

TITLE

ROAD TRAFFIC NOISE, BLOOD PRESSURE AND HEART RATE: POOLED
ANALYSES OF HARMONIZED DATA FROM 88,336 PARTICIPANTS

AUTHORS

Wilma Zijlema PhD^{1,11}, Yutong Cai MSc², Dany Doiron MSc^{3,4}, Stéphane Mbatchou MSc³,
Isabel Fortier PhD³, John Gulliver PhD², Kees de Hoogh PhD^{2,4,5}, David Morley PhD², Susan
Hodgson PhD², Paul Elliott PhD², BioSHaRE, Timothy Key PhD⁶, Havard Kongsgard MSc⁷,
Kristian Hveem MD PhD⁷, Amadou Gaye PhD⁸, Paul Burton PhD⁹, Anna Hansell PhD²,
Ronald Stolk MD PhD¹, Judith Rosmalen PhD¹⁰

¹University of Groningen, University Medical Center Groningen, Department of
Epidemiology, Groningen, the Netherlands

²MRC-PHE Centre for Environment and Health, Department of Epidemiology and
Biostatistics, School of Public Health, Imperial College London, London, United Kingdom

³Maelstrom Research group, Research Institute of the McGill University Health Centre (RI-
MUHC), Montréal, Québec, Canada

⁴Swiss Tropical and Public Health Institute, Basel, Switzerland

⁵University of Basel, Basel, Switzerland

⁶Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford,
Oxford, United Kingdom

⁷HUNT Research Centre, Department of Public Health and General Practice, Norwegian
University of Science and Technology, Levanger, Norway

⁸National Human Genome Research Institute, Metabolic, Cardiovascular and Inflammatory
Disease Genomics Branch, Bethesda, USA

⁹School of Social and Community Medicine, University of Bristol, Bristol, United Kingdom

¹⁰University of Groningen, University Medical Center Groningen, Departments of Psychiatry

and Internal Medicine, Groningen, the Netherlands

¹¹ISGlobal, Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain,
Universitat Pompeu Fabra (UPF), Barcelona, Spain, CIBER Epidemiología y Salud Pública
(CIBERESP), Madrid, Spain

SHORT TITLE

NOISE, BLOOD PRESSURE AND HEART RATE

CORRESPONDING AUTHOR

Wilma L. Zijlema, PhD

ISGlobal, Centre for Research in Environmental Epidemiology (CREAL)

Barcelona Biomedical Research Park (PRBB)

Doctor Aiguader 88, 08003 Barcelona, Spain

Tel: +34 932147341, Fax: +34 93 214 73 02, E-mail: wilma.zijlema@isglobal.org

ABSTRACT

Introduction

Exposure to road traffic noise may increase blood pressure and heart rate. It is unclear to what extent exposure to air pollution may influence this relationship. We investigated associations between noise, blood pressure and heart rate, with harmonized data from three European cohorts, while taking into account exposure to air pollution.

Methods

Road traffic noise exposure was assessed using a European noise model based on the Common Noise Assessment Methods in Europe framework (CNOSSOS-EU). Exposure to air pollution was estimated using a European-wide land use regression model. Blood pressure and heart rate were obtained by trained clinical professionals. Pooled cross-sectional analyses of harmonized data were conducted at the individual level and with random-effects meta-analyses.

Results

We analyzed data from 88,336 participants, across the three participating cohorts (mean age 47.0 (\pm 13.9) years). Each 10 dB(A) increase in noise was associated with a 0.93 (95% CI 0.76;1.11) bpm increase in heart rate, but with a decrease in blood pressure of 0.01 (95% CI -0.24;0.23) mmHg for systolic and 0.38 (95% CI -0.53;-0.24) mmHg for diastolic blood pressure. Adjustments for PM₁₀ or NO₂ attenuated the associations, but remained significant for DBP and HR. Results for BP differed by cohort, with negative associations with noise in LifeLines, no significant associations in EPIC-Oxford, and positive associations with noise >60 dB(A) in HUNT3.

Conclusions

Our study suggests that road traffic noise may be related to increased heart rate. No consistent evidence for a relation between noise and blood pressure was found.

KEYWORDS: blood pressure, heart rate, noise, air pollution, epidemiology, meta-analysis

SOURCES OF FUNDING

The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n°261433 (Biobank Standardisation and Harmonisation for Research Excellence in the European Union - BioSHaRE-EU). DataSHIELD development has also been partly funded under a strategic award from MRC and Wellcome Trust underpinning the ALSPAC project; and the Welsh and Scottish Farr Institutes funded by MRC, BBMRI-LPC (EU FP7, I3 grant).

BioSHaRE, and the involved cohorts LifeLines (BRIF 4568) and HUNT3 (BRIF 2365) are engaged in a Bioresource Research Impact Factor (BRIF) policy pilot study, details of which can be found at <https://www.bioshare.eu/content/bioresource-impact-factor>.

The Lifelines Biobank initiative has been made possible by funds from FES (Fonds Economische Structuurversterking), SNN (Samenwerkingsverband Noord Nederland) and REP (Ruimtelijk Economisch Programma). LifeLines is a facility that is open for all researchers. Information on application and data access procedure is summarized on www.lifelines.net. We thank all the participants of EPIC-Oxford and data collection teams for generously helping us in this research. EPIC-Oxford is supported by Cancer Research UK C8221/A19170), and the UK Medical Research Council (MR/M012190). The Nord-Trøndelag Health Study (The HUNT Study) is collaboration between HUNT Research Centre (Faculty of Medicine, Norwegian University of Science and Technology NTNU), Nord-Trøndelag County Council, Central Norway Health Authority, and the Norwegian Institute of Public Health. P.E. is supported by the Imperial College Healthcare NHS Trust and Imperial College Biomedical Research Centre funded by the National Institute for Health Research (NIHR), the Medical Research Council and Public Health England (MRC-PHE) Centre for Environment and Health, the NIHR Health Protection Research Unit on Health Impact of

Environmental Hazards and he is an NIHR Senior Investigator.

