Deliverable 7.6
Scientific paper on the relation between the harmonized complex variables and risk factors and specific health outcomes

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1. The Environmental Determinants of Health Project

Background
The aim of the Environmental Determinants of Health Project (or Environmental Core Project - ECP) was to study how environmental exposures affect chronic multifactorial diseases. The focus was on environmental exposure to road-traffic noise and air pollution, with harmonized exposure measures being assigned to participants across multiple cohorts in different countries, resulting in a very large dataset and wide exposure differentials, maximising the statistical power to detect the subtle but important effects of these environmental exposures. These exposures were linked to retrospectively harmonised health outcomes, and associations adjusted for harmonised covariates and confounding factors, using existing cohort data. Regarding end points, as well as the well-known chronic disorders associated with air pollution/noise, including cardiovascular and pulmonary diseases, this Core Project also aimed to study the impact of exposure on common somatic symptoms.

The substantive analyses linking the environmental exposures to the health outcomes were undertaken by the PhD student’s working within the ECP:

Wilma Zijlema, who studied the effect of environmental noise on blood pressure/heart rate and common somatic symptoms; and the effect of air pollution on depression;

Samuel Cai, who studied road traffic noise, air pollution and cardiorespiratory health.

Environmental Exposures
Substantive work was undertaken to develop appropriate harmonised air pollution and noise exposure models which were used to assign exposure measures to each cohort participant.

Air pollution estimates used the ESCAPE Land Use Regression model (Beelen R, Hoek G et al. 2013, Eeftens M, Beelen R et al. 2012) to assign address-level annual average estimates of Nitrogen dioxide, Nitrogen oxides, particulate matter with diameter ≤10μm (PM10), PM2.5 (diameter ≤2.5μm), PM2.5 absorbance and PM coarse (diameter 2.5-10μm) to LifeLines, EPIC-Oxford and UK Biobank. Satellite based air pollution estimates (Vienneau D, de Hoogh K et al. 2013) were used to assign Nitrogen dioxide and PM10 air pollution exposures to participants in all four of the ECP cohorts.

With respect to noise exposure, we developed a harmonised pan-European noise exposure model based on a modified Common NOise aSSessment methOdS (CNOSSOS) model (Morley DW, de Hoogh K et al. 2015), which we used to assign address-level annual average estimates of daytime, evening, overnight, 16 hour mean and A-weighted 24 hour noise exposure to participants in each of the four ECP cohorts.

These environmental exposure data have been returned to each cohort accompanied with detailed meta-data.

Participating cohorts/biobanks
The key cohorts participating in the ECP (and for which the aforementioned environmental exposure data have been assigned) are listed below. More details of each cohort can be found on the BioSHaRE website (https://www.bioshare.eu/studies).

- EPIC-Oxford - 57,000 participants recruited in 1993-1999 from across the UK
- HUNT - 50,000 participants recruited in 1984-1986 from the Nord-Trøndelag County, Norway
- Lifelines - 95,000 participants recruited in 2007-2013 from the Groningen, Friesland, Drenthe regions of the Netherlands
- UK Biobank - 500,000 participants recruited in 2006-2010 from across the UK

Wilma Zijlema is also using data from the FinRisk and KORA cohorts in her study of the effect of ambient air pollution on depression.

- FinRisk – 10,000 participants recruited in 2007 from Helsinki, Vantaa and Turku, Finland
- KORA – 18,000 participants recruited in 2004-2008 from the Augsburg area, Germany

The harmonization of exposure data, as well as the harmonization of common somatic symptoms has been undertaken in collaboration with existing European consortia.
2. **Overview of research projects**

1. Long-term air pollution, noise and systemic inflammation, lipids and glucose in European adults - Samuel Cai
2. Ambient air pollution, traffic noise and adult prevalent asthma: a BioSHaRE approach - Samuel Cai
3. Road traffic noise, air pollution and incidence of cardiovascular diseases - Samuel Cai
4. Road traffic noise, blood pressure and heart rate - Wilma Zijlema
5. Road traffic noise and common somatic symptoms - Wilma Zijlema
6. Study the association of air pollution and depression - Wilma Zijlema
7. Description of environmental exposures in LifeLines - Wilma Zijlema
8. Associations between air pollution and respiratory health in large European cohorts – Dany Doiron
3. Research projects

3.1 Long-term traffic air pollution, noise and systemic inflammation, lipids and glucose in European adults

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Abstract
Investigating adverse blood biochemistry profile may provide information on biological pathways underpinning associations between traffic-related air pollution or noise and cardiovascular disease. We evaluated the long-term effects of each exposure on certain biochemistry markers in two European biobanks (HUNT3, LifeLines).

