ^d
Men	29 (52.7)	40 (72.7)	0.030 ^e
Smoking history			
Never smoker	28 (50.9)	23 (41.8)	0.34 ^e
Ex smoker	27 (49.1)	32 (58.2)	
Metabolic disorder (T2D ^a or IGT ^a)	23 (41.8)	41 (74.6)	0.0005 ^f
Self-reported history ^b			
Myocardial infarction	1 (1.8)	5 (9.1)	0.21 ^f
Angina pectoris	4 (7.3)	2 (3.6)	0.68 ^f
Coronary heart disease	4 (7.3)	3 (5.5)	1.00 ^f
Hypertension	23 (41.8)	38 (69.1)	0.0040 ^e
Use of medication ^c			
Agents acting on renin-angiotensin-system	14 (25.5)	26 (47.3)	0.017 ^e
Beta blocker	7 (12.7)	21 (38.2)	0.0022 ^e
Calcium channel blockers	3 (5.5)	8 (15.6)	0.11 ^e
Antidiabetics	7 (12.7)	11 (20.0)	0.30 ^e
Diuretics	12 (21.8)	24 (43.6)	0.015 ^e
Nitrates	0 (0.0)	1 (1.8)	1.00 ^f
Statins	4 (7.3)	15 (27.3)	0.0055 ^e
Antihypertensive drugs	18 (32.7)	36 (65.5)	0.0006 ^e
Hearing impairment ^d (%)	1 (1.8)	14 (25.5)	0.0003 ^e
If yes: Physician diagnosed	1 (100.0)	11 (78.6)	1.00 ^f
Wearing hearing aid	0 (0.0)	2 (14.3)	1.00 ^f
Employed (%)	38 (69.09)	3 (5.5)	<.0001 ^e

^aParticipants with T2D were classified based on self-report of a diagnosis by a physician, self-reported medication use, or a fasting glucose level >125mg/dl or 2h glucose level ≥200mg/dl in an oral glucose tolerance test (OGTT). IGT was specified as having 2h OGTT glucose levels ≥140mg/dl but <200mg/dl..

^bEver physician diagnosed.

^cAt least once during the study period (Mar 17th 2007 to Dec 17th 2008).

^dNot validated.

P-values determined with ^eStudent's *t*-test, ^fchi-square test or ^gFisher's exact test.

Abbreviations: T2D, type 2 diabetes; IGT, impaired glucose tolerance; SD, standard deviation.

TABLE S4. *Description of diary entries (N=4,148).*

Diary based information	Diary entries N (%)	5-minute segments N (%)
Whereabouts		
Indoors	2,268 (54.78)	14,020 (65.5)
Outside, not in traffic	159 (3.8)	917 (4.3)
In traffic	1,687 (40.7)	4,904 (22.9)
Unclear	34 (0.8)	1,578 (7.4)
Physical activity		
Sleeping/Reclining	110 (2.7)	329 (1.5)
Very light/light exertion	3,766 (90.8)	20,032 (93.5)
Moderate/vigorous/heavy exertion	272 (6.6)	1,058 (4.9)

TABLE S5. *Spearman correlation coefficients for ECG parameters.*

ECG measures	HR	SDNN	LF	HF	LF/HF Ratio
HR	1	-0.22	-0.18	-0.31	0.15
SDNN		1	-0.21	-0.16	-0.02
LF			1	0.41	0.40
HF				1	-0.59
LF/HF Ratio					1

Abbreviations: HF, high frequency; HR, heart rate; LF, low frequency; SDNN, standard deviation of normal-to-normal intervals.

TABLE S6. *Adjusted immediate and delayed associations between five-minute averages of L_{eq} and ECG measures.*

ECG measures	< 65 dB(A)	\geq 65 dB(A)
	% change (95%CI)	% change (95%CI)
HR		
concurrent	1.48 (1.37, 1.60)*	0.18 (0.05, 0.31)*
0-5min	0.29 (0.17, 0.41)*	0.09 (-0.04, 0.22)
5-10min	0.12 (0.01, 0.24)*	0.08 (-0.04, 0.21)
10-15min	0.09 (-0.02, 0.21)	0.15 (0.02, 0.28)*
SDNN		
concurrent	5.74 (5.13, 6.36)*	-0.67 (-1.30, -0.04)*
0-5min	-0.53 (-1.12, 0.05)	-0.08 (-0.71, 0.56)
5-10min	-0.69 (-1.26, -0.12)*	-0.09 (-0.73, 0.54)
10-15min	-0.67 (-1.26, -0.13)*	-0.21 (-0.84, 0.43)
LF power		
concurrent	-3.77 (-5.49, -2.02)*	4.42 (2.59, 6.32)*
0-5min	0.26 (-1.53, 2.09)	3.69 (1.86, 5.56)*
5-10min	2.14 (0.37, 3.95)*	1.50 (-0.30, 3.33)
10-15min	2.24 (0.49, 4.02)*	1.74 (-0.07, 3.57)
HF power		
concurrent	-8.56 (-10.31, -6.78)*	2.89 (0.95, 4.87)*
0-5min	-1.31 (-3.21, 0.62)	3.45 (1.50, 5.44)*
5-10min	0.87 (-1.01, 2.79)	1.58 (-0.34, 3.55)
10-15min	1.90 (-0.04, 3.80)	1.67 (-0.26, 3.63)
LF/HF ratio		
concurrent	4.89 (3.48, 6.32)*	1.38 (0.03, 2.75)*
0-5min	0.98 (-0.38, 2.36)	-0.09 (-1.43, 1.26)
5-10min	0.96 (-0.36, 2.31)	-0.18 (-1.52, 1.17)
10-15min	0.12 (-1.17, 1.43)	0.05 (-1.29, 1.40)

**P*-value of fixed effect for L_{eq} as piecewise linear term in additive mixed model < 0.05

Abbreviations: dB(A), A-weighted decibels; change, change of outcome mean per 5 dB(A) increase in noise exposure; CI, confidence interval; HR, heart rate; SDNN, standard deviation of normal-to-normal intervals; HF, high frequency; LF, low frequency; min, minute;

TABLE S7. Associations of physical activity on HR as well as physical activity and HR on HRV parameters.

