Challenges for Environmental Epidemiology in Evidence-Based Public Health

The Example of Second-Hand Smoke

CUMULATIVE DISSERTATION THESIS

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submitted by
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List of abbreviations

CI	confidence interval
COPD	chronic obstructive pulmonary disease
DANN	deoxyribonucleic acid
DYNAMO-HIA	Dynamic Modeling for Health Impact Assessment
e.g.	exempli gratia
et al.	et alia
etc.	et cetera
FCTC	Framework Convention on Tobacco Control
GEDA	Gesundheit in Deutschland aktuell (*German Health Update*)
HIA	Health Impact Assessment
IARC	International Agency for Research on Cancer
IHD	ischemic heart disease
LDL	low density lipoprotein
Mg	Milligrams
P	Publication
PDCA	Plan-do-check-act
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
RR	Relative risk
SHS	second-hand smoke
WHO	World Health Organization

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List of scientific papers forming the basis of this thesis

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[2] ***Fischer, F.***, Kraemer, A. (2016). Health Impact Assessment for Second-Hand Smoke Exposure in Germany – Quantifying Estimates for Ischaemic Heart Diseases, COPD, and Stroke. *International Journal of Environmental Research and Public Health*, 13 (2), 198. [IF: 2,06]

[3] ***Fischer, F.***, Kraemer, A. (2016). Factors associated with secondhand smoke exposure in different settings: Results from the German Health Update (GEDA) 2012. *BMC Public Health*, 16 (1), 327. [IF: 2,26]

[4] ***Fischer, F.***, Kraemer, A. (submitted). Secondhand Smoke Exposure at Home among Middle and High School Students in the United States – Does the Type of Tobacco Product Matter?. *BMC Public Health*. [IF: 2,26]

[5] ***Fischer, F.***, Minnwegen, M., Kaneider, U., Kraemer, A., Khan, M. M. H. (2015). Prevalence and Determinants of Secondhand Smoke Exposure Among Women in Bangladesh, 2011. *Nicotine and Tobacco Research*, 17 (1), 58-65. [IF: 2,80]

[6] ***Fischer, F.*** (2016). Challenges in creating evidence in environmental health risk assessments: The example of second-hand smoke. *Challenges*, 7 (1), 2. [IF: n.a.]

Abstract

Background and objectives: Evidence-based public health uses a population-centered approach to provide the basis for activities in the field of public health. However, research in public health tends to cover complex and context-dependent issues. This is particularly true for studies dealing with environmental risk factors. The synopsis aims at synthesizing the (methodological) challenges that are linked to environmental epidemiology and evidence-based public health, using the example of SHS exposure.

Methods and materials: The synopsis is based on six publications, which rely on different methodological concepts. The publications focus on several aspects related to SHS exposure, be it 1) the impact of SHS exposure on health, or 2) the effects of legislation to reduce SHS exposure, 3) factors associated with SHS exposure in different countries, including results from different settings or different types of SHS exposure, or 4) a summary of challenges in creating evidence in environmental health risk assessments.

Results: Environmental epidemiology has much to contribute to facilitate population health. Although there may be several shortcomings in environmental epidemiological studies dealing with SHS exposure, this type of observational research is necessary. Standardized approaches in public health are needed, particularly for the assessment of exposure and outcome in (environmental) epidemiological studies. Nevertheless, a focus on only one gold standard is not justified. Since public health acts on several levels, an interdisciplinary approach that uses the most appropriate methods from the respective disciplines of research traditions to create evidence is necessary. All decisions in public health should be evidence-based, irrespective of the area of interest.

Conclusion: The need for evidence-based public health is obvious in all stages of the public health action cycle (assessment, policy formulation, implementation, and evaluation). Therefore, public health researchers must succeed in using the most appropriate methods. Perhaps an approach termed “evidence-based environmental epidemiology” will be formulated in the future. However, all types of research conducted in public health must use sound methods. That, besides the inclusion of patient values and expertise, is the main prerequisite to calling the concept “evidence-based”.