Residential air pollution (NO₂ and PM₁₀) at address of residence were estimated for 2007 using a pan-European Land Use Regression model. Road traffic noise was modeled for 2009 using a simplified Common Noise Assessment Methods in Europe (CNOSSOS-EU). DataSHIELD was used to virtually pool data of 144,082 participants aged≥20 years for individual-level cross-sectional analysis. Generalized linear models were fitted to assess associations with high-sensitivity C-reactive protein (hs-CRP), blood lipids and for (LifeLines only) fasting blood glucose for samples taken during recruitment 2006-13.

PM₁₀ was associated with increases in hsCRP of 2.2% (95%CI: 0.2 to 4.4), triglycerides by 0.032 mmol/L (95%CI: 0.020 to 0.044) per 3.1 μg/m³ and fasting blood glucose by 0.045 mmol/L (95%CI: 0.031 to 0.059) per 3.7 μg/m³. The latter two associations were robust to adjustments for day-time noise. Significant associations with these markers were also observed for NO₂ with similar effect sizes. Noise was associated with increases in fasting blood glucose by 0.016 mmol/L (95%CI: 0.008 to 0.024) per 5.3 dB(A) day-time exposures. Significance remained after adjustments for air pollution.

Long-term exposure to traffic air pollution and noise are significantly associated with adverse blood biochemistry. Our findings provide some mechanistic insight into the link between air pollution/noise and cardiovascular disease.

Status and planning
This paper is in draft form, with planned submission to BMJ Heart in Dec 2015 as ‘Long-term traffic air pollution, noise and systemic inflammation, lipids and glucose in European adults. Authorship: Yutong Cai, Marta Blangiardo, Paul R Burton, BioSHaRE, Kees de Hoogh, Dany Doiron, Isabel Fortier John

3.2 Ambient air pollution, traffic noise and adult prevalent asthma: a BioSHaRE approach

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Abstract
We investigated effects of both ambient air pollution and traffic noise on adult asthma prevalence, using harmonised data from three European biobanks established in 2006-2013 (HUNT3, LifeLines, UK Biobank).

Residential exposures to ambient air pollution (NO2 and PM10) were estimated by a pan-European Land Use Regression model for year 2007. Traffic noise for year 2009 was modelled at home address by adapting a standardised noise assessment framework (CNOSSOS-EU). A cross-sectional analysis of 646,731 participants aged ≥20 years was undertaken using DataSHIELD to virtually pool data for individual-level analysis. Multivariate logistic regression models were fitted to assess effects of each exposure on lifetime and current asthma prevalence.

A 10 µg/m3 increase in NO2 or PM10 was associated with a 1.9% (95%CI: 1.1% to 2.8%) and 12.8% (95%CI: 9.5% to 16.3%) increase in lifetime asthma prevalence respectively, independent of confounders. Effects were larger in those aged ≥50 years, ever-smokers and less educated groups. Noise exposure was not significantly associated with current asthma prevalence.

This study suggests that long-term ambient PM10 exposure is associated with asthma prevalence in western European adults. Traffic noise is not associated with asthma prevalence, but its potential to impact on asthma exacerbations needs further investigation.

Status and planning
This paper is in draft form, with planned submission European Respiratory Journal in Nov 2015 as ‘Ambient air pollution, traffic noise and adult prevalent asthma: a BioSHaRE approach’. Authorship: Yutong Cai, Wilma L Zijlema, Dany Doiron, Marta Blangiardo, Paul R Burton, Isabel Fortier, Amadou Gaye, John Gulliver, Kees de Hoogh, Kristian Hveem, Stéphane Mbatchou, David W Morley, Ronald P Stolk, Paul Elliott, Anna L Hansell, Susan Hodgson
3.3 Road traffic noise, air pollution and incidence of cardiovascular diseases

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Summary
Research has reported links between ambient air pollution or road traffic noise and certain cardiovascular diseases in some European studies. In the recent concluded ESCAPE (European study of Cohorts for Air Pollution Effects) project, in which study-level estimates for a range of air pollutants were meta-analysed, results were not entirely consistent. Evidence is also accumulating in recent years for the traffic noise effects on cardiovascular diseases but this is relatively limited at this stage and more research are needed. Further, only a few studies to date looking at these two environmental risk factors jointly to investigate the cardiovascular effects at individual-level.

