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(Un)Healthy in the city

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General Discussion

The aim of this dissertation was to investigate whether the living environment, and in particular traffic-related noise and air pollution, adversely affects health. A part of this research was undertaken in multiple European cohort studies, from which data were harmonized and pooled. Our secondary aim was to evaluate the advantages and disadvantages of such combining of multiple cohort studies for environmental epidemiology.
In this chapter we will discuss the main findings of this dissertation, the methodological strengths and limitations, the implications of our study findings, and directions for future research.

SUMMARY OF MAIN FINDINGS

Relations between the environment and health

The title of this dissertation is "(un)healthy in the city: adverse health effects of traffic-related noise and air pollution." We cannot simply assume that city living is associated with increased exposure to environmental stressors, and therefore adversely affects the health of urban residents. This was underlined by our study described in Chapter 3, where we investigated the associations of urbanity and four disorders with a large burden of disease. Our results suggest a differential health impact of urbanity according to type of disease. Living in an urban environment appears to be associated with better cardiometabolic health, but with worse respiratory function and mental health. These findings were in agreement with previous research [1–4]. The question that followed was how these urban-rural health differences could be explained. We postulated what underlying mechanisms could help explain the differential associations between health and degree of urbanity. Previous research has given numerous indications of harmful environmental exposures associated with city living. Health differences may arise because of environmental factors to which people are directly exposed [5]. LifeLines participants living in urban neighborhoods had highest exposure to air pollution (nitrogen dioxide; Figure 1) and road traffic noise (Figure 2), compared to participants in neighborhoods of lower degree of urbanity. Differences in lifestyle may also underlie urban-rural health differences, and may occur when one environment is, for example, more suitable for physical activity than another [6]. Furthermore, selective migration, for instance when specific environments attract or repel persons with certain health-related characteristics, has also been proposed as a mechanism explaining urban-rural health differences [5].

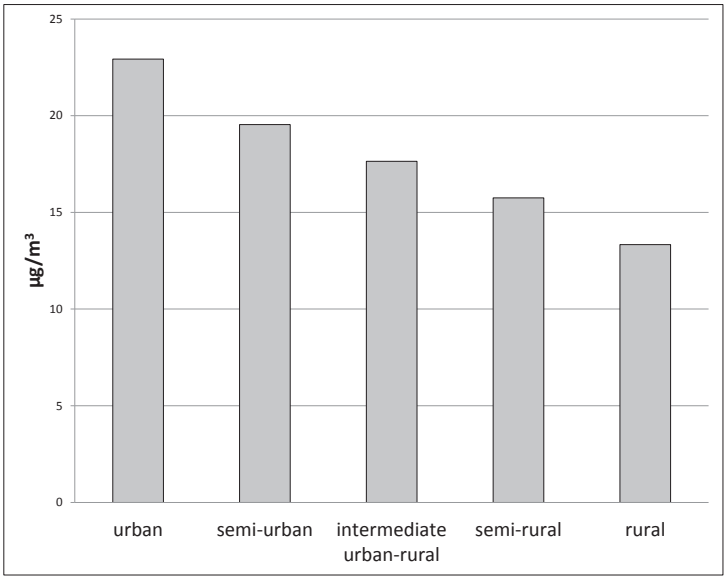

Figure 1. Median exposure to ambient nitrogen dioxide (NO_2) according to degree of urbanity within the LifeLines Cohort Study.

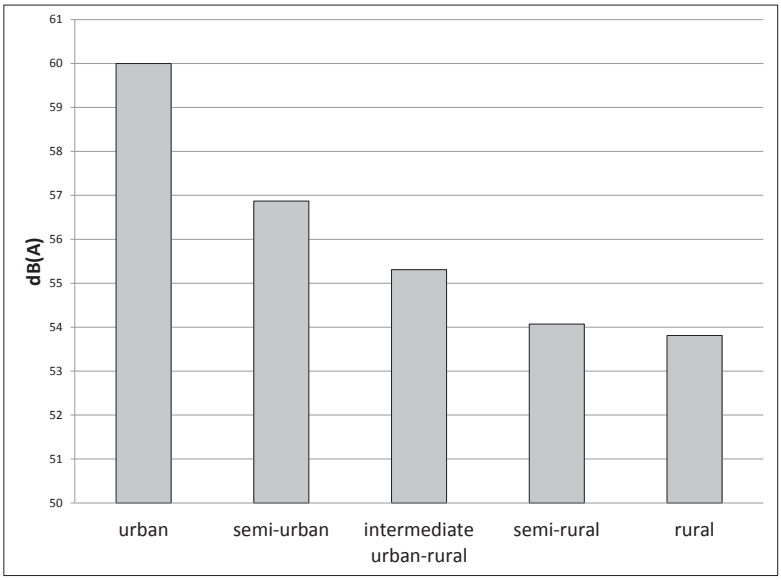

Figure 2. Median exposure to road traffic noise (L_{den}; average A-weighted noise level estimated over a 24 hour period) according to degree of urbanity within the LifeLines Cohort Study.