1. Introduction

Improving the evidence is an important goal for research and practice in public health. The availability of evidence-based information about risk factors and their associations with adverse health outcomes helps to ensure that policies designed to improve populations' health may lead to their desired effects (Fielding and Briss, 2006). Evidence-based public health, therefore, uses a population-centered approach to provide the basis for activities in the field of public health (Brownson et al., 2009b; Gerhardus et al., 2010). However, research in public health tends to cover complex and context-dependent issues (Rychetnik et al., 2002). This is particularly true for studies dealing with environmental risk factors, where the exposure is involuntary, often infrequent, and sometimes even not observable.

One example of such a risk factor is second-hand smoke (SHS) exposure. Evidence of the adverse health effects attributable to SHS exposure is available, and concern about these effects has contributed to the declining social acceptance of smoking, which resulted in legislation bringing in smoking bans and action to reduce SHS exposure (Öberg et al., 2011; Paoletti et al., 2012; Prokhorov et al., 2013). Nevertheless, SHS still remains the most important contaminant of indoor air (Law and Hackshaw, 1996; Öberg et al., 2011). To develop and establish suitable strategies for the protection of non-smokers—but also smokers—from the harms of SHS exposure, evidence on the magnitude of the association between SHS exposure and adverse health outcomes is needed just as much as evidence on the impact of tobacco-control strategies. This evidence is to be generated in the field of public health, supported by adjacent scientific disciplines.

The present synopsis aims at synthesizing the (methodological) challenges that are linked to environmental epidemiology and evidence-based public health, using the example of SHS exposure. The cumulative dissertation consists of the following six publications[1], which are shortly described within this synopsis:

[1] ***Fischer, F.***, Kraemer, A. (2015). Meta-analysis of the association between second-hand smoke exposure and ischaemic heart diseases, COPD and stroke. *BMC Public Health*, 15, 1202.

[2] ***Fischer, F.***, Kraemer, A. (2016). Health Impact Assessment for Second-Hand Smoke Exposure in Germany – Quantifying Estimates for Ischaemic Heart Diseases, COPD, and Stroke. *International Journal of Environmental Research and Public Health*, 13 (2), 198.

[1] The numeration of the publications will be used throughout the synopsis.

[3] ***Fischer, F.***, Kraemer, A. (2016). Factors associated with secondhand smoke exposure in different settings: Results from the German Health Update (GEDA) 2012. *BMC Public Health*, 16 (1), 327.

[4] ***Fischer, F.***, Kraemer, A. (submitted). Secondhand Smoke Exposure at Home among Middle and High School Students in the United States – Does the Type of Tobacco Product Matter?. *BMC Public Health*.

[5] ***Fischer, F.***, Minnwegen, M., Kaneider, U., Kraemer, A., Khan, M. M. H. (2015). Prevalence and Determinants of Secondhand Smoke Exposure Among Women in Bangladesh, 2011. *Nicotine and Tobacco Research*, 17 (1), 58-65.

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The main focus will not be on the specific results of these publications, but on the overarching aspects that are of concern for evidence-based public health derived from environmental epidemiological studies.

2. Evidence-based decision-making in public health based on research in environmental epidemiology

At the most basic level, evidence involves the available body of information based on studies to indicate whether a belief, proposition, or association is true or valid (Jewell and Abate, 2001). The concept of evidence-based practice is well-established in several disciplines, such as psychology (Presidential Task Force on Evidence-Based Practice, 2006), social work (Gambrill, 2003), and nursing (Melnyk et al., 2000). It can be assumed that it is best established in medicine (Brownson et al., 2009b). Almost 25 years have passed since a group of researchers coined the term “evidence-based medicine” to provide a more scientific and systematic approach to the practice of medicine (Evidence-Based Medicine Working Group, 1992). The origins of this concept can be traced back to the work of Archibald Cochrane. He noted that many medical treatments lacked scientific effectiveness (Cochrane, 1972). The group around Gordon Guyatt and David Sackett, as the main promoters of evidence-based medicine, aimed to integrate the best available external clinical/research evidence with clinical expertise and patient values (Sackett et al., 1996; Sackett et al., 2000).

