(Un)Healthy in the city

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General Introduction

ENVIRONMENTAL EPIDEMIOLOGY

Many human diseases can be attributed to environmental factors. Environmental factors can be viewed as those that are not genetic, and include factors that are as broad as for example diet, exercise, and social relationships. In environmental epidemiology, and in this dissertation, we refer to environmental factors as those factors that are outside the immediate control of individuals [1]. Exposures of interest are for example air pollution, traffic noise, electromagnetic fields, and chemical agents. Environmental epidemiology comprises the study of the link between the environment and population health by combining data on environmental exposures and health.

A famous example of how a combination of disease statistics and related spatial data could trace a disease outbreak, is the case of John Snow. During the 1854 cholera outbreak in London, John Snow used spatial maps of disease clusters to identify the source of the outbreak as the public water pump on Broad Street. He is seen as the founding father of epidemiology and taught us that spatial data can help to investigate adverse health outcomes of environmental exposures. Another example is the London smog of 1952. During one week in December 1952, a dense smog descended on London. A combination of foggy weather, coal-burning homes and polluting factories led to pollution levels that were 5 to19 times higher than current regulatory standards. Mortality increased substantially during the smog period, and was still increased for a long period thereafter. It has been estimated that 12,000 excess deaths can be attributed to the acute and persistent effects of the 1952 London smog. It became clear that incidences of elevated exposures do not only result in acute effects on public health, but also in chronic health problems [2].

Reductions of harmful exposures have led to substantial improvements in public health. Examples are the introduction of proper sanitation [3], control of particulate air pollution [4], and more recently the introduction of smoke-free legislation [5]. Although the benefits for public health have been acknowledged, there is still a lot to gain in environmental epidemiology. For some exposures, health effects already occur at levels much lower than previously expected. In addition, studying harmful environmental exposures and their effects on public health is important because many individuals may be affected by the same pollution source, and individuals often have no control over their exposures. Moreover, environmental exposures often interfere with a variety of bodily processes, potentially affecting a wide range of diseases [6].

PERCEIVED EXPOSURES AND PERCEIVED HEALTH

Besides the actual exposure to environmental factors, also perceived exposure and concerns about the health risks associated with the exposure might influence health outcomes [1]. When studying particular exposures, for example electromagnetic fields or living in the vicinity of nuclear power plants, the public's perception of the health risks is as relevant to health as the exposure itself. Moreover, sometimes perceived exposures have stronger associations with diminished health than the actual exposures [7–9]. People may attribute common health complaints to environmental factors, regardless of the actual level of exposure. Individuals that perceive exposure to possibly harmful environmental agents, sometimes attribute their health complaints to the environment. The assessment of common somatic symptoms such as headache, stomachache, and palpitations is therefore becoming increasingly relevant to environmental epidemiology. However, evidence that certain environmental sources cause these symptoms is currently lacking [7,10].

ADVERSE HEALTH EFFECTS OF TRAFFIC-RELATED NOISE AND AIR POLLUTION

The research in this dissertation focusses on adverse health effects associated with traffic-related air pollution and noise. Many individuals are exposed to polluted air [11,12]. Evidence of harmful health effects of air pollution has accumulated over the recent years. Exposure to air pollution is associated with morbidity and mortality due to respiratory [13] and cardiovascular diseases [14–16]. Recent studies have also linked air pollution to other adverse health effects, including diabetes mellitus [17–19], depressed mood [20,21], and adverse birth outcomes [22–24]. Environmental noise has also been related to a variety of adverse effects [25], including annoyance, hearing loss, sleep disturbance, cognitive impairment, and cardiovascular disease [26]. It is estimated that in Western Europe, each year, at least one million healthy life years are lost due to traffic-related noise [27]. Both air pollution and traffic noise are associated with the highest burden of disease in Europe related to environmental exposures [12]. Road traffic is a common source for both noise and air pollution. Individuals exposed to road traffic noise are probably also exposed to air pollution from traffic. Some adverse health effects can be attributed to noise or air pollution, or both. It is therefore important to distinguish between the two exposures. Previous studies often did not take into account the simultaneous effects of traffic-related noise and air pollution.

However, the research community is becoming increasingly aware of the need for disentangling effects of noise and air pollution [28–30].

POSSIBLE MECHANISMS

Mechanisms that may explain how the environment affects health are the breeder and drift hypotheses. These hypotheses try to explain spatial variations in health. The breeder hypothesis refers to the idea that health differences arise because of environmental factors to which people are directly exposed [31]. Examples could be exposure to air pollution [32] and traffic noise [33], or exposure to harmful chemicals, for example pesticides [34]. Spatial variation in behavior may also explain health differences. It has been shown that urban living can evoke certain (un)healthy lifestyles, such as smoking [35], physical activity [36], alcohol use [37], and diet choices [38]. The drift hypothesis states that selection processes might result in spatial health differences. Selection occurs when healthy persons stay, while ill persons move, or vice versa. Furthermore, specific places may attract or repel persons with certain health-related characteristics [31]. The general stress model has also been used to explain environmental effects on health. Environmental exposures can be seen as stressors, which directly or indirectly affect bodily stress systems. Responses including increased heart rate and blood pressure, bronchodilation, and release of stress hormones are triggered. Long-term activation of the stress system may lead to allostatic load, also known as the 'wear and tear' on our bodies. Over longer periods, allostatic load might lead to disease [39].