outcome	exposure	% change ^a	(95% CI)
HR	moderate PA	1.67*	(0.67, 2.67)
	high PA	6.49*	(5.38, 7.59)
SDNN	HR	-0.35*	(-2.03, -1.42)
	moderate PA	-10.50*	(-54.22, -27.93)
	high PA	-15.85*	(-67.56, -45.09)
LF power	HR	-3.92*	(-18.83, -17.39)
	moderate PA	12.31	(-13.54, 269.41)
	high PA	28.36*	(55.03, 682.96)
HF power	HR	-4.22*	(-20.13, -18.62)
	moderate PA	-1.48	(-57.25, 101.58)
	high PA	8.36	(-37.08, 254.73)
LF/HF ratio	HR	0.34*	(1.02, 2.35)
	moderate PA	11.24	(-1.33, 194.06)
	high PA	15.43*	(11.43, 276.75)

^a%-change in outcome mean per increase in physical activity category compared to the lowest activity level and per increase of 1 beat/min in HR, respectively.

*p-value<0.05

Abbreviations: CI, confidence interval; HR, heart rate; SDNN, standard deviation of normal-to-normal intervals; HF, high frequency; LF, low frequency; PA, physical activity

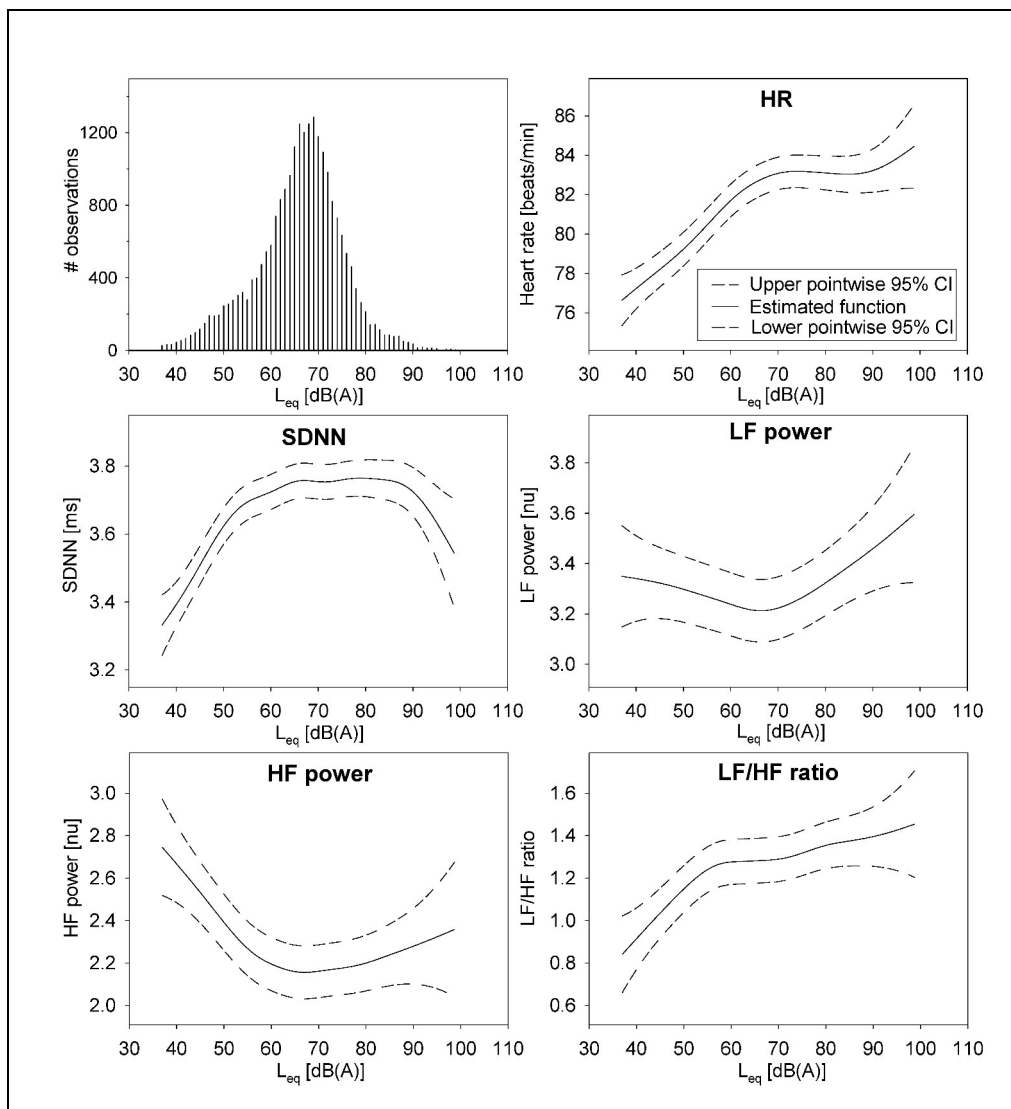


FIGURE S1. Number of observations (upper left panel) and estimated exposure-response functions of immediate associations between five-minute averages of L_{eq} and ECG measures.

Abbreviations: CI, confidence interval; dB(A), A-weighted decibels; HF, high frequency; HR, heart rate; L_{eq} , equivalent continuous sound pressure levels; LF, low frequency; nu, normalized units; SDNN, standard deviation of normal-to-normal intervals.

7 Elevated Particle Number Concentrations Induce Immediate Changes in Heart Rate Variability: A Panel Study in Individuals with Impaired Glucose Metabolism or Diabetes

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Elevated particle number concentrations induce immediate changes in heart rate variability: a panel study in individuals with impaired glucose metabolism or diabetes

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Abstract

Background

The health effects of short-term exposure to ambient ultrafine particles in micro-environments are still under investigation.

Methods

Sixty-four individuals with type 2 diabetes and impaired glucose tolerance recorded ambulatory electrocardiograms over five to six hours on 191 occasions in a panel study in Augsburg, Germany. Personal exposure to particle number concentrations (PNC) was monitored for each individual on 5-minute basis concurrently and particulate matter with an aerodynamic diameter $< 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) was acquired from a central monitoring site on an hourly basis.