According to their idea of evidence-based medicine, it can be defined as “the process of systematically finding, appraising, and using contemporaneous research findings as the basis for clinical decisions” (Rosenberg and Donald, 1995) or “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients” (Sackett et al., 1996). The stages of evidence-based medicine are described as 1) the assessment and synthesis of external evidence (by using appropriate methods and study designs) and 2) the use of probabilistic reasoning that takes a clinical attitude, as well as the patients’ values and preferences, into account (Gray, 1997; Sackett et al., 1996). Over time, discussions in the scientific community led to the impression that only evidence from explanatory randomized controlled trials (RCTs) can be classified as reliable. This narrowed definition of external evidence focusing on RCTs as a “gold standard” came up with the development of clinical guidelines (Fernandez et al., 2015; Moten et al., 2016). Nevertheless, the role of the RCTs as a gold standard is controversial for several reasons. The most important criticism of this aspect, among others, deals with the fact that evidence based on RCTs may sometimes be unattainable for methodological or ethical reasons. This is particularly true for evidence that is or has to be generated in the “real world”, apart from clinical trials. Furthermore, critics hold that the so-called hierarchy of evidence downgrades other sorts of (clinical) evidence and leaves no way of integrating results from other study designs into an overall assessment of the evidence (Ashcroft, 2004). Nevertheless, the rise of evidence-based medicine is an important movement and represents a meaningful epistemological turn in medicine (Ashcroft, 2004; Davidovitch and Filc, 2006).

2.1 Evidence-based public health

In recent years, a more evidence-based approach to public health has emerged, based on the advances of evidence-based medicine. Gray (1997) published one of the first articles mentioning the concept of evidence-based public health in 1997. This approach followed the emergence of evidence-based medicine to facilitate health policies and interventions based on results from scientifically sound studies (Davidovitch and Filc, 2006; Kohatsu et al., 2004). There are several connections between evidence-based medicine, evidence-based public health, and epidemiology. The concept of evidence-based medicine evolved from clinical epidemiology (Heller and Page, 2002; Jenicek, 1997). Therefore, the fundamental role of epidemiology in all kinds of evidence-based decisions in medicine or public health has to be highlighted (Jenicek, 1997). In addition, the focus of evidence-

based medicine is also the population and not just the individual patient, as it is in clinical practice (Heller and Page, 2002). Jenicek (1997) published a review describing the links between epidemiology, evidence-based medicine, and evidence-based public health. Within this review, epidemiology was claimed as the foundation for both evidence-based medicine and evidence-based public health (Jenicek, 1997).

Evidence-based public health is needed to develop, implement, and evaluate interventions and policies of scientific reasoning to promote the health of (sub-)populations (Brownson et al., 2003; Brownson et al., 1999). Because of the similarities between the concepts of evidence-based medicine and evidence-based public health, the latter can be described as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of communities and populations in the domain of health protection, disease prevention, health maintenance and improvement (health promotion)" (Jenicek, 1997). More recent definitions claimed evidence-based public health as a process of integrating science-based interventions with community preferences to improve the health of populations (Kohatsu et al., 2004), which is also very similar to the definition of evidence-based medicine, but with a much broader focus on interventions in (sub-)populations instead of the best intervention for individual patients. The term "science-based" in this context includes the involvement of a range of disciplines aside from epidemiology, which provide the science base for public health. These are, among others, medicine, toxicology, molecular biology, anthropology, nutrition, psychology, sociology, economics, and political science, which go along with the development and implementation of adequate and target- and need-oriented public health interventions. Furthermore, a relatively deliberately broad definition includes both quantitative and qualitative approaches to gathering information that can affect public health practice (Kohatsu et al., 2004).