ETHICS STATEMENT

All individual participants provided written informed consent and study protocols were approved by the local ethical committees.

DISCLOSURES None.

INTRODUCTION

Traffic-related noise poses a significant risk to human health (WHO, 2011). Higher noise exposure has been associated with increased risks for cardiovascular disease (Fecht et al., 2016; Halonen et al., 2015). Noise is generally believed to provoke stress through perceived discomfort (Bluhm et al., 2004), and also to result in subconscious activation of stress systems (Recio et al., 2016). Direct or indirect activation of the sympathetic and endocrine systems is followed by increases in heart rate, blood pressure, and release of stress hormones (Chrousos and Gold, 1992). Noise-induced sleep disturbance may also disrupt secretion of stress hormones, affecting metabolism and the cardiovascular system, ultimately resulting in cardiovascular disease (Münzel et al., 2014).

Some studies have found associations between traffic noise and hypertension (Foraster et al., 2014; van Kempen and Babisch, 2012) but in other studies the relation was less clear (Babisch et al., 2014; Sorensen et al., 2011), or only observed in specific subgroups (e.g. diabetes patients) (Dratva et al., 2012). These inconsistencies may be due to differences in the assessments of noise exposure, covariates, blood pressure or differences across statistical approaches used (van Kempen and Babisch, 2012).

The role of air pollution in the relation between traffic noise and hypertension is unclear. Exposure to ambient air pollution is also associated with hypertension (Cai et al., 2016) and cardiovascular morbidity and mortality (Brook et al., 2010). As road traffic is the main common source for both noise and air pollution, it is important to distinguish the cardiovascular effects of each. Until recently, studies did not take into account exposures to traffic-related noise and air pollution simultaneously. A systematic review based on nine studies up to 2012 suggested a likely independent effect of both traffic-related noise and air pollution on cardiovascular disease (Tétreault et al., 2013), which was further supported by a recent updated review (Stansfeld, 2015). However, as only a handful of studies were

available, a definitive conclusion on the respective roles of air pollution and noise on cardiovascular disease cannot yet be drawn, which warrants further research.

Compared to blood pressure studies, there are far fewer studies investigating the association with heart rate in adults to date (Holand et al., 1999; Raggam et al., 2007),

The aim of this cross-sectional study was to investigate associations between road traffic noise, blood pressure and heart rate, while taking into account exposure to ambient air pollution. We investigated these associations in 88,336 adults from three European cohorts: LifeLines, EPIC-Oxford and HUNT3. We used a harmonized approach and federated data analyzes to enable comparisons of results between different studies and regions.

METHODS

Study populations

This study was undertaken within the Biobank Standardisation and Harmonisation for Research Excellence in the European Union (BioSHaRE-EU) project, using a harmonized approach to noise and air pollution exposure, health data and potential confounders. Within BioSHaRE, tools were developed for data harmonization and federated data analyses (Doiron et al., 2013). Data were obtained from three European cohorts: LifeLines (the Netherlands) (Scholtens et al., 2014), EPIC-Oxford (United Kingdom) (Davey et al., 2003), and HUNT3 (Norway) (Krokstad et al., 2013). LifeLines is a multi-disciplinary prospective population based cohort study examining the health and health-related behaviors of persons living in the North East region of the Netherlands. Recruitment occurred through general practitioners, online self-registration, and subsequent inclusion of participants' family members. EPIC-Oxford (the Oxford cohort of the European Prospective Investigation into Cancer and Nutrition) is a nationwide study in the UK aimed at investigating how diet influences the risk for cancers and other chronic diseases. Participants were recruited via

general practice and postal recruitment. In addition to inclusion of members of the general population, recruitment was focused on including participants with a wide range of dietary habits as well as vegetarians and vegans. HUNT3 (the 3rd survey of the Nord-Trøndelag Health Study) is a prospective population based study from the Nord-Trøndelag County in Norway, examining health related lifestyle, prevalence and incidence of somatic and mental illness and disease, health determinants, and associations between disease phenotypes and genotypes. Recruitment occurred through national census data. All individual participants provided written informed consent and study protocols were approved by the local ethical committees.

The present study included baseline data with road traffic noise and air pollution estimates available for 156,424 participants, aged between 18 and 92 years. Participants with incomplete data regarding blood pressure and heart rate measurements (n = 33,059; mainly because in EPIC-Oxford this was only measured in a subsample), educational level (n=19,052, mainly because this data was lacking in HUNT3 and was used from HUNT2, see covariates paragraph), BMI (n=146), and alcohol use and smoking status (n=15,831) were excluded. Participants with incomplete data regarding antihypertensive medication use (n=2) were excluded from the corresponding analyses.

Road traffic noise exposure assessment

Exposure to road traffic noise was assessed at individual home addresses using the Common Noise Assessment Methods in Europe (CNOSSOS-EU) noise model (Kephalopoulos et al., 2014). The CNOSSOS-EU framework contains empirically derived equations to determine average noise level based on traffic flow, and sound propagation based on known environmental factors and physical processes. Quantitative data of road networks, traffic flows, land cover, building height, and meteorology were obtained from local sources. Propagation effects such as distance from receiver to the noise source, land cover type,

building obstruction, and meteorological conditions are included as sound propagation parameters in the model. Traffic data originated from year 2009 and land cover data from 2006. Detailed land cover data at the scale of our study regions were not available to allow positioning of the receptor at the most exposed façade. Therefore a coarser land cover data set was used to approximate urban fabric. A fixed baseline traffic flow was assigned to participants living on minor roads that were not captured in the national level traffic datasets. Some lower resolution data inputs were used within the CNOSSOS-EU noise model to obtain comparable exposure estimates across the wide regions in our study. Model validation showed adequate performance for exposure ranking: discrimination between noisier and quieter areas gave Spearman's rank = 0.75; $p < 0.001$. The lower resolution data derived model has however relatively large errors in the predicted noise levels (root mean square error (RMSE) = 4.46 dB(A)) (Morley et al., 2015). The noise metric L_{den} (day-evening-night time period of 24 hours) is used. L_{den} is the average A-weighted noise level, estimated over a 24 hour period, with a 10 dB penalty added to the night (23.00–07.00 hours), and a 5 dB penalty added to the evening period (19.00–23.00 hours), to indicate people's extra sensitivity to noise during the night and evening.