Results

More than 11,000 5-minute intervals were available for heart rate and measures of heart rate variability including SDNN (standard deviation of NN intervals). A concurrent decrease in 5-minute SDNN of -0.56% (95% confidence limits (CI): -1.02% ; -0.09%) and a 5-minute delayed increase in heart rate of 0.23% (95% CI: 0.11% ; 0.36%) was observed with an increase in personal PNC of $16,000 \text{ per cm}^3$ in additive mixed models. Models evaluating the association of concurrent 5-minute personal PNC and of 1-hour $\text{PM}_{2.5}$ showed independent effects on SDNN.

Conclusion

The data suggest that freshly emitted ultrafine particles and aged fine particulate matter are both associated with changes in cardiac function in individuals with type 2 diabetes and impaired glucose tolerance in urban areas.

Keywords

Epidemiological study, Heart rate variability, Personal exposure, Type 2 diabetes, Ultrafine particles

Background

Over the past decade, ambient particulate matter has been established as a likely causal risk factor for cardiovascular disease morbidity and mortality [1]. In particular, exacerbation of cardiovascular disease has been observed within individuals with diabetes during episodes of high ambient air pollution exposures [2-4]. It has been noted that ambient particles [5,6] as well as exposure to traffic [7,8] might trigger myocardial infarctions within one or two hours. It is hypothesized that these associations may be a

consequence of a direct effect on the electric system of the heart [1]. The effects of air pollution on heart rate (HR) and heart rate variability (HRV) were extensively studied [1] since Pope et al. [9,10], Peters et al. [11], and Gold et al. [12] initially reported these associations. The most consistent evidence with respect to cardiovascular disease exists for fine particulate matter with an aerodynamic diameter smaller than 2.5 μm (PM_{2.5}) [1]. Especially, particles from mobile sources are suggested to be linked strongly to cardiovascular disease exacerbation [13]. Particles from emitted mobile sources are much smaller, mostly in the ultrafine range below 100 nm and have the potential to act systemically in organisms [14,15].

Recent evidence from controlled exposures to ultrafine carbon particles suggested altered autonomic function during the exposure in subjects with type 2 diabetes [16]. The study presented here aimed to assess the immediate impact of personal exposure particle to number concentrations (PNC) on HR and HRV measured by ambulatory electrocardiograms (ECG) during five to six hour periods in individuals with diagnosed type 2 diabetes or impaired glucose tolerance (IGT). Specifically, we assess the impact of personally measured PNC during the morning hours on heart rate variability. We build on previous analyses that assessed the association between centrally monitored ambient air pollution and cardiac function within the same study [17]. We had previously reported associations between 1-hour PM_{2.5} and decreased heart rate variability upon concurrent exposure as well as exposures occurring up to 4 hours before the ECG recording.

Results and discussion

Patient characteristics

Sixty-four non-smoking panel members were recruited for repeated measurements of personal exposure to PNC and parallel ECG recording. Table 1 describes the baseline characteristics of the 32 individuals with confirmed diagnosis of type 2 diabetes and 32 individuals with IGT recruited based on the KORA F4 study [18,19]. No differences were observed between the type 2 diabetes patients and the individuals with IGT concerning their age, gender, body mass index or disease history. Glycosylated hemoglobin A1c (HbA1c) concentrations above 6.5% were more frequently observed in individuals with diabetes than those with IGT. Diabetes prescriptions were taken by more than half of the participants with diabetes and one participant with IGT. More than 14,000 repeated 5-minute ECG measures and more than 1,200 1-hour ECG measures were available (Table 1). Patients with diabetes had lower HR and HRV on a 5-minute basis. This difference was no longer apparent for HRV based on 1-hour ECG recordings.

Table 1 Description of study participants and 5-minute ECG measures

	All (N = 64)			Type 2 diabetes (N = 32)			IGT (N = 32)			p-value		
	Mean	(SD)		Mean	(SD)		Mean	(SD)				
Age (years)	66.0	(8.1)		66.8	(6.7)		65.3	(9.4)		0.47 ^a		
BMI (kg/m ²)	30.0	(4.7)		30.8	(4.3)		29.3	(4.9)		0.18 ^a		
	N	(%)		N	(%)		N	(%)				
BMI (kg/m ²)	34	(53)	≤30	15	(47)	19	15	(59)		0.32 ^b		
	30	(47)	>30	17	(53)	13	13	(41)				
Smoking	26	(41)	never smoker	10	(31)	16	16	(50)		0.20 ^c		
	37	(58)	ex smoker	21	(66)	16	16	(50)				
	1	(2)	occasional smoker	1	(3)	0	0	(0)				
Employed	50	(78)	no	27	(84)	23	23	(72)		0.23 ^b		
	14	(22)	yes	5	(16)	9	9	(28)				
HbA1c	49	(77)	<6.5%	18	(56)	31	31	(97)		<0.0001 ^c		
	15	(23)	≥6.5%	14	(44)	1	1	(3)				
History of	4	(6)	Coronary heart disease	3	(9)	1	1	(3)		0.61 ^c		
	5	(8)	Angina pectoris	2	(6)	3	3	(9)		1.00 ^c		
	6	(9)	Myocardial infarction	5	(16)	1	1	(3)		0.20 ^c		
	41	(64)	Hypertension	21	(66)	20	20	(63)		0.79 ^b		
	21	(33)	None of these diseases	9	(28)	12	12	(38)		0.42 ^b		
Medication use	18	(28)	Antidiabetics	17	(53)	1	1	(3)		<0.0001 ^c		
	19	(30)	Beta blockers	12	(38)	7	7	(22)		0.17 ^b		
	13	(20)	Statins	10	(31)	3	3	(9)		0.06 ^c		
	28	(44)	None of the above	6	(19)	22	22	(69)		<0.0001 ^c		
ECG	N	(SD)	N	N	(SD)	N	Mean	(SD)				
5 min-intervals	14,874	(15.6)	HR	79.3	(15.6)	7,312	77.7	(15.6)	7,562	80.8	<0.0001 ^a	
	14,874	(30.1)	RMSSD	30.8	(30.1)	7,312	28.0	(27.3)	7,562	33.5	<0.0001 ^a	
	14,874	(25.1)	SDNN	47.1	(25.1)	7,312	45.9	(24.6)	7,562	48.2	<0.0001 ^a	
1 h-intervals	1,203	(14.4)	HR	79.1	(14.4)	597	77.3	(14.4)	606	80.8	<0.0001 ^a	
	1,203	(31.7)	RMSSD	33.9	(31.7)	597	32.5	(32.2)	606	35.1	(31.2)	0.16 ^a
	1,203	(27.1)	SDNN	76.7	(27.1)	597	77.5	(26.0)	606	76.0	(28.2)	0.32 ^a

IGT: impaired glucose tolerance, SD: standard deviation, BMI: body mass index, HR: heart rate, RMSSD: root mean square of successive differences, SDNN: standard deviation of NN-intervals, ^at-test, ^bChi-square test, ^cFisher's exact test.