This highlights the idea that there cannot be one gold standard for methodological approaches such as RCTs, as is the case in evidence-based medicine. The comparatively broad perspective of evidence-based public health is intended to include different perspectives and to use a method that is adequate for answering a certain research question, to facilitate (further) evidence that should be included in the decision-making processes. An evidence-based approach to public health could potentially have several direct and indirect effects (Lhachimi et al., 2016). For that reason, public health interventions and policies are much more complex than those in any other research discipline. Although evidence-based public health has borrowed the term "intervention" from clinical disciplines, a clearly defined and measurable single intervention is lacking in the public

health arena. Public health interventions for a given issue are characterized by multiple approaches or aspects that include different operations within a community (Brownson et al., 2009b). Whereas a causal chain in clinical interventions usually leads directly from an intervention to an outcome, in public health the intervention frequently focuses on a risk factor as the mediator between intervention and outcome (Attena, 2014). The context becomes more uncertain, variable, and complex when moving from clinical interventions to population-level and policy interventions (Dobrow et al., 2004). In addition, population-based studies generally require a longer time period between intervention and outcome (Brownson et al., 2009b). To cover these different kinds of complexities, Eriksson (2000) proposed four domains in which sufficient information is needed to promote an evidence-based approach in public health: 1) Distribution of health (e.g. indicators of social inequality), 2) determinants of health, 3) impact of disease or health problem on the individual as well as society, and 4) methods for changing health determinants.

2.2 Environmental epidemiology

Dahlgren and Whitehead (1991, 1993) defined different levels of (social) determinants of health. They described a social ecological theory to health. According to them, health is determined by a complex interaction between individual (lifestyle) factors, social and community networks, living and working conditions, and general socioeconomic, cultural, and environmental conditions. Therefore, the levels lead from very narrow aspects to much broader aspects. The most distant level from the perspective of an individual person is the broad concept of "environment", which can furthermore be divided into a natural, built, or social environment (Dahlgren and Whitehead, 1991, 1993). Irrespective of this framework, in the understanding of environmental health, "environment" can also be defined as everything that is external to a human being (Last, 2001). Nevertheless, there are also other ideas on environment and perspectives on its interaction with health, such as distinctions between 1) inner and outer environment, 2) personal and ambient environment, 3) solid, liquid, and gaseous environments, and 4) physical, chemical, biological, and psychosocial environments (Merrill, 2008).

Environmental health is a fairly broad concept, whereas environmental epidemiology focuses on populations and emphasizes identifying causal relationships between a risk factor and an outcome (Merrill, 2008). Environmental epidemiology is a distinct area of epidemiological studies. This is a result of the fact that populations exposed are large and diverse. Studying the effects, however, is quite complex, because an effect may be small or

not easy to define (Pekkanen and Pearce, 2001). Nevertheless, the importance of environmental epidemiology lies in the large number of people affected and the opportunity to protect a large part of different population groups through public health actions. Historically, findings from environmental epidemiology are well-known in the public health community, and led to significant improvements in the health of human populations. For example, one of the earliest and most influential epidemiological studies was performed by John Snow, when he used a quantitative approach to trace the cause for London's cholera outbreak to sewage in drinking water (Overhage et al., 2013; Snow, 1855).

At least three features of environmental epidemiology distinguish it from general epidemiology. First, many environmental risk factors, or at least anthropogenic factors, are modifiable. Second, environmental factors are spatially distributed. Third, environmental exposures vary temporally. Therefore, within the course of a person's lifetime, exposures come and go or vary in intensity. All of these aspects pose different challenges for creating evidence regarding the effects of a certain risk factor on different kinds of outcomes (Thomas, 2009). Risk assessment of environmental factors involves four stages: First, the hazard should be identified. Next, the exposure and dose-response relationship are assessed. The final step is risk characterization (Brunekreef, 2008). During this process, the Bradford Hill criteria for causality must be considered (Hill, 1965).