Ambient air pollution exposure assessment

Exposure to particulate matter with a diameter $\leq 10 \mu\text{m}$ (PM_{10}) and nitrogen dioxide (NO_2) at individual home addresses was estimated using a land use regression (LUR) model for Western Europe on a resolution of 100x100 m (Vienneau et al., 2013). Geographical Information System-derived land use, topographic data, and satellite-derived estimates of ground-level concentration of $\text{PM}_{2.5}$ (as an indicator of PM_{10}) and NO_2 were used to predict the dependent variables ambient concentrations of PM_{10} and NO_2 obtained from regulatory

monitoring (EuroAirnet, years 2005-2007). Models were evaluated against measured PM₁₀ and NO₂ concentrations at an independent subset of measurement sites. LUR models explained 55-60% (NO₂) and 38-47% (PM₁₀) of the variation in measured concentrations (Vienneau et al., 2013).

Blood pressure and heart rate measurements

Systolic and diastolic blood pressure and heart rate measurements were conducted by trained clinical professionals within each participating cohort. In LifeLines, measurements took place at the research facilities according to a standardized protocol. Blood pressure and heart rate were measured 10 times within a period of 10 minutes, using an automated Dinamap Monitor (GE Healthcare, Freiburg, Germany). Cuff size was chosen according to the arm circumference. Participants were in a seated position and were instructed not to talk. The final two accurate recordings were averaged for systolic and diastolic blood pressure and heart rate. In EPIC-Oxford, blood pressure and heart rate measurements took place at the participant's general practice. No standardized method of blood pressure measurement was used and only a single measurement was taken (Appleby et al., 2002). In HUNT3, blood pressure and heart rate were measured using a Dinamap 845XT (Critikon, Tample, FL, USA), and measurements took place at the research facilities. Cuff size was chosen according to the arm circumference, and participants were in a seated position with the arm rested on a table. Measurements were carried out three times, and the average of the second and third recording was used in the analyses.

Covariates

Data on age, sex, educational level, alcohol intake, smoking status, body mass index, and medication use were harmonized according to the DataSHaPER (DataSchema and Harmonization Platform for Epidemiological Research) methodology (Fortier et al., 2011,

2010). DataSHaPER provides a template to facilitate harmonization and pooling of data between studies. First, ‘target variables’ needed to answer our research question were identified. Relevant data were then identified within all studies, and the potential for harmonization was evaluated. When harmonization was deemed possible, cohort-specific data were transformed into a common, harmonized format in order to be co-analyzed. Educational level was defined as highest level of education completed by the participant. Categories were adapted from the UNESCO Revision of the International Standard Classification of Education. Education data were obtained from the question “What is your highest completed education?” in LifeLines and EPIC-Oxford. Educational level was only questioned in HUNT2 (the 2nd survey of the Nord-Trøndelag Health Study) but not in HUNT3; we used such data for the same participants who answered this question in HUNT2. Harmonization of education data resulted in two categories: “primary and secondary education” and “tertiary education”. Alcohol use was defined as grams of alcohol consumed on average per week. If information about serving size for different drinks was not mentioned, then the average serving size in each country was imputed to allow derivation of grams of alcohol. Smoking status (never smoker/ex smoker/current smoker) was assessed with questionnaires. Height and weight were measured without heavy clothing and shoes. Body Mass Index (BMI, kg/m²) was calculated subsequently. Antihypertensive medication use (yes/no) was either self-reported by a question targeting the use of antihypertensive medication (HUNT3) or extracted from a list of medications using the following Anatomical Therapeutic Chemical (ATC) Codes (C02, C03, C04, C07, C08, C09) or equivalent in other classifications (LifeLines). Data on medication use were available in LifeLines and HUNT3, not in EPIC-Oxford. Address history was available from municipal registries, and were available in LifeLines and HUNT3.

Statistical analyses

The associations between road traffic noise, systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were investigated with two statistical approaches:

1. Pooled linear regression analyses of harmonized data for the three cohorts were conducted at the individual level using the DataSHIELD approach (Wolfson et al., 2010). DataSHIELD enables federated analysis of multiple studies by analyzing individual-level harmonized data from each cohort without physically pooling the data, which stay behind the firewalls of the cohort's host computers. As a result, individual data can be simultaneously analyzed without transferring data externally. DataSHIELD offers a solution to practical, ethical, and legal issues associated with data sharing and analysis (Gaye et al., 2014). We used the `ds.glm` function in DataSHIELD (version 4.1.0), which is comparable to the `glm` function in the R statistical environment (R Core Team, 2013).

2. Cohort-specific linear regression analyses were also undertaken using the `ds.glm` function in DataSHIELD (version 4.1.0). Subsequently, study specific associations were combined using random effects meta-analyses (using the DerSimonian-Laird estimator) to account for heterogeneity between the cohorts (DerSimonian and Laird, 1986). The I^2 statistic (Higgins et al., 2003) was used to quantify heterogeneity of cohort specific results. Meta-analyses were performed in R (version 3.1.2) using the `rma` function from the `metaphor` package (Viechtbauer, 2010).

Associations with 24-hour (L_{den}) road traffic noise were initially adjusted for age, sex, educational level, alcohol use, smoking status, and BMI, and additionally for PM_{10} , or NO_2 . The pooled linear regression analyses (approach 1) were also adjusted for cohort, to account for study-specific effects. Effect estimates are presented as regression coefficients with 95% confidence intervals (CI) per 10 dB(A). In addition, associations between road traffic noise, BP, and HR were analyzed with noise classified into categories of <55 dB(A), 55-60 dB(A),

and >60 dB(A) (pooled analyses), and for the cohort-specific analyses into <55 dB(A), 55-60 dB(A), 60-65 dB(A), and >65 dB(A) for LifeLines and EPIC-Oxford, and <50 dB(A), 50-55 dB(A), 55-60 dB(A), and >60 dB(A) for HUNT3 due to different ranges of L_{den} .