In Chapter 3, it was found that living in more urbanized areas was related to a decreased lung function and impaired mental health. In line with the differential lifestyle hypothesis, we found that individuals from urban areas were more often current smokers, and this may have influenced the association between urbanity and lung function. Our findings from Chapter 3 may also be explained by increased exposure to air pollution in urban areas. It is well established that air pollution can lead to a variety of adverse health effects [7], including decreased respiratory health [8,9]. Recently, research has provided some indications that exposure to air pollution can adversely affect the brain [10–16], and that it may be associated with impaired mental health [17–20]. We studied the association between exposure to air pollution and depressed mood (Chapter 4), but found no consistent evidence to support this hypothesis. Differential exposure to air pollution may explain the urban-rural differences in respiratory health, but our findings do not provide support for such an explanation for the urban-rural differences in depression. Next to air pollution, environmental noise may also play a role in impaired neurocognitive function, mood disorders, and neurodegenerative disease [21]. We did not study road traffic noise as a primary risk factor for depressed mood, but we did adjust our analyses for air pollution and depressed mood for road traffic noise. The adjusted associations between road traffic noise and depressed mood were mostly positive, but not statistically significant. There may be a link between noise and mood disorders, but this cannot be concluded with certainty from our study.

In contrast to decreased respiratory function and worsened mental health, urban living was related to a lower risk for cardiometabolic disease (Chapter 3). However, we observed that road traffic noise was related to elevated resting heart rate (Chapter 7), suggesting that individuals from urban areas, that are more highly exposed to noise, may be at risk for cardiovascular disease. Road traffic noise was, however, not associated with elevated blood pressure in the included cohorts. Exposure to air pollution may also be related to adverse cardiovascular effects, including hypertension and cardiovascular disease [22,23]. We therefore adjusted our analyses with road traffic noise, blood pressure, and heart rate for air pollution exposure. However, associations between exposure to noise, blood pressure and heart rate were only partly explained by exposure to air pollution. The adjusted associations between air pollution and blood pressure were negative and mostly statistically significant, while positive and statistically significant associations between air pollution and heart rate were observed. These findings suggest a possible link between exposure to air pollution and cardiovascular outcomes, but since we found opposite relations for blood pressure and heart rate, these findings should be interpreted with caution. Other risk factors, for example

lifestyle factors, that are more strongly related to cardiometabolic health, are probably more likely to explain urban-rural differences in cardiometabolic health. However, smoking and the number of days on which participants were physically active could not explain the association between urbanity and metabolic syndrome, suggesting that these lifestyle differences were not responsible for the urban-rural differences in metabolic syndrome. Also, while findings in Chapter 7 relate to cardiovascular outcomes, findings from Chapter 3 comprise a broader health outcome: the metabolic syndrome. This is a clustering of risk factors associated with atherosclerosis and coronary heart disease, including increased waist circumference, elevated triglycerides, low high density lipoprotein (HDL) cholesterol, hypertension, and elevated fasting glucose levels [24]. Environmental risk factors may have differential impacts on each of the components of metabolic syndrome.

Common somatic symptoms have also been related to various environmental exposures [25,26]. In Chapter 6, we found that exposure to road traffic noise and the reporting of common somatic symptoms, such as headache, chest pain, and breathing trouble, were not related. Annoyance from road traffic noise, however, was related to increased symptom reporting. We found that this relationship was only for a small part influenced by the personality facets hostility and vulnerability to stress, suggesting that the simultaneous reporting of increased annoyance and symptoms is not due to a general tendency to be vulnerable to stress [27]. The correlation between modelled road traffic noise and road traffic noise annoyance was low. This indicated that individuals highly exposed to road traffic noise, are not necessarily annoyed by traffic noise, and vice versa. Previous studies also reported discrepancies between actual and perceived exposures in relation to somatic symptom reporting [28,29], indicating that the perception of being exposed to a potentially harmful environmental source is sometimes more strongly associated with diminished health than the actual exposure.