Until now, many systematic assessments of epidemiological evidence were not able to draw causal hypotheses. This is a result of interstudy heterogeneity in design, methods, and reporting. Therefore, public health decision-making is severely limited because of the absence of concordance among study results (LaKind et al., 2015). This leads to a desideratum for evidence-based epidemiology (Overhage et al., 2013), which is particularly important in environmental epidemiologic research, for which the accurate characterization of an individual's level of exposure is highly relevant but also highly challenging.

Nevertheless, there have been several successful examples of results from environmental epidemiological studies leading to policy changes. For example, epidemiology played a central role in informing policy choice and evaluating the consequences in the area of tobacco control to protect smokers, as well as non-smokers who are exposed to SHS (Aldrich et al., 2015; Galea, 2013).

3. Second-hand smoke

Tobacco is one of the largest contributors to indoor air pollution. SHS is responsible for many adverse health effects in non-smokers (Thompson, 2014). SHS exposure, also known as tobacco smoke pollution or exposure as a result of passive smoking, is expressed as the "sum of exposures in the multiple microenvironments where a person spends time" (Avila-Tang et al., 2013). The smoke dilutes in the ambient air, diffuses, and spreads through it (Jousilahti et al., 2002; Klus, 1990). The indoor SHS concentration depends on the number of tobacco products smoked over a period of time, the volume of the room, the ventilation rate, and other processes that may eliminate pollutants (Apelberg et al., 2013; Leone et al., 2004; Reardon, 2007; Svendsen et al., 1987). The exposure mainly consists of the smoke released from the burning end of a smoldering cigarette, pipe, or cigar ("side-stream smoke", 85%) and, to a lesser extent, the smoke exhaled from the lungs of an active smoker nearby ("main-stream smoke", 15%) (Ahijevych and Wewers, 2003; Dunbar et al., 2013). Main-stream smoke travels through the unburnt tobacco and exits directly into the oral cavity and respiratory tract of the smoker (Spitzer et al., 1990). The composition of side-stream smoke differs substantially from main-stream smoke because of the different temperatures at which the substances burn and the oxygen supply (Svendsen et al., 1987). Side-stream smoke is considered more toxic than main-stream smoke because it contains a higher concentration of many dispersed pollutants over a longer exposure time (Pagani and Fitzpatrick, 2013; Remmer, 1987; Schick and Glantz, 2005; Witschi et al., 1997a; Witschi et al., 1997b). For example, side-stream smoke includes approximately five times as much carbon monoxide (which decreases the ability of hemoglobin to carry oxygen to the tissues), three times as much benzopyrene (which is a tumor- and plaque-producing compound), and 50 times as much ammonia (an eye and respiratory system irritant) as main-stream smoke (Ciruzzi et al., 1998; Leone et al., 2004; Raupach et al., 2006; Taylor et al., 1992). Furthermore, particulates are larger in main-stream smoke as in side-stream smoke. Therefore, side-stream smoke may reach more distant alveolar spaces in the lung (Leone et al., 2004; Stober, 1984).

Inhaled tobacco smoke contains, for both active and passive smokers, more than 4,700 different chemicals, such as nicotine—a pesticide (U.S. Department of Health and Human Services, 2006). More than 200 of these chemicals are confirmed carcinogens and respiratory toxins (Best, 2009; Dunbar et al., 2013; IARC, 2004; King et al., 2010; U.S. Department of Health and Human Services, 2006, 2014). For this reason, it is likely that SHS exposure causes some or all of the complications caused by active smoking. Chronic