We performed additional analyses for evaluation of effect modification of the associations by sex and age. First, the main effects (e.g. L_{den} and age) and their interaction were included in the models. If statistical significance ($p < 0.05$) of the interaction term was observed, analyses were stratified for that variable. We also explored the impact of antihypertensive treatment (AHT) by stratifying the analyses by three groups: known hypertensives (taking antihypertensive medication), possible uncontrolled hypertensives (no AHT and SBP ≥ 130 mmHg, DBP ≥ 85 mmHg), and non-elevated BP (no AHT and SBP ≤ 129 mmHg, DBP ≤ 84 mmHg). Impact of residential mobility was explored by restricting the analyses to participants that lived at their current address for <5 and ≥ 5 years. Additional analyses for medication use and residential mobility were undertaken in LifeLines and HUNT3, since data on medication use and address history were not available in EPIC-Oxford.

RESULTS

Data from 88,336 participants, with a mean age of 47.1 (± 13.9 , range 18-96) years, were available for this study. Pooled and cohort specific population characteristics are summarized in Table 1. Median level of road traffic noise (L_{den}) exposure was highest in EPIC-Oxford (54.9 dB(A)) and lowest in HUNT3 (49.3 dB(A)). Median levels of PM_{10} varied between 11.1 (HUNT3) and 23.6 (LifeLines) $\mu g/m^3$, and NO_2 levels varied between 11.7 (HUNT3) and 25.6 (EPIC-Oxford) $\mu g/m^3$ (Table 1 and Figure 1). Spearman rank correlations between road traffic noise and PM_{10} , and road traffic noise and NO_2 , were $r=0.06$ and 0.06 respectively in EPIC-Oxford, $r=0.07$ and -0.05 in HUNT3, and $r=0.40$ and 0.46 in LifeLines (all $p < 0.001$).

Mean levels of SBP ranged from 123.4 to 132.7 mmHg, with highest mean level observed in HUNT3. Mean levels of DBP and HR were reasonably similar between the cohorts (Table 1). Use of antihypertensive medication was 10.3% in LifeLines and 25.9% in HUNT3.

Results from pooled linear regression analyses, cohort-specific analyses, and meta-analyses

Pooled linear regression analyses, adjusted for age, sex, education, alcohol use, smoking, BMI, and cohort, showed significant associations between noise (per 10dB(A)) and DBP ($\beta = -0.38$; 95% CI -0.53; -0.24) mmHg, and HR ($\beta = 0.93$; 95% CI 0.76; 1.11) bpm) but not SBP ($\beta = -0.01$; 95% CI -0.24; 0.23) mmHg (Table 2). Additional adjustment for PM₁₀ or NO₂ resulted in attenuation of the associations (DBP: a 8 and 29% decrease respectively; HR: a 25 and 33% decrease respectively), but associations remained significant for DBP and HR (Table 2).

Cohort-specific linear regression analyses showed heterogeneous results. In LifeLines, models unadjusted for air pollution yielded significant negative associations between noise and SBP, whereas in EPIC-Oxford no association and in HUNT3 a positive association was found, although not statistically significant (Figure 2). For DBP, results for LifeLines and EPIC-Oxford showed similar negative associations, while these were null for HUNT3 (Figure 2). Noise was consistently associated with higher HR, although not statistically significant in EPIC-Oxford (Figure 2). Confounding by air pollution was strongest in LifeLines, and less pronounced in EPIC-Oxford and HUNT3.

When we combined the cohort-specific estimates using random-effects meta-analyses, associations were generally smaller and less precise, as observed from the wider confidence intervals, if compared to the results from the pooled individual data regression analyses. I² values indicated moderate to high heterogeneity among cohort-specific results for SBP (69.5% unadjusted for air pollution, 71.8% adjusted for PM₁₀, 58.0% adjusted for NO₂) and DBP (63.3% unadjusted for air pollution, 31.5% adjusted for PM₁₀, and 0% NO₂).

Heterogeneity of the results for HR ranged from 86.0% unadjusted for air pollution, to 0% adjusted for NO₂ or PM₁₀.

Analyses with the categorical noise variable and SBP, DBP, and HR resulted in similar conclusions as with the analyses with noise as a continuous variable for the pooled analyses (Table 3/Figure 3). Cohort-specific analysis revealed that in HUNT3, the highest noise category (>60 dB(A)) was associated with statistically significantly higher SBP ($\beta= 4.83$; 95% CI 2.59; 7.06 mmHg) and DBP ($\beta= 1.58$; 95% CI 0.21; 2.95 mmHg) compared with the lowest noise category (<50 dB(A)) (Table 3, Figure 3).

Effect modification

Since we observed significant interactions with sex ($p_{\text{interaction}} < .0001$ for SBP, DBP, and HR) and age ($p_{\text{interaction}} < 0.001$ for SBP, DBP, and HR) stratified analyses were carried out by these variables (Table 4). Results were stronger for males than females, with a larger negative association between noise and DBP in males than in females, and a larger positive association between noise and HR in males than in females. We observed no statistically significant association for SBP.

The negative associations between noise and SBP and DBP were only statistically significant in those aged 45 years and younger. In participants aged 65 years and older, noise was non-significantly associated with both higher SBP and DBP. No clear trend by age was observed for the association between noise and HR.

There were statistically significant negative associations between noise and both SBP and DBP in participants without hypertension. In those who were hypertensive (known hypertensives and possible uncontrolled hypertensives) there were no significant associations between noise and both SBP and DBP, but we did observe positive regression

coefficients in the group with possible uncontrolled hypertension. The association between noise and elevated HR was lower in those with antihypertensive medication use (Table 4).

Associations remained in the same directions as in the total sample for participants that lived <5 and ≥ 5 years at their current home address, but the association between road traffic noise and DBP was no longer statistically significant for participants living longer than 5 years at their current address (Table 4).