Antidiabetic medications include: insulins and analogues for injection and inhalation.

Personal exposures to particle number concentrations

Table 2 describes the distribution of the personal PNC measurements and the distribution of particle concentrations at the central monitoring site. Substantially higher variation in personal PNC was observed during personal monitoring compared to the background level (Table 2). Figure 1 describes an example indicating that elevated levels of PNC may occur during times spent in traffic, while indoor concentrations may be substantially lower in the absence of indoor sources. Elevated personal PNC were observed when individuals spent time in traffic (median = 17,884 cm⁻³, N = 3,523), when cooking (median = 43,612 cm⁻³, N = 285) or exposed to environmental tobacco smoke (ETS) (median = 21,929 cm⁻³, N = 148). In contrast, personal PNC concentrations were lower during times spent at home without cooking or ETS exposure (median = 8,833 cm⁻³, N = 6,930). By design of the study, participants were commuting within the urban area of Augsburg in the morning and midday hours. Thereby, personal exposures were impacted by the morning rush-hour as well as by lower traffic volumes during midday and were there deviating from concentrations measured at an urban background monitoring site within the city center. Subject-specific Spearman correlation coefficients between 1-hour personal PNC concentrations and 1-hour ambient Ultrafine particles (UFP) had a median of 0.35 and ranged from -0.60 at the 10th percentile to 0.90 at the 90th percentile. Personally measured PNC characterise the exposure to mobile source emissions or other sources of freshly emitted particles and are determined by the personal activities as well as meteorological influences in the region of Augsburg, Germany [20,21].

Table 2 Description of personal 5-minute particle measurements from 191 study visits and 1 hour- of ambient particle measurements and meteorology recorded between March 2007 and December 2008

	N	Mean ± SD	Min	25%	Median	75%	Max	IQR
Personal measurements of PNC (5-minute averages)								
PNC [N/cm ³]	11,872	20,822 ± 39,233	521	6,354	11,134	21,987	698,225	15,633
Ambient measurements at stationary monitoring site(1-hour averages)								
UFP [N/cm ³]	14,699	9,518 ± 6,902	937	4,892	7,629	12,049	80,858	7,157
ACP [N/cm ³]	14,699	2,060 ± 1,535	88	1,020	1,657	2,615	17,377	1,595
PM ₁₀ [µg/m ³]	15,466	18.3 ± 14.1	0.0	8.4	15.3	24.4	159.8	16.0
PM _{2.5} [µg/m ³]	15,461	13.7 ± 11.2	0.0	5.8	10.9	18.1	106.5	12.3
Air temperature [°C]	15,398	10.8 ± 7.9	-8.4	4.7	10.8	16.5	33.8	11.8
Relative humidity [%]	15,398	76.9 ± 18.3	21.0	63.3	81.3	92.8	100.0	29.5

SD: standard deviation, IQR: interquartile range, PNC: Particle number concentrations, PM₁₀: particulate matter with an aerodynamic diameter <10 µm, PM_{2.5}: particulate matter with an aerodynamic diameter <2.5 µm, ACP: accumulation mode particles (100–800 nm), UFP: ultrafine particles (10-100 nm).

Figure 1 Example of personal measurements of PNC. Data was collected starting and ending at the KORA Study Center on November 27th 2007.

Ambient UFP were only moderately correlated with PM₁₀ and PM_{2.5} measured at the same central monitoring site (spearman correlation coefficients of 0.49 and 0.42, respectively). In contrast, accumulation mode particles (ACP) were highly correlated to 1-hour PM₁₀, PM_{2.5} and UFP (Spearman correlation coefficients of 0.79, 0.75 and 0.70, respectively).

Changes in heart rate variability in response to particle exposure

Table 3 shows the associations between 5-minute personal exposures to PNC and HR and HRV assessing concurrent and exposures lagged up to 15 minutes. It shows a slightly delayed response of HR and an immediate decrease in SDNN. Different responses of HR and SDNN to PNC may be reasonable given the fact that correlation between HR and SDNN differed substantially between individuals with a median Spearman correlation of -0.10 and a range between -0.53 and 0.55 .

Table 3 Associations between personal measurements of 5-minute average particle number concentrations and 5-minute ECG-measures

	concurrent		0 - 4 min		5 - 9 min		10 - 14 min	
	%-change	95% CI	%-change	95% CI	%-change	95% CI	%-change	95% CI
HR	-0.06	-0.18; 0.07	0.23**	0.11; 0.36	0.16*	0.04; 0.28	-0.01	-0.13; 0.11
SDNN	-0.56*	-1.02; -0.09	0.36	-0.11; 0.83	0.02	-0.45; 0.48	-0.15	-0.62; 0.32
RMSSD	-0.13	-0.74; 0.48	0.08	-0.54; 0.70	0.14	-0.48; 0.77	-0.16	-0.77; 0.46

Analyses considered concurrent and up to 15-minutes delayed exposures and adjusted for trend, meteorology and time of day. Effect estimates are shown for an increase of $16,000$ particles cm^{-3} .

*p-value <0.05 , **p-value <0.01 , CI: confidence interval, HR: heart rate, RMSSD: root mean square of successive differences, SDNN: standard deviation of NN intervals.

Associations between PNC and SDNN appear to be more pronounced in individuals with diabetes than in individuals with IGT (Figure 2). Exploratory analyses extending the time-lag between 5-minute personal exposure to PNC and HR, SDNN or RMSSD up to one hour showed no consistent pattern beyond 15 minutes.