exposure to SHS is suggested to be, on average, 80%–90% as harmful as chronic active smoking (Dinas et al., 2014). Scientific evidence has confirmed a dose-response relationship with no risk-free level of exposure (threshold dose) (Giovino, 2007; Jin et al., 2013; Smith et al., 2000; WHO, 2008). For the association between SHS exposure and lung cancer, this dose-response relationship has been estimated to be linear. Here, the excess risk associated with SHS exposure is about 1% of that from smoking 20 cigarettes per day, which is consistent with the exposure (Hackshaw et al., 1997; Law and Wald, 2003). In contrast, the dose-response relationship between SHS exposure and ischemic heart diseases (IHD) did not confirm a linear relationship. A meta-analysis including five large prospective epidemiological studies concerning the association between active smoking (around 20 cigarettes per day) and cardiovascular diseases calculated a relative risk (RR) of 1.78 (Law et al., 1997). Overall, active smoking exposes smokers to approximately 150–200 times the SHS concentration, and 100- to 300-fold total smoke dose experienced by a non-smoker (Smith and Ogden, 1998). Despite the much lower smoke exposure, several studies investigating the association between SHS exposure and cardiovascular diseases estimated an RR of around 1.3 (Barnoya and Glantz, 2005; He et al., 1999; Law et al., 1997; Rostron, 2013; Smith et al., 2000; Thun et al., 1999).

A study by Repace and Lowrey (1985) estimated that the exposure to SHS for the non-smoking adult population was about 1.43 mg of tar per day. Compared with this amount, a smoker is expected to inhale about 200–400 mg of tar per day (depending on the type of cigarette and frequency of smoking) (Howard and Thun, 1999; Svendsen et al., 1987). Other studies estimated that the level of exposure to SHS, measured by biochemical markers, is equivalent to 0.1–2 cigarettes per day (Feyerabend et al., 1982; Hein et al., 1991; Hugod et al., 1978; Jarvis et al., 1984; Matsukura et al., 1984; Wald et al., 1984).

3.1 Toxicology and pathophysiology

There is a broad scientific consensus that SHS exposure is linked to carcinogenesis, in particular lung cancer (Hackshaw et al., 1997; Lee et al., 1986; Schick and Glantz, 2005; Vineis et al., 2005; Wald et al., 1986; Wells, 1998). This association is comprehensible, as more than 50 carcinogens have been identified in SHS (U.S. Department of Health and Human Services, 2006). Although the causal relationship is well-established in studies with animals, evidence for the underlying mechanisms in humans is still lacking. Nevertheless, data from active smokers may help to explain the framework of tumor induction in humans caused by SHS exposure. The most plausible mechanism is metabolic

activation following carcinogen uptake, which may lead to damage of the deoxyribonucleic acid (DNA). Tobacco-related carcinogens are associated with a decreased capacity of DNA to repair itself, which is associated with an increased risk of non-small-cell lung cancer (Shen et al., 2003). Multiple genetic changes may accumulate in (lung) cancer (U.S. Department of Health and Human Services, 2006).

The scientific community first focused on the associations between SHS exposure and lung cancer. Subsequently, however, other outcomes were also included in the research, such as IHD (He et al., 1999; Law et al., 1997; Thun et al., 1999), respiratory diseases (Chen, 2008; Coultas, 1998; Jindal and Gupta, 2004), and stroke (Bonita et al., 1999; McGhee et al., 2005; You et al., 1999). Several mechanisms may lead to an increased likelihood of adverse effects in the cardiovascular and respiratory system (Ahijevych and Wewers, 2003; Ambrose and Barua, 2004; Barnoya and Glantz, 2005, 2006; Rostron, 2013; Rubenstein et al., 2004; Sargent et al., 2004). These include increased platelet activation and subsequent thrombosis (Glantz and Parmley, 1991, 1995, 2001), inhibition of vascular endothelium and changes in endothelial functioning (Davis et al., 1989), impairment of coronary artery dilatation capacity (Celermajer et al., 1996; Otsuka et al., 2001; Schächinger et al., 2000; Sumida et al., 1998), decreases in antioxidant substances (Valkonen and Kuusi, 1998), aortic stiffening (Stefanadis et al., 1998), and impaired heart-rate variability (Pope et al., 2001). These mechanisms may cause a reduction in vascular flow and therefore the development of atherosclerosis (Powell, 1998; U.S. Department of Health and Human Services, 2006). The mechanisms by which SHS exposure increases the risk of heart disease are multiple and interact with each other (Barnoya and Glantz, 2005).