DISCUSSION

In our study of three European population-based cohort studies including 88,336 participants, exposure to road traffic noise was related to elevated resting HR. No consistent evidence for a relation between road traffic noise and BP was found. Subgroup analyses indicated that associations between road traffic noise and elevated BP may be more likely in individuals older than 65 years and in those with potential uncontrolled hypertension.

Unlike some previous studies we did not find a consistent association between road traffic noise and elevated BP. We found no evidence for an association between road traffic noise and SBP, and we observed negative associations between road traffic noise and DBP. The negative association with DBP was observed in younger age groups, those who are not on antihypertensive medication, and those who have lived in their house for $<$ five years. These results are unexpected, but we observed marked heterogeneity between cohorts with negative associations appearing to be driven by associations in the LifeLines Cohort Study, a younger cohort from the Netherlands.

One possible explanation for lack of clear associations with BP is exposure misclassification. In a study in Spain by Foraster et al. (2014), nighttime traffic noise was estimated for both

outdoor and indoor exposure. While indoor traffic noise was associated with hypertension and increased SBP, associations with outdoor noise were less consistent. Indoor noise estimates may be a better reflection of an individual's 'true' exposure. We modeled at the national scale, which resulted in a less detailed noise exposure estimation than might have been possible at the local scale, where higher resolution input data are generally available and result in higher resolution model output (Morley et al., 2015). A study investigating associations between road traffic noise, PM_{2.5}, and hypertension in a German cohort, found no associations in their study population from the Greater Augsburg region, but did find associations for those living in the city of Augsburg, for which they had a more detailed noise exposure assessment (Babisch et al., 2014). However, we did observe associations between road traffic noise and HR suggesting that the model was sufficient to allow us to discriminate exposure contrasts across our population. Van Kempen and Babisch (2012) reported a positive association between road traffic noise and hypertension based on their meta-analysis of 24 studies (van Kempen and Babisch, 2012). The pooled effect estimates increased with increasing years of residence in the van Kempen and Babisch meta-analysis (2012). We observed that the negative association between road traffic noise and DBP in the subgroup that lived ≥ 5 years at their current home address became smaller and was no longer statistically significant, a change of results in the same direction as van Kempen and Babisch (2012). This may be related to exposure misclassification and to the somewhat older participants in this subsample. Younger participants tend to relocate more frequently, are healthier, and potentially more exposed to noise.

The association between noise and elevated heart rate is a novel finding. Most of the previous studies that have investigated relations between noise and heart rate have done so in experimental settings (Goyal et al.; Holand et al., 1999; Raggam et al., 2007) or in children

(Belojevic et al., 2008; Regecová and Kellerová, 1995; van Kempen et al., 2006). Some of these studies also reported inconsistent results for BP and HR (Belojevic et al., 2008; Regecová and Kellerová, 1995). Additional general population studies are needed to replicate our results for noise and heart rate.

We found that additional adjustment for PM₁₀ or NO₂ generally resulted in attenuation of the associations between noise, BP, and HR. However, associations with DBP and HR remained statistically significant, indicating that these associations cannot be entirely explained by exposure to air pollution. Foraster et al. (2014) reported that the associations between indoor noise and SBP were not confounded by NO₂, while there was confounding by NO₂ in the analyses with outdoor noise, and Babisch et al. (2014) reported that inclusion of air pollutants in their analyses only slightly diminished the associations between noise and hypertension. In another study from the Netherlands, no evidence for confounding by air pollution was observed (de Kluizenaar et al., 2007). Exposure to air pollution may have some effect on the relation between noise, BP, and HR, but more studies are needed to disentangle these effects.

Our study has several strengths and limitations. A major strength of this study is its sample size. With data from 88,336 participants, our study is one of the largest studies examining noise and cardiovascular effects to date. The use of the novel software DataSHIELD to conduct virtual pooling increased power further and allowed us to examine interactions in a number of subgroups. Data originated from three different study regions, enabling comparison across different areas. Another strength of the study was harmonization of both exposure estimation and cohort data. However, there was still large heterogeneity between cohorts so we have also reported results for each cohort separately. At the time of our study, we were not able to use mixed models that take into account heterogeneous multi-cohort data in the

virtually pooled analyses, as this statistical technique was not yet implemented in DataSHIELD. Furthermore, selection of participants in each cohort may have affected our results – firstly, those in Lifelines were younger, while recruitment in EPIC-Oxford was focused on including vegetarians and vegans. Because of this selection for potentially ‘health conscious’ persons, participants in EPIC-Oxford may be healthier than participants in the other cohorts (Crowe et al., 2013, 2011). Associations for SBP and HR were smaller in EPIC-Oxford than for the other cohorts. Secondly, recruitment of EPIC-Oxford participants started in 1993, which is earlier than in LifeLines and HUNT3. Participants that were recruited later may have more controlled blood pressure levels due to improvements in clinical practice.

Although exposure ranges of road traffic noise and ambient air pollution of the three cohorts combined were relatively large, median levels were relatively low, if compared to other European cohorts (e.g.(Fuks et al., 2014)). It is therefore unclear to what extent the conclusions of our study can be generalized to regions with higher levels of noise and air pollution. Correlation between road traffic noise and the air pollutants were low in the EPIC-Oxford and HUNT3 cohorts. Lower resolution predictor variables were used for the road traffic noise model and varied by region. For example, the road network for the Netherlands had a good coverage of minor roads, but the road network for the UK and Norway only had major roads included. The higher correlation between noise and air pollution for LifeLines may be driven by a more complete representation of the road network. Improvement of road network coverage with traffic flows on a national scale could aid estimation of road traffic noise exposure in future large-scale epidemiological studies (Morley and Gulliver, 2016). Furthermore, although large efforts were made to harmonize the study data, blood pressure and heart rate data could not be completely harmonized. Measurement procedures differed between the cohorts, and could have resulted in variations in outcome data and measurement bias. Blood pressure and heart rate measurements in EPIC-Oxford were conducted only once,

while they are known to be highly variable. In addition, measurements were standardized in LifeLines and HUNT3, but not in EPIC-Oxford. Measurement errors reduce the power to detect an association, and will bias associations toward the null. Lack of information on AHT in EPIC-Oxford has limited us to take into account the effect of AHT on the relation between noise and blood pressure and heart rate. Data harmonization of education level resulted in a harmonized variable with only two categories (primary and secondary education; tertiary education), resulting in information loss of the education data. We were not able to use any other data to account for socioeconomic status, and residual confounding by socioeconomic status may therefore remain. There may also be residual confounding by dietary habits and physical activity, since it was not possible to harmonize data on the lifestyle factors, and could therefore not be included in our models.