Taken together, these findings suggest that the living environment is associated with adverse health effects, but this is only partly explained by environmental noise or air pollution.

USING MULTIPLE COHORT STUDIES IN ENVIRONMENTAL EPIDEMIOLOGY

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 [30,31] and federated data analyses [32,33]. In Chapters 4 and 7, we reported on studies undertaken with harmonized data from multiple European studies. In Chapter 4, data from a total of 70,928 participants from four European cohort studies were used. In Chapter 7, data from a total of 91,718 participants were obtained from three European cohort studies. We used harmonized exposure assessment methods to estimate levels of road traffic noise [34] and air pollution [35–37] for large geographical areas. With these data combined, we had a very large and rich dataset for our research. The advantages of such an approach are widespread. We were able to make use of very large sample sizes, so that we could detect the small effect sizes that are common in environmental epidemiology. Using data from large geographical areas resulted in wide exposure ranges of road traffic noise and air pollution. Furthermore, results could be compared across regions, in which not only the exposures, but also genetic, social and cultural factors vary. This makes the generalizability of our results larger. Being able to generalize study results across large regions in Europe is important for establishing European exposure norms and guidelines. Although exposure ranges were large, median levels of road traffic noise and air pollution were relatively low, if compared to other cohorts from Southern Europe [22] or Asia [19]. It is therefore unclear to what extent the conclusions in this dissertation can be generalized to regions with higher levels of noise and air pollution. Another advantage of our study population was that they all originated from general population based cohorts. Many of these cohorts were established with the aim of investigating a broad range of research questions (e.g. LifeLines, HUNT, KORA), or with more specific aims, for example investigating the relation between diet and cancer (EPIC-Oxford). However, none of these cohorts were specifically set up to investigate relations between environmental exposures and adverse health outcomes. Chances of self-selection are probably higher for cohorts that were specifically set up to investigate effects of a particular environmental exposure. Risk of bias due to self-selection is probably not very high in our research.

The findings from this dissertation also illustrate some of the difficulties that arise with multi-cohort studies. In our study on air pollution and depressed mood (Chapter 4), we used two different harmonized air pollution exposure models, but results from these two models differed. Associations of NO_2 and PM_{10} from EU-wide models and depressed mood in LifeLines were consistently positive and significant, while associations of NO_2 and PM_{10} from ESCAPE models in LifeLines were initially positive and significant, but no longer significant and sometimes negative when adjusted for additional covariates. The main difference between the ESCAPE and EU-wide exposure models is that ESCAPE models were constructed

for the Netherlands and Belgium, whereas the EU-wide models were developed for a much larger area in Western Europe. As a result, ESCAPE models may perform better on a regional scale, while EU-wide models may make comparisons across multiple study areas easier. Especially for NO_2, the EU-wide models may explain less of the spatial variation, if compared to the ESCAPE models [38]. The use of harmonized exposure models for large regions may be at the expense of the ability to detect spatial variation within those regions. Further assessment of the performance of these harmonized exposure models and replication our study findings is needed.

Also in Chapter 4, we reported opposite associations between air pollution and depressed mood in LifeLines and HUNT. NO_2 and PM_{10}, estimated with the EU-wide model, were positively associated with depressed mood in LifeLines, while negative associations were found in HUNT. Associations in the other two studies (KORA and FINRISK) were not statistically significant. Regardless of whether there is a true effect of air pollution on depressed mood, these findings underline the importance of multi-cohort studies. If the association between air pollution and depressed mood was studied in only one cohort, conclusions could have been different. Moreover, if we could have used data from additional cohort studies, results from these additional cohorts might have changed our conclusions. Given these contradicting results, replication of these findings in cohort studies from other geographical areas is needed.

In our study about noise, blood pressure and heart rate (Chapter 7), we pooled individual level data from three studies, enabling us to undertake our analyses within one large dataset. Analyzing data from 91,718 participants resulted in high statistical power. We could not use this approach to our data analysis in Chapter 4, where we studied the association between air pollution and depressed mood. The reason for this was that the outcome assessment of depressed mood was largely heterogeneous between the studies, and pooling of these heterogeneous data could not be justified.