This proposed paper aims to quantify the separate and joint effects of air pollution and noise exposure on incident cardiovascular outcomes at the individual level, specifically total cardiovascular diseases (ICD-10 codes I00-I99), ischemic heart disease (ICD-10 codes I20-I25), cerebrovascular disease (ICD-10 codes I60-I69). We propose to pool data from three biobanks (UK Biobank, EPIC-Oxford, and HUNT2) to address our research questions. This paper will help better understand the environmental determinants of cardiovascular disease by disentangling the health effects of these two exposures and thereby inform targeted preventive strategies and contribute to scientific knowledge.

Status and planning
As of 30 November 2015, all data across three biobanks were harmonised and relevant scripts in DataSHIELD are in the final phase of refinement. Analyses of the data are planned to start at Dec 2015 and finish by March 2016.

The first manuscript is planned to be submitted to an international, peer-reviewed scientific journal in summer 2016.
3.4 Study the association of road traffic noise and blood pressure/heart rate

Research Team

W.L. Zijlema, JGM Rosmalen, University Medical Center Groningen (UMCG), The Netherlands

A manuscript describing this research has been submitted for publication to Environmental Health Perspectives as Road traffic noise, blood pressure and heart rate: Pooled analyses of harmonized data from 91,718 participants from LifeLines, EPIC-Oxford, and HUNT3. Wilma Zijlema, Yutong Cai, Dany Doiron, Stéphane Mbatchou, Isabel Fortier, John Gulliver, Kees de Hoogh, David Morley, Susan Hodgson, Paul Elliott, BioSHaRE, Timothy Key, Havard Kongsgard, Kristian Hveem, Amadou Gaye, Paul Burton, Anna Hansell, Ronald Stolk, Judith Rosmalen.

Abstract

BACKGROUND Exposure to road traffic noise may increase blood pressure and heart rate. Findings from previous studies have been inconsistent, which may be due to differences between study populations and study methods.

OBJECTIVES We investigated associations between road traffic noise, blood pressure and heart rate, with harmonized data from three European cohorts.

METHODS Data were obtained from LifeLines (the Netherlands), EPIC-Oxford (UK), and HUNT3 (Norway). 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. Systolic (SBP) and diastolic blood pressure (DBP), and heart rate (HR) measurements were conducted by trained medical professionals. Pooled cross-sectional analyses of harmonized data were conducted both at the individual level and with random-effects meta-analyses.

RESULTS Data from 91,718 participants, across three participating cohorts (mean age 47.0 (±13.9) years) were available for this study. The pooled median day-evening-night level of road traffic noise was 53.5 (interquartile range 4.6) dB(A). In adjusted pooled linear regression analyses, HR was associated with a 0.95 (95% CI 0.78;1.12) bpm increase per 10 dB(A), but there was a -0.07 (95% CI -0.30;0.17) and -0.42 (95% CI -0.57;-0.27) mmHg decrease in SBP and DBP, per 10 dB(A) respectively. Additional adjustments for PM10 or NO2 attenuated the associations, but they remained significant for DBP and HR. Results for BP (but not HR) differed by cohort, with negative associations with noise in Lifelines, no significant associations with EPIC-Oxford and positive associations of noise >60 dB(A) in HUNT3. Associations calculated with random-effects meta-analyses were generally smaller and less precise.

CONCLUSION Our study suggests that road traffic noise may be related to increased heart rate. No consistent evidence for a relation between road traffic noise and elevated blood pressure was found.
3.5 Association of road traffic noise and common somatic symptoms

Research Team

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Abstract

Objectives: We investigated the role of a stress-sensitive personality on relations between noise, noise annoyance and somatic symptom reporting. First, we investigated the cross-sectional association of road traffic noise exposure and somatic symptoms, and its modification by hostility and vulnerability to stress. Second, we investigated the cross-sectional association of noise annoyance from eight sources (e.g. road traffic, aircraft, neighbours) and somatic symptoms, and it’s confounding by hostility and vulnerability to stress.

Methods: Data were obtained from LifeLines, a general population cohort from the Netherlands. Road traffic noise was estimated using the Common Noise Assessment Methods in Europe (CNOSSOS-EU) noise model. Noise annoyance, hostility, vulnerability to stress, and somatic symptoms were assessed with validated questionnaires.

Results: Poisson regression models adjusted for demographic and socioeconomic variables indicated no association of noise exposure and somatic symptoms (incidence rate ratio (IRR) 1.001; 95% confidence interval (CI) 1.000–1.001; n = 56,937). Interactions of noise exposure and hostility and vulnerability to stress were not statistically significant. Small positive associations were found for noise annoyance from each of the eight sources and somatic symptoms, when adjusted for demographic and socioeconomic variables (e.g. for road traffic noise annoyance IRR 1.014, 95% CI 1.011–1.018; n = 6177). Additional adjustment for hostility and vulnerability to stress resulted in small decreases of the IRRs for noise annoyance from each of the eight sources, but the associations remained statistically significant.