Figure 2 Effects of personally measured 5-minute PNC on SDNN based on 5-minute ECG recordings in patients with diabetes or impaired glucose tolerance. Effect estimates are shown for an increase of $16,000$ particles cm^{-3} .

We had previously shown associations between 1-hour ambient air pollution concentrations and cardiac function occurring up to a lag of 4 hours [17]. We had chosen one hour intervals of exposure and ECG recordings *a priori* as we considered this the minimal time scale for a central monitoring site in an urban background location to represent population average exposures. In Table 4 we compare the association between 1-hour averages of personal PNC and ambient UFP, ACP, PM_{10} and $\text{PM}_{2.5}$ and concurrent measures of HR and HRV over 1-hour. No consistent associations between personal or ambient particles number concentrations (PNC, UFP, ACP) and HR were observed. In contrast, PM_{10} and $\text{PM}_{2.5}$ were associated both with SDNN and RMSSD as reported previously [17]. The association between $\text{PM}_{2.5}$ and HRV was stronger in individuals with IGT than those with type 2 diabetes, but the differences did not achieve statistical significance. In line with our results, Chan and colleagues observed significant decreases in SDNN and RMSSD in association with an increase of $10,000$ particles/ cm^3 in personally measured particles in the size range between 20 nm and 1 μm in a prospective panel study [22]. Adverse changes in HR and HRV were also observed in association with ambient UFP in panel or cross-over studies [23-28] and with concentrated UFP in controlled chamber studies [29,30] albeit some associations were not significant. However, some studies reported no or even positive associations between HRV and UFP [31-33].

Table 4 Associations between ambient 1-hour average air pollution concentrations at the central monitoring site and 1-hour average ECG-measures

	HR		SDNN		RMSSD	
	%-change	95% CI	%-change	95% CI	%-change	95% CI
Personal PNC	0.13	-0.19; 0.45	-0.93 [†]	-2.01; 0.16	0.53	-0.70; 1.77
UFP	0.40	-0.16; 0.95	0.99	-0.66; 2.64	-0.12	-2.40; 2.21
ACP	0.35	-0.39; 1.09	-0.30	-2.23; 1.64	-1.58	-5.19; 2.18
PM ₁₀	0.67	-0.20; 1.54	-2.78*	-4.98; -0.59	-5.00*	-8.88; -0.95
PM _{2.5}	0.63	-0.44; 1.71	-3.27*	-5.84; -0.69	-6.86**	-11.73; -1.72

Analyses considered concurrent exposures and adjusted for trend, meteorology and time of day. Effect estimates are shown for an increase in interquartile range as given in Table 2.

[†]p-value <0.1, *p-value <0.05, **p-value <0.01, CI: confidence interval, HR: heart rate, RMSSD: root mean square of successive differences, SDNN: standard deviation of NN-intervals, PNC: Particle number concentrations, PM₁₀: particulate matter with an aerodynamic diameter <10µm, PM_{2.5}: particulate matter with an aerodynamic diameter <2.5µm, UFP: ultrafine particles (10-100µm); ACP: accumulation mode particles (100-800 nm).

Effect estimates were larger for the 1-hour PM_{2.5} than for personal PNC and associations between 1-hour PM_{2.5} concentrations and 5-minute HRV strengthened when adjusting for personal PNC (Figure 3). PM_{2.5} measured at an urban background monitoring site quantifies the overall particulate matter level predominantly determined by the meteorological conditions. In the present study, we demonstrate therefore that particle exposures determined by personal proximity to sources and by urban background levels both are associated with changes in cardiac function on a very immediate time scale.

Figure 3 Two pollutant models for 5-minute personal PNC and 1-hour ambient PM_{2.5} on 5-minute HR and HRV parameters, in patients with diabetes or impaired glucose tolerance. Effect estimates are shown for an increase of 16,000 particles cm⁻³ and 12 µg m⁻³ PM_{2.5}.

Earlier studies have observed associations between hourly concentrations of PM_{2.5} and the onset of myocardial infarction in Boston, MA [5] and Rochester, NY [6]. Moreover, times spent in traffic were associated with the onset of myocardial infarction [7,8] and controlled exposure studies suggest that effects of diesel exposures might be enhanced by exercise [34]. Previous studies have in many instances indicated that personal exposures to PM_{2.5} or to gaseous pollutants are associated with changes in HRV [26,35-51]. The study participants ranged from healthy adults to patients with cardiovascular diseases or asthma and were studied in different settings around the world. We had chosen individuals with impaired glucose metabolism because individuals with type 2 diabetes had been shown to be susceptible to air pollution [2-4]. A study of controlled human exposures to concentrated ultrafine particles showed immediate effects on subjects with metabolic syndrome, however, did not observe changes in HRV one hour after the exposure [30]. In contrast, in a study in subjects with type 2 diabetes indicated a decrease in the high frequency component of heart rate variability and increased heart rates persisting up to 48 hours [16]. Furthermore, there is an emerging body of evidence linking ambient air quality as one of the risk factors to type 2 diabetes [52]. Data from controlled animal experiments [53] as well as analyses in prospective population-based cohort studies [54-58] support this association. Systemic inflammation, activation of innate immunity in the lung and an imbalance of the autonomic nervous system induced

by air pollution exposures jointly potentially provide the link to insulin resistance and diabetes exacerbation [52]. Sudden changes in cardiac function may predispose susceptible individuals to sudden cardiac deaths during episodes with elevated particle concentrations [59]. Most likely, different underlying intrinsic mechanisms are activated by 5-minute PNC and 1-hour PM_{2.5}. We hypothesize that shortly elevated PNC may activate irritant receptors and lead thereby to changes in the autonomic control [60]. In contrast, we hypothesize that the changes in HRV observed in association with PM_{2.5} are associated with an activation of host defense on an alveolar level, which may involve translocation of particle components, immediate systemic oxidative stress response and an activation of leukocytes [52].

Sensitivity analyses

Associations were robust in sensitivity analyses and a summary is given in Figure 4 for the association between personally measured personal PNC and SDNN. No statistically significant difference was observed in individuals without beta-blockers intake or statin use. By selecting individuals with impaired glucose tolerance, we intended to study the impact of particles in individuals who were not heavily treated by beta-blockers or statins as these medications may obliterate the effects of particle exposures [61,62].