All these above mechanisms may (partly) explain how environmental factors affect health and knowledge regarding these mechanisms may provide targets for prevention strategies.

USING MULTIPLE BIOBANKS FOR ENVIRONMENTAL EPIDEMIOLOGY: BIOSHARE

One of the major challenges in environmental epidemiology is detecting the small risks associated with environmental exposures. Risks are small because environmental exposures often occur in low concentrations and in complex mixtures (e.g. traffic-related air pollution and noise). Many of the health outcomes of interest have other underlying risk factors which effects may be much stronger than those of the environmental exposure under study [6]. For example, a myocardial infarc-

tion may result from a combination of genetic predisposition, lifestyle risk factors, and exposure to noise and air pollution [40]. As a consequence, risks associated with environmental exposures are often difficult to detect. Although effect sizes are generally small, the disease burden associated with environmental exposures is large [11,12]. Large populations are simultaneously affected by various exposures during their lives. Furthermore, even small increases in population risks can lead to a vast increase in population burden of disease, and vice versa [41].

Studies with large numbers of participants and broad exposure ranges are needed to investigate the complex interaction between the environment and the development of multifactorial chronic diseases. Single studies may not provide adequate numbers of subjects, but collaboration across large regions could make important contributions to understanding environmental causes of disease. Therefore, population studies must be harmonized and standardized, enabling the assembling of data in valid and effective ways. To this end, we used multiple European cohort studies to study harmful health effects of the environment.

Previously, consortia of collaborating studies (e.g. the HYENA (Hypertension and Exposure to Noise near Airports) study [42], ESCAPE (European Study of Cohorts for Air Pollution Effects)[43]) contributed largely to the current knowledge of the link between environmental exposures and disease. However, practical, ethical, legal, and consent-related restrictions of sharing and pooling individual-level study data form a challenge to collaboration across studies [44–46]. Consequently, previous consortia of collaborating studies mostly combined study data on an aggregated level, while combining individual-level data could result in more statistical power, and offers increasing flexibility in data analysis [46].

This dissertation was written within the framework of the European harmonization initiative BioSHaRE (Biobank Standardisation and Harmonisation for Research Excellence in the European Union; www.bioshare.eu). Within BioSHaRE, tools were developed for data harmonization and federated data analyses. Harmonization tools enable the optimal extraction of common data from studies that have collected extensive data and samples under different design protocols (retrospective harmonization) [47,48]. In addition, harmonized exposure models for ambient air pollution and for road traffic noise were partly developed and implemented in several cohort studies participating in the BioSHaRE project (prospective harmonization). Federated data analyses enable researchers to comprehensively analyze individual-level data from multiple studies, while keeping the original data strictly secure, overcoming challenges regarding data sharing and pooling [46].

RESEARCH QUESTIONS AND OBJECTIVES

In this dissertation, we focused on adverse health effects of air pollution and road traffic noise. We investigated the (simultaneous) exposure to traffic-related noise and air pollution, and their relations with various adverse health outcomes. A part of this research was undertaken in multiple European cohort studies, from which data were harmonized and pooled. This has led to two central questions:

1. Is the living environment, and in particular traffic-related noise and air pollution, affecting health?
2. Can we harmonize and pool individual data from multiple cohort studies, and does this enable us to better understand relations of environmental exposures and adverse health outcomes?

OUTLINE OF DISSERTATION

In *chapter 2,* we describe the exposure assessment methods that were used in the LifeLines Cohort Study. 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. Environmental exposure and health data assessed in LifeLines were used throughout the research presented in this dissertation. The methods for exposure assessment of road traffic noise and ambient air pollution that were used are presented here.

In *chapter 3,* the associations of degree of urbanity and lung function, metabolic syndrome, anxiety and depression are described. Many people live in urban areas these days, and urban residents may be more exposed to harmful factors than their rural counterparts. Here, we report on health differences associated with urbanity in the Northern part of the Netherlands.

In *chapter 4,* the associations of ambient air pollution and depressed mood are described. For this study, we analyzed data from four European cohorts. We also investigated whether exposure to noise influenced the relation between air pollution and depressed mood.

In *chapter 5,* we report on a systematic review of symptom questionnaires. The aim was to identify suitable questionnaires for the assessment of common somatic symptoms in large-scale population based cohort studies. Identifying suitable questionnaires is useful for the prospective harmonization of somatic symptom assessment.

In *chapter 6,* we describe the association of road traffic noise and common somatic symptoms in the LifeLines Cohort Study. Associations between road traffic noise exposure, as estimated with a noise model, annoyance from noise, and somatic symptoms are investigated. Secondly, we investigate whether certain personality facets were modifiers or confounders of the relationship between noise, noise annoyance and symptoms.

In *chapter 7,* we report on the results of a study investigating associations between road traffic noise, air pollution, blood pressure, and heart rate. Federated analyses of harmonized data from three European cohorts were conducted at the individual level using a novel software approach developed within BioSHaRE.

In *chapter 8,* a general discussion of the main findings is presented. We also discuss the methodological strengths and limitations, the implications of our study findings, and directions for future research.

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