Conclusions: Personality facets hostility and vulnerability to stress did not modify the relation between road traffic noise exposure and somatic symptom reporting, or confound relations between noise annoyance and symptoms.
3.6 Association of air pollution and depression

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A manuscript describing this research has been accepted for publication in the International journal of hygiene and environmental health. The association of air pollution and depression in four European cohorts, Wilma Zijlema, Kathrin Wolf, Rebecca Emeny, Karl-Heinz Ladwig, Annette Peters, Havard Kongsgard, Kristian Hveem, Kirsti Kvaløy, Tarja Yli-Tuomi, Timo Partonen, Timo Lanki, Marloes Eeftens, Kees de Hoogh, Bert Brunekreef, BioSHaRE, Ronald Stolk, Judith Rosmalen.

Abstract
BACKGROUND Exposure to ambient air pollution may be associated with impaired mental health, including depression. Evidence originates mainly from animal studies and epidemiological studies in specific subgroups.

OBJECTIVES We investigated the association between air pollution and depression in four European general population based cohorts.

METHODS Data were obtained from LifeLines (the Netherlands), KORA (Germany), HUNT (Norway), and FINRISK (Finland). Residential exposure to particles (PM2.5, PM2.5absorbance, PM10) and nitrogen dioxide (NO2) was estimated using land use regression (LUR) models developed for the European Study of Cohorts for Air Pollution Effects (ESCAPE) and using European wide LUR models enhanced with satellite derived air pollution estimates. Depression was assessed with interviews and questionnaires. Logistic regression analyses were used to investigate the association between air pollution and depression, and random-effects meta-analysis was used to calculate combined estimates.

RESULTS A total of 70,928 participants were included in our analyses. Depression prevalence in the cohorts ranged from 1.6% in KORA to 11.3% in FINRISK. Cohort specific associations of the air pollutants and depression showed heterogeneous results. For example, positive associations were found for NO2 in LifeLines (odds ratio [OR]= 1.34; 95% CI: 1.17, 1.53 per 10 µg/m3 increase in NO2), whereas negative associations were found in HUNT (OR= 0.79; 95% CI: 0.66, 0.94 per 10 µg/m3 increase in NO2). Meta-analyses showed no statistically significant associations between any of the air pollutants and depression.

CONCLUSIONS Our meta-analysis of four European general population cohorts found no consistent evidence for an association between ambient air pollution and depression.
### 3.7 Description of environmental exposures in LifeLines

#### Research Team

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#### Abstract

**Background**

Lifelines is a prospective population-based cohort study investigating the biological, behavioral and environmental determinants of healthy ageing among 167,729 participants from the North East region of The Netherlands. The collection and geocoding of (history of) home and work addresses allows linkage of individual-level health data to detailed exposure data. This article describes the reasons for choosing particular assessments of environmental exposures in LifeLines and informs researchers on the backgrounds of available data.

**Methods**

Exposure to ambient air pollution was estimated using land use regression (LUR) models developed for European Study of Cohorts for Air Pollution Effects (ESCAPE) and European wide LUR models enhanced with satellite derived air pollution estimates. Road traffic noise exposure was assessed using a model based on Common Noise Assessment Methods in Europe (CNOSSOS-EU). Data on noise annoyance, perceived exposure to power lines, mobile phone masts and mobile phone use, perceived living environment, and neighborhood characteristics are also available. A comprehensive medical assessment and questionnaires were completed in order to assess determinants of health and well-being. Blood and urine samples were collected from all participants and genome wide association data are available for a subsample of 15,638 participants.

**Results**

Mean age was 45 years (standard deviation (SD) 13 years), and 59% were female. Median levels of NO\textsubscript{2} and PM\textsubscript{10} based on ESCAPE models were 15.7 (interquartile range (IQR) 4.9) µg/m\textsuperscript{3} and 24.0 (IQR 0.6) µg/m\textsuperscript{3} respectively. Median levels of road traffic noise were 54.0 (IQR 4.2) dB(A) for daytime noise and 45.1 (IQR 4.2) dB(A) for nighttime noise.