Figure 4 Sensitivity analyses of the association between concurrent exposure to personally measured PNC and SDNN. *Regression coefficient as reported in Table 3.

Excluding time periods when the participants recorded ETS exposures or cooking rendered consistent results, but suggested that indoor sources contributed to the observed associations. We employed two different ways to adjust for physical activity. Neither adjusting for the diary entries of physical activity nor for heart rate did change the effect estimates. Models including personal noise exposure showed stronger associations with personal PNC (Figure 3) and increased 5-minute SDNN (3.35% [95% CI: 2.95% ; 4.11%] per 5 db[A]) as reported previously [63]. These analyses suggested that the associations of PNC and noise with ECG-parameters were potentially confounding each other. To further test the impact of the model choices, we conducted sensitivity analyses for the immediate effect of PNC on SDNN. Including a time trend within the measurements or including the previous segments of SDNN as a predictor did not change the effect estimates substantially (5-minute SDNN: -0.56% [-0.98%;-0.13%] or -0.42% [-0.77%;-0.06%] per 16,000 cm⁻³ PNC, respectively).

Limitations

The study assessed personal measurements of PNC which is a novel marker for personal exposure to fresh combustion particles. The study thereby overcomes one large limitation of previous panel studies. By employing direct measurements of PNC it also provides different and novel information compared to studies of personal PM_{2.5} or gaseous pollutants [26,35-49]. However, the measurement devices are usually operated by technical personnel to measure indoor and outdoor particle concentrations and were not designed for study participants. As a consequence we were only able to achieve 80% of the planned hourly measurements albeit stringent examiner training, review of the

instruction sessions by audiotape, and written instructions for the participants. The missing measurements had no certain pattern and were related to diligence in following the instructions by the study participants. Diaries were kept by the participants, but no geographic positioning system data was acquired. ECG data and personal PNC data were processed independently. While the examiners and the participants were aware of the study hypotheses, information on their HR was not available and levels of PNC were not discussed with respect to limit or guideline values as these do not exist.

Timing of the measurements were based on recorded times from the instruments and the study protocols. Discrepant times were checked individually, discussed with the study nurses and corrected wherever possible.

Each day's measurement provided control data for the individual and correlation within the day and the individual was considered. Analyses proved to be relatively robust against other assumptions of the covariance structure. Confounding by physical activity, a potentially important individual time-varying factor was considered but did not prove to be strong and resulted in changes of the effect estimates of less than 10%.

There were no statistically significant differences with respect to age, body mass index, HbA1c concentrations, history of cardiovascular disease and medication use when comparing the study participants to all individuals with either diabetes or IGT in the underlying sample of the KORA cohort study. Participants of the panel study were more likely to be unemployed, many of them already retired. In addition, the proportion of ex-smokers was higher in the present study than in the overall sample.

As this study is assessing short-term impacts of urban area ambient particulate matter, it does not address the question, whether long-term exposure to particulate matter is associated with an increased risk for incident diabetes as recently shown [54-58]. However, the data reported here provides evidence that short-term exposure to ambient particulate matter may contribute to cardiovascular disease exacerbation in individuals with impaired glucose metabolism or diabetes.

Conclusion

The data presented here shows changes in HRV associated with personally measured PNC and ambient PM_{2.5} suggesting that both freshly emitted ultrafine particles as well as aged aerosol in urban areas are associated with changes in cardiac function. The study suggests that personal activities and elevated particle concentrations in micro-environments may modify personal exposures and thereby impact on cardiac function. The study was conducted in individuals with type 2 diabetes and IGT suggesting that these subgroups of the population might be at risk for cardiovascular disease exacerbation when transiently exposed to fresh and aged urban particulate matter.

Methods

Study design

A prospective panel study was conducted in Augsburg, Germany, between March 19, 2007 and December 17, 2008. Individuals with diabetes mellitus type 2 or impaired glucose tolerance (IGT) were recruited from an ongoing examination of 3,080 individuals as part of the KORA F4 cohort study (Cooperative Health Research in the Region of Augsburg) as described in detail elsewhere [18,19]. Type 2 diabetes was defined on based on a validated physician diagnosis, or newly diagnosed diabetes (≥ 7.0 mmol/l fasting or ≥ 11.1 mmol/l 2-h glucose) determined by an oral glucose tolerance test. IGT was defined according to the 1999 World Health Organization diagnostic criteria [64]. Exclusion criteria for the present study were 1) current active smoking, 2) intake of platelet aggregation inhibitors except for acetylsalicylic acid, 3) a myocardial infarction and/or interventional procedure (PTCA, bypass surgery) less than 6 months before the beginning of the study, and 4) chronic inflammatory diseases such as Crohn's disease, colitis ulcerosa, and rheumatoid arthritis. Furthermore, individuals were not included in case of 1) an implanted pacemaker, 2) atrial fibrillation, 3) allergy to latex, and 4) thrombosis or shunt in an arm to standardize HRV analyses. All individuals participated in repeated visits scheduled every 4–6 weeks on the same weekday and at the same time of the day.

Ethics and consent statement

The study was conducted in compliance with the Helsinki Declaration. Ethical approval for the study was granted by the Ethics Committee of the Bayerische Landesärztekammer, München, Germany. The study protocol including the participant information and the consent form were part of the ethics review. The study participants gave informed written consent before entering into the study.

ECG monitoring

In the personal monitoring program, participants were equipped for five to six hours with an electrocardiogram (ECG) device during their second up to the fifth visit as described previously [17]. ECGs were recorded with a 12-lead Mortara H12 digital Holter recorder (Mortara Instrument, Milwaukee, WI, USA). Analyses of heart rate variability were restricted to ECGs that had at least 200 beats available for 5-minute intervals. Heart rate (HR) and time domain parameters of HRV, the standard deviation of all normal-to-normal (NN) intervals (SDNN), and the root mean square of successive NN interval differences (RMSSD) were determined on a 5-minute and an hourly basis. Only individuals with at least one ECG recording with duration of at least two hours were used for analysis.