As discussed earlier, variability in exposure ranges and disease outcomes is required to establish small effects in environmental epidemiology, and increases generalizability of the results. But variability in methods for exposure and outcome assessment is undesirable, since it makes comparisons between studies more difficult, and introduces heterogeneity when data are pooled. Using a large study area also increases risk of residual confounding, when heterogeneity of these areas is large [39]. Moreover, additional heterogeneity is introduced in the likely event that the different cohort studies used different methodologies for participant recruitment. With the pooling of individual data originating from multiple studies, suitable statistical techniques should be in place to analyze

these data. In Chapter 7, we therefore used two statistical methods to address this heterogeneity. Pooled regression analyses, adjusted for cohort, yielded larger effect estimates than the random-effects meta-analyses. Furthermore, results from random-effects meta-analyses were less precise. This is probably due to the heterogeneity among the cohort-specific results. Random-effects meta-analyses provide more conservative pooled estimates and confidence intervals when data is heterogeneous [40], which is probably the reason for the different results as compared to the individual-level pooled analyses. More appropriate statistical techniques, for example mixed models, that take into account heterogeneous multi-cohort data, should be used in future research.

With the harmonization and pooling of multi-cohort data, the researcher is strongly dependent on the data that is available at that stage. We aimed to investigate relations between road traffic noise and common somatic symptoms in multiple European studies, but did not succeed in finding sufficient studies that assessed common somatic symptoms. Prospective harmonization (i.e. implementing standardized and harmonized measures) of symptom questionnaires may offer a solution to this by recommending a standard assessment method. If the recommended standard is implemented in future cohort studies, this will largely contribute to collaboration between cohort studies. As a first step for prospective harmonization, we performed a systematic review of symptom questionnaires (Chapter 5). We identified 40 symptom questionnaires and evaluated them based on validity and reliability, and their fitness for purpose in large scale studies. Based on these criteria, we recommended two symptom questionnaires that seemed most fit for use in large scale studies: the Patient Health Questionnaire-15 (PHQ-15) and the Symptom Checklist-90 Somatization Scale (SCL-90 SOM) [41]. We stressed that there is a need for use of standardized and harmonized symptom questionnaires. The standardized and harmonized assessment of common somatic symptoms in large-scale population studies could greatly benefit research on environmental stressors and common somatic symptoms, by enabling the comparisons between studies, and the sharing and pooling of data.

Another important challenge is that with the pooling of heterogeneous data, it is almost inevitable that data is lost. Detailed information in one study may be lost if it is to be harmonized with less detailed information from another study. For example, in Chapter 7, the harmonization of data on educational degree was challenging because the cohorts all used different questions to assess educational degree. We eventually used a categorical variable with only two categories, because in some studies only little information was available, while in other studies much more detailed information on educational degree was available. When using

data from multiple studies that are retrospectively harmonized, it is important to find a balance between the gains and losses: increasing the sample size, exposure range, while not losing too much detailed data due to harmonization.

Finally, in practical terms, difficulties with data sharing between studies may arise. Firstly, obtaining the data can be challenging since cohorts have different procedures for data access. Harmonization of data access procedures would greatly simplify the sharing of cohort data. Data sharing may lead to data ownership issues. Furthermore, geocoded data, that is needed to estimate environmental exposures, is highly privacy sensitive, because it can possibly lead back to a participant's home address. To protect participant privacy, addresses and corresponding geocodes are stored in a file separately from all other participant data. Subsequently, environmental exposure estimates are linked to the geocodes, after which only the exposure estimates are linked to the main database, with all other anonymized participant data. With this procedure, addresses and geocodes can never be associated with other participant data, and privacy protection is ensured. Still, scientific boards of cohort studies may be hesitant to share this type of data. Because of these legal and ethical concerns, agreement on data sharing took additional time, or sometimes agreement on data sharing was not reached at all.

In summary, harmonization and pooling of data from multiple cohort studies can largely contribute to environmental epidemiological research. But it is important to invest in high quality harmonization, take into account heterogeneity of data, and be aware of ethical and legal challenges associated with the sharing of spatial data.