CONCLUSIONS

In our study with 88,336 participants from the Netherlands, UK, and Norway, road traffic noise was associated with elevated resting heart rate. No consistent evidence for a relation between road traffic noise and blood pressure was observed and results for blood pressure were heterogeneous between cohorts. These findings partly support the idea that road traffic noise is a risk factor for cardiovascular disease.

REFERENCES

Appleby, P.N., Davey, G.K., Key, T.J., 2002. Hypertension and blood pressure among meat eaters, fish eaters, vegetarians and vegans in EPIC-Oxford. *Public Health Nutr.* 5, 645–

654. doi:10.1079/PHN2002332

- Babisch, W., Wolf, K., Petz, M., Heinrich, J., Cyrys, J., Peters, A., 2014. Associations between traffic noise, particulate air pollution, hypertension, and isolated systolic hypertension in adults: the KORA study. *Environ. Health Perspect.* 122, 492–8. doi:10.1289/ehp.1306981
- Belojevic, G., Jakovljevic, B., Stojanov, V., Paunovic, K., Ilic, J., 2008. Urban road-traffic noise and blood pressure and heart rate in preschool children. *Environ. Int.* 34, 226–31. doi:10.1016/j.envint.2007.08.003
- Bluhm, G., Nordling, E., Berglind, N., 2004. Road traffic noise and annoyance--an increasing environmental health problem. *Noise Health* 6, 43–9.
- Brook, R.D., Rajagopalan, S., Pope, C.A., Brook, J.R., Bhatnagar, A., Diez-Roux, A. V, Holguin, F., Hong, Y., Luepker, R. V, Mittleman, M.A., Peters, A., Siscovick, D., Smith, S.C., Whitsel, L., Kaufman, J.D., 2010. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. *Circulation* 121, 2331–78. doi:10.1161/CIR.0b013e3181dbee1
- Cai, Y., Zhang, B., Ke, W., Feng, B., Lin, H., Xiao, J., Zeng, W., Li, X., Tao, J., Yang, Z., Ma, W., Liu, T., 2016. Associations of Short-Term and Long-Term Exposure to Ambient Air Pollutants With Hypertension: A Systematic Review and Meta-Analysis. *Hypertens. (Dallas, Tex. 1979)* 68, 62–70. doi:10.1161/HYPERTENSIONAHA.116.07218
- Chrousos, G.P., Gold, P.W., 1992. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *JAMA* 267, 1244–52.
- Crowe, F.L., Appleby, P.N., Allen, N.E., Key, T.J., 2011. Diet and risk of diverticular disease in Oxford cohort of European Prospective Investigation into Cancer and Nutrition (EPIC): prospective study of British vegetarians and non-vegetarians. *BMJ* 343, d4131.

- Crowe, F.L., Appleby, P.N., Travis, R.C., Key, T.J., 2013. Risk of hospitalization or death from ischemic heart disease among British vegetarians and nonvegetarians: results from the EPIC-Oxford cohort study. *Am. J. Clin. Nutr.* 97, 597–603.
doi:10.3945/ajcn.112.044073
- Davey, G.K., Spencer, E.A., Appleby, P.N., Allen, N.E., Knox, K.H., Key, T.J., 2003. EPIC-Oxford: lifestyle characteristics and nutrient intakes in a cohort of 33 883 meat-eaters and 31 546 non meat-eaters in the UK. *Public Health Nutr.* 6, 259–69.
doi:10.1079/PHN2002430
- de Kluizenaar, Y., Gansevoort, R.T., Miedema, H.M., de Jong, P.E., 2007. Hypertension and road traffic noise exposure. *J. Occup. Environ. Med.* 49, 484–492.
doi:10.1097/JOM.0b013e318058a9ff
- DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. *Control. Clin. Trials* 7, 177–88.
- Doiron, D., Burton, P., Marcon, Y., Gaye, A., Wolffenbuttel, B.H., Perola, M., Stolk, R.P., Foco, L., Minelli, C., Waldenberger, M., Holle, R., Kvaloy, K., Hillege, H.L., Tasse, A.M., Ferretti, V., Fortier, I., 2013. Data harmonization and federated analysis of population-based studies: the BioSHaRE project. *Emerg. Themes Epidemiol.* 10, 12.
doi:10.1186/1742-7622-10-12
- Dratva, J., Phuleria, H.C., Foraster, M., Gaspoz, J.-M., Keidel, D., Kuenzli, N., Liu, L.-J.S., Pons, M., Zemp, E., Gerbase, M.W., Schindler, C., 2012. Transportation Noise and Blood Pressure in a Population-Based Sample of Adults. *Environ. Health Perspect.* 120, 50–55. doi:10.1289/ehp.1103448
- Fecht, D., Hansell, A.L., Morley, D., Dajnak, D., Vienneau, D., Beevers, S., Toledano, M.B., Kelly, F.J., Anderson, H.R., Gulliver, J., 2016. Spatial and temporal associations of road

traffic noise and air pollution in London: Implications for epidemiological studies.