Personal particle number concentration monitoring

Personal exposure to PNC was measured using a portable condensation particle counter model 3007 (TSI Inc., USA) which covered a diameter range from 10 nm to 1 μm . Participants were instructed on how to restart the measurements if tilting might have resulted in an automated stop of the measurements. They carried the device in a specially designed carrier bag within an inlet at the top. Moreover, participants were asked to keep a diary on their activities during the 5–6 hours of personal measurements including information on times spent indoors or outdoors, times spent in traffic, indoor activities such as cooking and sources such as environmental tobacco smoke exposures (ETS). The participants were instructed to always keep the device close by, but at least within the same room at a central location. Diary information was checked for plausibility and used to process the measurement data. In four instances, participants did not carry the PNC device with them for short periods of time (8 minutes, 10 minutes, 30 minutes or 1 hour). These data were excluded from the analyses. Usually, measurements started around 7:30 a.m.; participants were free to go wherever they liked and returned at around 1 p.m. Three portable condensation particle counters were employed during the study. All of them were serviced before the start of the study and comparison measurements were conducted in March 2007. Additional service periods were conducted every six months. More detail is provided in [20].

Central site air pollution monitoring

Ambient air pollution was measured at a central measurement site in Augsburg throughout the complete study period as described previously [65,66]. The measurement location was in urban background approximately 1 km to the south-east of the city center. Particle mass concentrations of $\text{PM}_{2.5}$ and PM_{10} (particulate matter ≤ 2.5 or 10 μm in aerodynamic diameter, respectively) were measured by two separate Tapered Element Oscillating Microbalance (TEOM, model 1400ab, Thermo Fisher Scientific Inc., USA). To correct the PM measurements for aerosol volatility effects, each TEOM was equipped with a Filter Dynamics Measurement System (FDMS, model 8500b, Thermo Fisher Scientific Inc., USA). Particle size distributions in the range from 3–900 nm were measured by a custom-built Twin Differential Mobility Particle Sizer (TDMPS) system consisting of two cylindrical, Vienna-type Differential Mobility Analyzers (DMA) covering complementary size ranges (3 to 23 nm as well as 18 to 900 nm). For the analysis we used the size fraction of ultrafine particles from 10 to 100 nm (ambient UFP) and of accumulation mode particles μm from 100 to 800 (ambient ACP)

Statistical analyses

Repeated continuous outcome data was analyzed using mixed models with random patient effects to accommodate repeated measures and to account for unobserved heterogeneity of the data. To account for dependencies of the outcome measures, covariance structure considered autocorrelation of the first order for measurements of the same day and correlation between measurements of the same individual at days apart. This was done within the framework of additive mixed models to allow for semi-parametric and non-parametric exposure-response functions. Models were selected

separately for HR, SDNN, and RMSSD as described previously [17]. Final models included for HR: time trend (linear), time of day (morning vs. afternoon), 1-hour air temperature (lag 2, polynomial of degree 2), 1-hour relative humidity (lag 1, linear); for SDNN: time trend (linear), time of day (morning vs. afternoon), 1-hour air temperature (concurrent, linear), 1-hour relative humidity (concurrent, linear); and for RMSSD: time trend (linear), time of day (morning vs. afternoon), 1-hour air temperature (lag 7, linear), 1-hour relative humidity (lag 4, linear).

Models were adjusted for ambient meteorology and temporal trends. Penalized splines were used to allow for non-linear confounder adjustment. Results are presented as %-change from the mean per 16,000 ultrafine particles cm^{-3} or the respective interquartile ranges together with 95% confidence intervals. A number of sensitivity analyses were conducted including models adjusting for personal 5-minute noise exposure measured as A-weighted equivalent continuous sound pressure levels (*Leq*) reported in units of A-weighted decibels [dB(A)] (Spark® model 703; Larson Davis Inc., Depew, NY, USA) as described elsewhere [63]. Data were analyzed using SAS statistical software (version 9.1; SAS Institute Inc., Cary, NC, USA).

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AP conceived the study design, obtained funding, supervised the study, directed the data analyses, drafted the manuscript and compiled its final version. RH and SB analyzed the data, JC and designed and supervised the air pollution monitoring, UG performed the data quality assurance, UK supervised the activity diary, WZ designed and performed the ECG analyses, AS contributed to the study design and supervised the field work, quality assurance and data analyses. All authors contributed to interpreting the results, commented on the manuscript and approved its final version.

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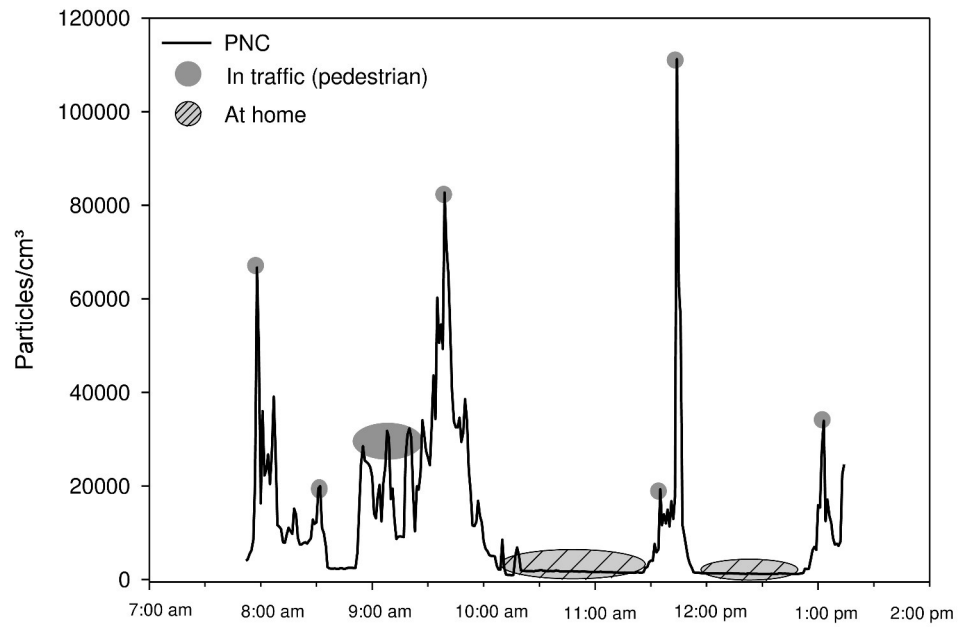


Figure 1 Example of personal measurements of PNC. Data was collected starting and ending at the KORA Study Center on November 27th 2007.