In comparison with lung cancer, there is one important difference in the association between SHS exposure and IHD. In lung cancer, adverse health effects result from long-term exposure, whereas in IHD these effects are not merely long-term and chronic but also acute (Davis et al., 1989; Wells, 1994). Acute effects from SHS exposure are tissue irritation, especially of the eyes, but also of the nose, throat and respiratory tract (Muramatsu et al., 1983; Trédaniel et al., 1994; Weber, 1984; Willes et al., 1992). Acute effects on the cardiovascular system in terms of a decrease in platelet sensitivity that leads to greater platelet aggregation and increased risk of coronary thrombosis have been observed after an exposure of 20 minutes to 8 hours (Metsios et al., 2010; Otsuka et al., 2001; Wells, 1994). Additionally, acute exposure to SHS reduces oxygen delivery and use in the myocardium (Gvozdjáková et al., 1992), causes mild coronary vasoconstriction, and damages the endothelium (Davis et al., 1989). The reductions in heart-rate variability occur

2 hours after exposure and increase the risk of myocardial infarction by around 10% (Pope et al., 2001; Sargent et al., 2004). Other acute effects include the deterioration of serum antioxidant defense, accelerated lipid peroxidation, and accumulation of low density lipoprotein (LDL). LDL cholesterol accumulation in macrophages is generally accepted as a key event of atherosclerosis (Brown and Goldstein, 1983; Pechacek and Babb, 2004; Valkonen and Kuusi, 1998). The effects of even brief passive smoking (minutes to hours) are often nearly as great as (chronic) active smoking (Barnoya and Glantz, 2005; Ding et al., 2009; Lippert and Gustat, 2012; Sargent et al., 2004).

Until now, only a few studies have investigated possible mechanisms underlying sex differences in adverse health outcomes, such as IHD related to SHS exposure. It is assumed that the anti-estrogenic effect of cigarette smoking—and therefore also the exposure to SHS—may be at least partly related to the increased risk of IHD in young female smokers (Baron et al., 1990). Furthermore, a study by Geisler et al. (1999) indicated that in smoking women undergoing estrogen replacement therapy, plasma levels of estrogen were 40%–70% lower than in non-smoking women. Additionally, a decrease in both estradiol and testosterone concentrations in smoking men has been reported (Hsieh et al., 1998). Therefore, hormonal factors seem to considerably influence vulnerability to SHS exposure. This may also explain gender differences in the effects of SHS exposure (Bolego et al., 2002).

3.2 Adverse health effects caused by SHS exposure

SHS is increasingly being recognized as a major public health concern and risk factor in population health. Consistent adverse health effects caused by SHS exposure were reported in a Cochrane review (Callinan et al., 2010). SHS is the cause of several chronic diseases, including respiratory and cardiovascular conditions such as myocardial infarction, and may, for example, lead to a 25%–30% increase in the risk of coronary heart disease (Been et al., 2013; Dunbar et al., 2013). Studies have indicated that the acute effects of SHS are also harmful (Dacunto et al., 2014; Dinas et al., 2014). The health consequences that are causally linked to SHS exposure differ between ages and sexes (U.S. Department of Health and Human Services, 2014). Some risk groups suffer more from the adverse health effects caused by SHS exposure, particularly children (Tanski and Wilson, 2011) and pregnant women (Lee et al., 2011; Lee et al., 2012; Nichter et al., 2010; Stillerman et al., 2008). At least 40% of children and around 30%–35% of adult non-smokers are regularly exposed to SHS worldwide (Been et al., 2013; Öberg et al., 2011). The main exposure occurs at home,

which is a common location for exposure to SHS (Jin et al., 2013; Singh and Lal, 2011). Concerning health behavior, it has been observed that children of smokers are more likely to become smokers themselves (Longman and Passey, 2013).