Environ. Int. 88, 235–242. doi:10.1016/j.envint.2015.12.001

Foraster, M., Künzli, N., Aguilera, I., Rivera, M., Agis, D., Vila, J., Bouso, L., Deltell, A., Marrugat, J., Ramos, R., Sunyer, J., Elosua, R., Basagaña, X., 2014. High blood pressure and long-term exposure to indoor noise and air pollution from road traffic. *Environ. Health Perspect.* 122, 1193–200. doi:10.1289/ehp.1307156

Fortier, I., Burton, P.R., Robson, P.J., Ferretti, V., Little, J., L’Heureux, F., Deschenes, M., Knoppers, B.M., Doiron, D., Keers, J.C., Linksted, P., Harris, J.R., Lachance, G., Boileau, C., Pedersen, N.L., Hamilton, C.M., Hveem, K., Borugian, M.J., Gallagher, R.P., McLaughlin, J., Parker, L., Potter, J.D., Gallacher, J., Kaaks, R., Liu, B., Sprosen, T., Vilain, A., Atkinson, S.A., Rengifo, A., Morton, R., Metspalu, A., Wichmann, H.E., Tremblay, M., Chisholm, R.L., Garcia-Montero, A., Hillege, H., Litton, J.E., Palmer, L.J., Perola, M., Wolffenbuttel, B.H., Peltonen, L., Hudson, T.J., 2010. Quality, quantity and harmony: the DataSHaPER approach to integrating data across bioclinical studies. *Int. J. Epidemiol.* 39, 1383–1393. doi:10.1093/ije/dyq139

Fortier, I., Doiron, D., Little, J., Ferretti, V., L’Heureux, F., Stolk, R.P., Knoppers, B.M., Hudson, T.J., Burton, P.R., Initiative, I.H., 2011. Is rigorous retrospective harmonization possible? Application of the DataSHaPER approach across 53 large studies. *Int. J. Epidemiol.* 40, 1314–1328. doi:10.1093/ije/dyr106

Fuks, K.B., Weinmayr, G., Foraster, M., Dratva, J., Hampel, R., Houthuijs, D., Oftedal, B., Oudin, A., Panasevich, S., Penell, J., Sommar, J.N., Sørensen, M., Tiittanen, P., Wolf, K., Xun, W.W., Aguilera, I., Basagaña, X., Beelen, R., Bots, M.L., Brunekreef, B., Bueno-de-Mesquita, H.B., Caracciolo, B., Cirach, M., de Faire, U., de Nazelle, A., Eeftens, M., Elosua, R., Erbel, R., Forsberg, B., Fratiglioni, L., Gaspoz, J.-M., Hilding, A., Jula, A., Korek, M., Krämer, U., Künzli, N., Lanki, T., Leander, K., Magnusson,

- P.K.E., Marrugat, J., Nieuwenhuijsen, M.J., Ostenson, C.-G., Pedersen, N.L., Pershagen, G., Phuleria, H.C., Probst-Hensch, N.M., Raaschou-Nielsen, O., Schaffner, E., Schikowski, T., Schindler, C., Schwarze, P.E., Søgaard, A.J., Sugiri, D., Swart, W.J.R., Tsai, M.-Y., Turunen, A.W., Vineis, P., Peters, A., Hoffmann, B., 2014. Arterial blood pressure and long-term exposure to traffic-related air pollution: an analysis in the European Study of Cohorts for Air Pollution Effects (ESCAPE). *Environ. Health Perspect.* 122, 896–905. doi:10.1289/ehp.1307725
- Gaye, A., Marcon, Y., Isaeva, J., LaFlamme, P., Turner, A., Jones, E.M., Minion, J., Boyd, A.W., Newby, C.J., Nuotio, M.-L., Wilson, R., Butters, O., Murtagh, B., Demir, I., Doiron, D., Giepmans, L., Wallace, S.E., Budin-Ljøsne, I., Oliver Schmidt, C., Boffetta, P., Boniol, M., Bota, M., Carter, K.W., deKlerk, N., Dibben, C., Francis, R.W., Hiekkalinna, T., Hveem, K., Kvaløy, K., Millar, S., Perry, I.J., Peters, A., Phillips, C.M., Popham, F., Raab, G., Reischl, E., Sheehan, N., Waldenberger, M., Perola, M., van den Heuvel, E., Macleod, J., Knoppers, B.M., Stolk, R.P., Fortier, I., Harris, J.R., Woffenbittel, B.H.R., Murtagh, M.J., Ferretti, V., Burton, P.R., 2014. DataSHIELD: taking the analysis to the data, not the data to the analysis. *Int. J. Epidemiol.* 43, 1929–44. doi:10.1093/ije/dyu188
- Goyal, S., Gupta, V., Walia, L., Effect of noise stress on autonomic function tests. *Noise Health* 12, 182–6. doi:10.4103/1463-1741.64976
- Halonen, J.I., Hansell, A.L., Gulliver, J., Morley, D., Blangiardo, M., Fecht, D., Toledano, M.B., Beevers, S.D., Anderson, H.R., Kelly, F.J., Tonne, C., 2015. Road traffic noise is associated with increased cardiovascular morbidity and mortality and all-cause mortality in London. *Eur. Heart J.* 36, 2653–61. doi:10.1093/eurheartj/ehv216
- Higgins, J.P.T., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. *BMJ* 327, 557–60. doi:10.1136/bmj.327.7414.557