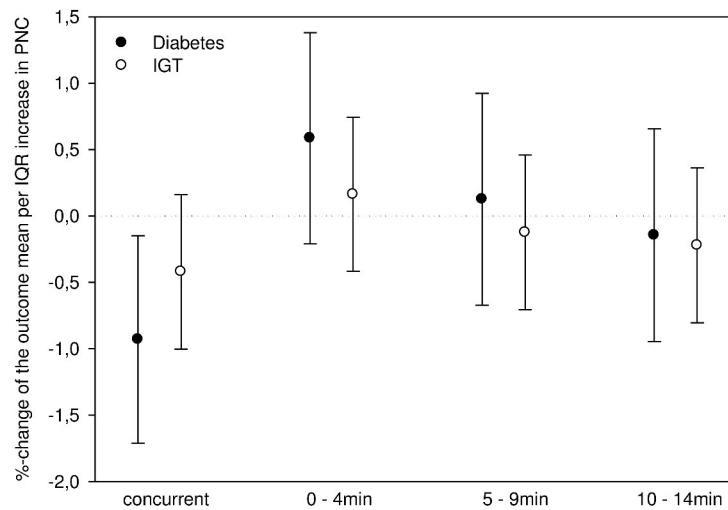


Figure 2 Effects of personally measured 5-minute PNC on SDNN based on 5-minute ECG recordings in patients with diabetes or impaired glucose tolerance. Effect estimates are shown for an increase of 16,000 particles cm^{-3} .

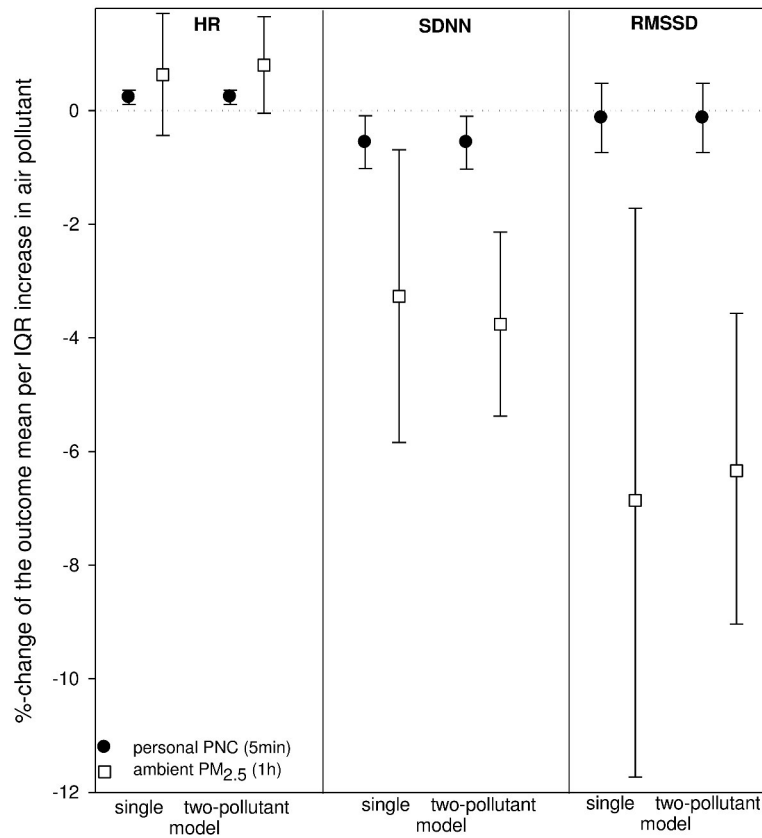


Figure 3 Two pollutant models for 5-minute personal PNC and 1-hour ambient $\text{PM}_{2.5}$ on 5-minute HR and HRV parameters. in patients with diabetes or impaired glucose tolerance. Effect estimates are shown for an increase of 16,000 particles cm^{-3} and 12 $\mu\text{g m}^{-3}$ $\text{PM}_{2.5}$.

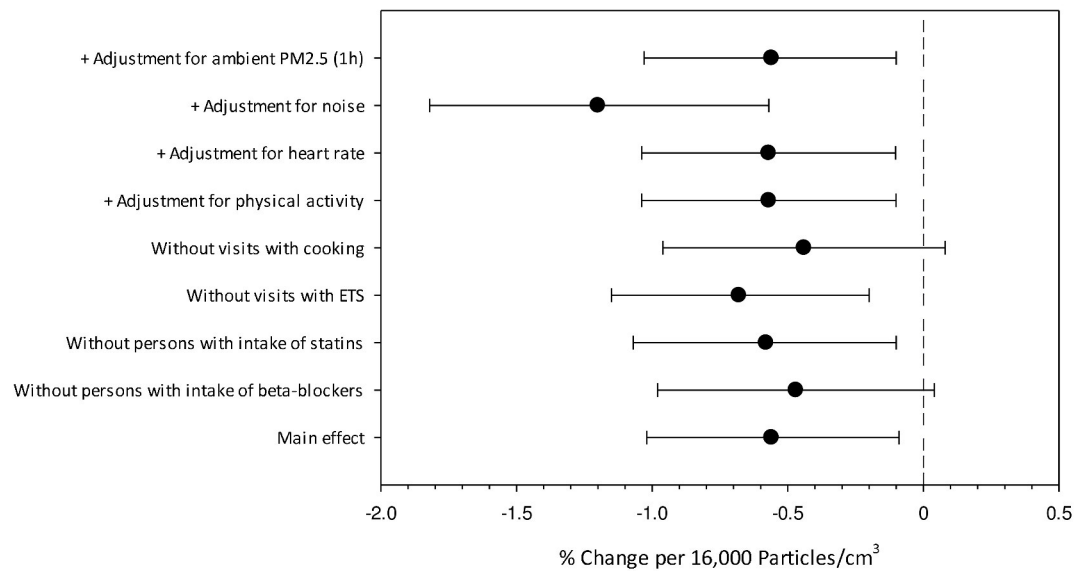


Figure 4 Sensitivity analyses of the association between concurrent exposure to personally measured PNC and SDNN. *Regression coefficient as reported in Table 3.

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