**Conclusions**

The combination of harmonized environmental exposures and extensive assessment of a variety of health outcomes makes LifeLines a great resource for environmental epidemiology. LifeLines aims to be a resource for the national and international scientific community.
3.8 Associations between air pollution and respiratory health in large European cohorts

Research Team
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Summary
Particulate matter (PM) air pollution and nitrogen dioxide (NO2) are two of the most important airborne contaminants influencing human health. While several very large studies have explored association between PM and NO2 and cardiovascular morbidity and mortality, there has also been much interest in respiratory health effects of air pollution. However, research specifically examining associations between PM/NO2 and pulmonary function as well as PM/NO2 and respiratory symptoms such as wheezing and shortness of breath and medication use is relatively recent and limited to relatively smaller studies. The proposed project involves harmonizing and combining data from two of Europe’s largest population health studies, the LifeLines Cohort Study & Biobank and UK Biobank, in order to:
(1) Explore associations between PM/NO2 exposure at place of residence and pulmonary function and,
(2) Explore the effect of PM/NO2 exposure at place of residence on prevalence respiratory symptoms (e.g. wheezing and shortness of breath), and respiratory medication use (i.e. bronchodilators).

Three lung function measurements collected at baseline assessment by UK Biobank and LifeLines studies will be used in analyses: Forced Expiratory Volume 1-second (FEV1), Forced Vital Capacity (FVC) and Peak Expiratory Flow (PEF). Standardized individual estimates of air pollution at place of residence developed in the context of the European Study of Cohorts for Air Pollution Effects (ESCAPE) will be used as main independent variable in statistical analyses. Exposure estimates for nitrogen dioxide (NO2) and particulate matter with aerodynamic diameters of less than 2.5 µm (PM2.5) and less than 10 µm (PM10) will be used. UK Biobank data managers will link these pollution estimates to individual participant data using home address postcodes. Important covariates used in analyses will include age, sex, education, income, body mass index, current and past smoking status, exposure to tobacco smoke at home and at work, time of year at assessment (to control for seasonal allergies), and length of time at current address. Cross-sectional association between FEV1, FVC and PEF and the PM/NO2 will be estimated using linear regression. In a separate analysis, association between prevalence respiratory symptoms such as wheezing and shortness of breath and respiratory medication use with PM/NO2 concentration at place of residence will be estimated using linear regression. The same confounding variables will be used for this second set of analyses.

Status and planning
Data analyses is ongoing and planned till Q1 2016
Reporting and publication of the results is planned for 2016.
### Summary

Environmental factors such as air traffic pollutants, traffic noise, lifestyle factors and behaviours, can negatively affect human health with large societal and economic costs. Long-term exposure such as air pollution has been associated to increased risk of obesity and diabetes. The reasons for this are probably many and the interaction processes are obviously very complex. Among several hypotheses, effects on obesity and diabetes may be associated with higher serum levels of the adipokine leptin, but this hypothesis has not been strongly evaluated in humans although Wang et al. (2014) recently found evidence of an association between serum leptin levels and estimated annual mean residential black carbon concentration.

The link between obesity and systemic oxidative stress support the notion that oxidative-stress-induced dysregulation of inflammation and adipokines may mediate the obesity-related metabolic derangement (Wu et al., 2009). The incidence of obesity, autoimmune (type 1 diabetes and LADA) and type 2 diabetes is increasing worldwide. Many risk factors for development of diabetes have been confirmed, however, usually unrelated between these two types of diabetes. Recently there has been an increasing interest in the effect of noise and air pollution on risk of developing type 2 diabetes and interestingly air pollution is found to be linked to childhood type 1 diabetes as well. This may indicate that there are some underlying mutual mechanisms concerning these kinds of exposures. Air pollutant PM$_{2.5}$, PM$_{10}$ and NO$_2$ exposures are found to be significantly associated with type 2 diabetes and even stronger in females (Eze et al., 2015; Rao et al., 2015). The same pollutants are also suggested to accelerate the manifestation of childhood diabetes (Beyerlein et al., 2015; Hathout et al., 2002). There are fewer studies related to traffic noise pollution compared to air pollution. However, one study found that long-term exposure to traffic noise (10-dB higher level of average over 5 years preceding diagnosis) was associated with increased risk of diabetes (not type specific) incidence (Sorensen et al., 2013) and a meta-analysis showed that people exposed to residential noise >60dB had about 20% higher risk for type 2 diabetes than those exposed to <60dB (Dzhambov, 2015). However, results from existing epidemiologic studies have been inconsistent and more studies are needed especially on adult onset autoimmune diabetes where to our knowledge there are no reports concerning this.

### Status and planning
As of 30 November 2015, application for data has been submitted to HUNT, LifeLines and UK Biobank, approval has been obtained for HUNT. Data harmonisation is ongoing and analyses and publication is planned for 2016.
References

Beelen R, et al.. Development of NO2 and NOx land use regression models for estimating air pollution exposure in 36 study areas in Europe – The ESCAPE project. Atmospheric Environment 2013 72(0): 10-23


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