METHODOLOGICAL LIMITATIONS

In addition to some of the difficulties with multi-cohort studies, as described above, our research also has some other limitations. One of the main challenges in environmental epidemiology is the exposure assessment. Although this is true for all epidemiologic research (e.g. recall and reporting bias in research on smoking habits, food intake, physical activity), exposure ascertainment of environmental sources includes additional challenges. We used indirect exposure assessments of road traffic noise and air pollution. These exposures were estimated at the home addresses of participants, assuming this to be a good indicator of personal exposure to road traffic noise and air pollution. There are a number of factors that are not taken into account when estimating exposure at home addresses. Daily mobil-

ity (e.g. traveling to work or school) and workplace exposure may be sources of exposure misclassification. For example, exposure misclassification arises when an individual lives in an area with low air pollution levels, but travels through areas with high pollution, and works in a place where levels may also be higher than in their residential area. Even when travel activities account for only a small part of daily life, they can account for a large portion of an individual´s total exposure to air pollution [42]. Exposure at the workplace can contribute largely to differential exposure, since individuals often spend a large amount of time at work. Combining exposures from both home and work locations will result in better estimations of an individual's exposure [43]. Ideally, personal monitoring of locations and exposures would be used, but this is nearly impossible for large-scale studies. However, the introduction of new technologies, including smartphone applications and small personal sensors, may be promising in providing better personal estimates of exposure to air pollution and other environmental hazards [44]. Another limitation of our exposure assessments is that road traffic noise and air pollution levels are estimated at the outdoor level, instead of indoor. For noise, a number of modifying factors may apply. Housing insulation (type of windows) and (bed)room orientation are characteristics that influence indoor noise exposure, and possibly modify relationships with disease outcomes. Other noise modifying factors include use of noise reducing remedies, hearing problems, and window opening habits [45]. Some of these factors may also apply to indoor air pollution exposure. We did not account for these factors in our studies, and this might have contributed to exposure misclassification of our study population. The exposure models used in our studies have proved to be sufficient in estimating the spatial variability in exposure to air pollution [35,36,38] and noise [34].

A general difficulty in environmental epidemiology includes the long latency period between exposure and disease, which complicates the identification of harmful exposures and their health risks. Long-term prospective studies or the retrospective assessment of exposures are needed to determine effects of long-term exposure to environmental agents. Our research was cross-sectional, and the observed relations cannot be interpreted as causal effects. The observed associations in our cross-sectional research are particularly useful for formulating hypotheses for future studies. Our findings should therefore be interpreted with caution, because reverse causality cannot be excluded. We cannot claim that these individuals have a certain disease because they live in a particular environment. Instead, individuals with a certain disease may have a preference to live in a certain environment. In our research on road traffic noise, blood pressure, and heart rate (Chapter 7), we did find similar associations if we restricted our analyses to a subgroup that lived at least 2 or 5 years at the same address. Although we are not

sure whether the road traffic noise exposure remained the same in that period, it gives some indication for little influence of length of residence on the association between road traffic noise, blood pressure and heart rate Nonetheless, accounting for length of residence still does not give indications for causality. It merely provides insights in possible mechanisms of noise effects, for example effects of habituation or conversely a long latency period.

In addition to traffic-related noise and air pollution exposure, there are clearly many other environmental exposures that may be related to urban-rural health differences, or to spatial variations in health in general. Other environmental risk factors with known public health impacts, high individual risks, and public concern are for example benzene, dioxins, second-hand smoke, formaldehyde, lead, ozone, and radon. Studying these risk factors were outside the scope of this dissertation, but are nonetheless important environmental risk factors for a variety of diseases [46].

IMPLICATIONS OF STUDY FINDINGS AND DIRECTIONS FOR FUTURE RESEARCH

Environmental policies and society

Policy makers and urban planners should pay attention to making urban areas more healthy. Prevention on a macro level, in addition to the individual level, could improve health of many individuals. By structurally changing people's environments and reducing risk factors for disease, effects on public health can be substantial [47]. Our findings provide further support for preventive policies aimed at reducing air pollution and traffic noise. Estimated effects of environmental exposures on disease may be small, also in our studies. Health impact assessments show small, but potentially wide spread health benefits of the reduction of environmental noise and air pollution. For example, a simulation study of speed limit reduction and traffic re-allocation showed that a 2% decrease in population exposure to NO_2, and a 1 to 4% decrease in noise exposure, resulted in small decreases of disease burden of <5% [48]. However, even small effects are relevant for public health, given the fact that so many individuals are exposed to air pollution and noise [46]. This was also underlined by a review focusing on the health impacts of policies promoting active travel, which encourage people to go walking and cycling instead of using their cars. These policies resulted in large individual health benefits for those who became more physically active. Health benefits from the reduction of noise and air pollution were smaller, but may be more wide-spread, since large populations are affected [49]. Living environments

that support active travel, and subsequently increase physical activity and air quality, have the potential to contribute to public health [6,50]. Another promising approach to improve public health is contact with nature. Living close to green spaces or other natural environments has been related to positive effects on health [51–53]. Health benefits have been observed with regard to life expectancy [51], birth outcomes [54], mental health [52,55], and self-reported general health [56]. This may occur through multiple mechanisms [53], one of them being that natural environments help reduce air pollution and noise [57,58].