- Holand, S., Girard, A., Laude, D., Meyer-Bisch, C., Elghozi, J.L., 1999. Effects of an auditory startle stimulus on blood pressure and heart rate in humans. *J. Hypertens.* 17, 1893–7.
- Kephalopoulos, S., Paviotti, M., Anfosso-Lédée, F., Van Maercke, D., Shilton, S., Jones, N., 2014. Advances in the development of common noise assessment methods in Europe: The CNOSSOS-EU framework for strategic environmental noise mapping. *Sci. Total Environ.* 482-483, 400–10. doi:10.1016/j.scitotenv.2014.02.031
- Krokstad, S., Langhammer, A., Hveem, K., Holmen, T.L., Midthjell, K., Stene, T.R., Bratberg, G., Heggland, J., Holmen, J., 2013. Cohort Profile: the HUNT Study, Norway. *Int. J. Epidemiol.* 42, 968–77. doi:10.1093/ije/dys095
- Morley, D.W., de Hoogh, K., Fecht, D., Fabbri, F., Bell, M., Goodman, P.S., Elliott, P., Hodgson, S., Hansell, A., Gulliver, J., 2015. International scale implementation of the CNOSSOS-EU road traffic noise prediction model for epidemiological studies. *Environ. Pollut.* 206, 332–341. doi:10.1016/j.envpol.2015.07.031
- Morley, D.W., Gulliver, J., 2016. Methods to improve traffic flow and noise exposure estimation on minor roads. *Environ. Pollut.* doi:10.1016/j.envpol.2016.06.042
- Münzel, T., Gori, T., Babisch, W., Basner, M., 2014. Cardiovascular effects of environmental noise exposure. *Eur. Heart J.* 35, 829–36. doi:10.1093/eurheartj/ehu030
- R Core Team, 2013. R: A language and environment for statistical computing.
- Raggam, R.B., Cik, M., Höldrich, R.R., Fallast, K., Gallasch, E., Fend, M., Lackner, A., Marth, E., 2007. Personal noise ranking of road traffic: subjective estimation versus physiological parameters under laboratory conditions. *Int. J. Hyg. Environ. Health* 210, 97–105. doi:10.1016/j.ijheh.2006.08.007
- Recio, A., Linares, C., Banegas, J.R., Díaz, J., 2016. Road traffic noise effects on cardiovascular, respiratory, and metabolic health: An integrative model of biological

- mechanisms. *Environ. Res.* 146, 359–370. doi:10.1016/j.envres.2015.12.036
- Regecová, V., Kellerová, E., 1995. Effects of urban noise pollution on blood pressure and heart rate in preschool children. *J. Hypertens.* 13, 405–12.
- Scholtens, S., Smidt, N., Swertz, M.A., Bakker, S.J., Dotinga, A., Vonk, J.M., van Dijk, F., van Zon, S.K., Wijmenga, C., Wolffenbuttel, B.H., Stolk, R.P., 2014. Cohort Profile: LifeLines, a three-generation cohort study and biobank. *Int. J. Epidemiol.* doi:10.1093/ije/dyu229. doi:10.1093/ije/dyu229
- Sorensen, M., Hvidberg, M., Hoffmann, B., Andersen, Z.J., Nordsborg, R.B., Lillelund, K.G., Jakobsen, J., Tjønneland, A., Overvad, K., Raaschou-Nielsen, O., 2011. Exposure to road traffic and railway noise and associations with blood pressure and self-reported hypertension: a cohort study. *Environ. Heal.* 10, 92. doi:10.1186/1476-069X-10-92
- Stansfeld, S.A., 2015. Noise Effects on Health in the Context of Air Pollution Exposure. *Int. J. Environ. Res. Public Health* 12, 12735–60. doi:10.3390/ijerph121012735
- Tétreault, L.-F., Perron, S., Smargiassi, A., 2013. Cardiovascular health, traffic-related air pollution and noise: are associations mutually confounded? A systematic review. *Int. J. Public Health* 58, 649–66. doi:10.1007/s00038-013-0489-7
- van Kempen, E., Babisch, W., 2012. The quantitative relationship between road traffic noise and hypertension: a meta-analysis. *J. Hypertens.* 30, 1075–1086. doi:10.1097/HJH.0b013e328352ac54; 10.1097/HJH.0b013e328352ac54
- van Kempen, E., van Kamp, I., Fischer, P., Davies, H., Houthuijs, D., Stellato, R., Clark, C., Stansfeld, S., 2006. Noise exposure and children's blood pressure and heart rate: the RANCH project. *Occup. Environ. Med.* 63, 632–639. doi:10.1136/oem.2006.026831
- Viechtbauer, W., 2010. Conducting meta-analyses in R with the metafor package. *J. Stat. Softw.* 36, 1–48.

- Vienneau, D., de Hoogh, K., Bechle, M.J., Beelen, R., van Donkelaar, A., Martin, R. V., Millet, D.B., Hoek, G., Marshall, J.D., 2013. Western European land use regression incorporating satellite- and ground-based measurements of NO₂ and PM₁₀. *Environ. Sci. Technol.* 47, 13555–64. doi:10.1021/es403089q
- WHO, 2011. Burden of disease from environmental noise. Quantification of healthy life years lost in Europe. WHO European Centre for Environment Health, Bonn Office.
- Wolfson, M., Wallace, S.E., Masca, N., Rowe, G., Sheehan, N.A., Ferretti, V., LaFlamme, P., Tobin, M.D., Macleod, J., Little, J., Fortier, I., Knoppers, B.M., Burton, P.R., 2010. DataSHIELD: resolving a conflict in contemporary bioscience-performing a pooled analysis of individual-level data without sharing the data. *Int. J. Epidemiol.* 39, 1372–1382. doi:10.1093/ije/dyq111

Figure legends

Figure 1. Distribution of estimated annual average road traffic noise (L_{den}) and air pollution levels for LifeLines, EPIC-Oxford, and HUNT3. Median, 25th and 75th percentiles are shown in the box, whiskers indicate 5% and 95% limits. Abbreviations: L_{den} = day-evening-night time annual average road traffic noise; PM_{10} = particulate matter with aerodynamic diameter $\leq 10 \mu m$; NO_2 = nitrogen dioxide.

Figure 2. Cohort specific and pooled associations between road traffic noise (L_{den}) and systolic blood pressure (SBP, in mmHg), diastolic blood pressure (DBP, in mmHg), and heart rate (HR, in beats per minute) per 10 dB(A). Pooled associations were estimated with random effects meta-analyses. Total $n=88,336$; LifeLines $n=56,307$; EPIC-Oxford $n=11,443$; HUNT3 $n=20,586$. Models were adjusted for age, sex, educational level, alcohol use, smoking status, and BMI. Models were additionally adjusted for NO_2 or PM_{10} if specified.

Figure 3. Pooled and cohort-specific associations between road traffic noise categories (L_{den}) and systolic blood pressure (SBP, in mmHg), diastolic blood pressure (DBP, in mmHg), and heart rate (HR, in beats per minute). Models were adjusted for age, sex, cohort, educational level, alcohol use, smoking status, and BMI.