It is clear that there are great opportunities for improving public health through the design of healthy living environments. Environmental epidemiology can make great contributions to this by informing policy makers and urban planners. Both individual-level and population-level benefits will contribute to public health.

Directions for future research

Future research should focus on investigating adverse health effects of environmental exposures in multiple international studies with broad exposure ranges. To this end, we call upon the use of standardized and harmonized exposure and outcome measures, enabling high quality research in multiple cohort studies. In two studies presented in this dissertation, we were able to use data from three (Chapter 7) or four (Chapter 4) cohort studies. Including data from additional cohort studies would have contributed to the generalizability of our results. Also, using data from additional studies could have contributed to more firm conclusions, since the contradicting results in our study complicated that. To accomplish collaboration between cohort studies, the research community should invest in possibilities for the sharing, harmonization, and pooling of data. Tools have been developed within the BioSHaRE project (e.g. DataSHaPER [30,31], and DataSHIELD [32,33,59]), but the availability of tools alone is not enough to ensure collaboration. What currently is needed, is the willingness to share data. A promising development in medical science in general, is the introduction of new journal policies that require authors to share data from clinical trials [60]. A similar initiative, not limited to clinical trials, was initiated by PLOS journals, that "requires authors to make all data underlying the findings described in their manuscript fully available without restriction, with rare exception" [61]. These developments will hopefully lead to the increase of data sharing.

As mentioned as an important limitation, our research was based on cross-sectional data. Impacts of many environmental exposures often only manifest after a longer time period. Therefore, prospective studies should be initiated, so that long-term adverse health effects of environmental exposures can be detected.

Future studies should also take into account residential history of participants, and if available, link these addresses to historical exposure data. This enables the study of adverse health effects of environmental exposures in a life course perspective. Such an approach needs additional information on motivations for home relocation. Motives for relocation, for example major life events, are important for the investigation of selective migration.

Disentangling the adverse health effects of traffic-related noise and air pollution is a major challenge in environmental epidemiology. Although it is increasingly acknowledged in environmental epidemiology [21,62], research should take into account the effects of correlated environmental exposures to which individuals are simultaneously subjected. Otherwise, health risks may be falsely attributed to an environmental exposure that is highly correlated with another [63]. Further attention should be given to exposure assessment for noise and air pollution. As discussed as one of the methodological limitations, in addition to exposure at the residence, future studies should also take into account exposures at schools, the workplace, and during commuting. In LifeLines, workplace addresses are currently being collected and geocoded, allowing for outdoor exposure estimation at both home and work location. Furthermore, for noise and air pollution exposure it would be advisable to estimate exposures indoors, in addition to outdoors. In addition, the research community should extensively investigate adverse health effects of environmental exposures in vulnerable subgroups. Children, patients, and groups with low socioeconomic status may be more vulnerable to environmental stressors [64]. Individuals who perceive they are exposed [28], who are disturbed by the exposure [27], and who have concerns about the health risks associated with the exposure may also have an increased risk for adverse health effects [65]. This too calls for large sample sizes, which may be obtained through the combined analyses of multiple studies. However, efforts should be made to ensure high quality data harmonization.

Lastly, research should explore practical solutions for making our living environments more healthy environments. For example, technical innovations could make motorized traffic more quiet and less polluting. In addition, we should think of how we can effectively modify our living environment, in order to make residents more physically active, improve their diets, and reduce their alcohol and tobacco use. The development of adequate and efficient prevention strategies requires involvement of professionals from multiple disciplines, including epidemiologists, policy makers, and urban planners, and may also benefit from collaboration with communities [47]. Future research could combine efforts from multiple disciplines, and contribute to the prevention of non-communicable diseases through the design of healthy living environments.

CONCLUDING REMARKS

This dissertation illustrates that the living environment may be associated with adverse health effects, but this is only partly explained by environmental noise or air pollution. The use of data from multiple cohort studies provides excellent opportunities for studying harmful environmental exposures. The scientific community should invest in the sharing and harmonization of their cohort data, supporting environmental epidemiological research on a large geographical scale.

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