However, in addition to exposure during childhood, exposure during pregnancy is also an important factor in children's health (Eiden et al., 2011). It has been estimated that a third to a half of non-smoking pregnant women are involuntarily exposed to SHS. Therefore, these women and their unborn children face an increased risk of a range of adverse health effects (Best, 2009; Mbah et al., 2013). Non-smokers, and particularly children living in households with at least one active smoker, are exposed to high levels of pollutants that negatively affect their health status (Kusel et al., 2013). Globally, the annual excess in deaths among children younger than five as a result of SHS exposure was estimated in 1997 at close to 6,000, thereby exceeding deaths from all injuries combined (Aligne and Stoddard, 1997). For this reason, child exposure to tobacco smoke in domestic settings has become an international concern (Brooks et al., 2011; Pagani and Fitzpatrick, 2013; Hawkins and Berkman, 2014).

3.3 Public health interventions to protect from SHS exposure

The above-mentioned aspects highlight the relevance of considering SHS a risk factor for adverse health effects. Therefore, several public health interventions have been implemented to protect the population from adverse health effects caused by SHS exposure. In particular, the publication of the Surgeon General's Report in 1986 (U.S. Department of Health and Human Services, 1986), in which SHS exposure was declared to be a cause of lung cancer in healthy non-smokers, led to an increase in the number of smoking bans and restrictions (Callinan et al., 2010). In 2003, the World Health Organization (WHO) ratified the Framework Convention on Tobacco Control (FCTC) (WHO, 2003). This is an evidence-based treaty that sets out a legislative framework for tobacco control, including recommendations for the development, implementation, and enforcement of national smoke-free legislation. Smoke-free legislation, consistent with the FCTC recommendations, has now been introduced in many countries (Mackay et al., 2010; Yach, 2014). The FCTC aims to offer price and tax measures, as well as non-price measures, to reduce the demand for tobacco (WHO, 2003).

Bans and policies for tobacco control can be implemented through public health policies or legislation affecting populations at a national, state, or community level (Callinan et al., 2010; Liang et al., 2016). A Cochrane review summarizing 25 studies observed consistent

positive health effects after the implementation of legislative smoking bans. All studies showed reductions in the duration of self-reported SHS exposure, ranging from 71% to 100%, or in the percentage of those exposed, ranging from 22% to 85% (Callinan et al., 2010). Other studies claim that smoke-free housing policies may be an effective strategy to reduce exposure to indoor SHS (Kingsbury and Reckinger, 2016). Nevertheless, a recent Cochrane review focused on the impact of institutional smoking bans. One of the main conclusions was that the evidence was not sufficient, because of low-quality primary studies (Frazer et al., 2016).

4. Objectives

Although a large number of studies have been published on the impact of SHS on health and on the effects of public health interventions to protect populations from SHS exposure, some evidence is still controversial, so that the need for adequate study designs remains (Künzli and Perez, 2009).

For that reason, the papers included in this cumulative dissertation aim to shed light on how evidence in the research field dealing with SHS exposure is created and what has to be considered for further research. The publications focus on several aspects related to SHS exposure, be it 1) the impact of SHS exposure on health (P1), or 2) the effects of legislation to reduce SHS exposure (P2), 3) factors associated with SHS exposure in different countries (P3–5), including results from different settings (P3) or different types of SHS exposure (P4), or 4) a summary of challenges in creating evidence in environmental health risk assessments using SHS exposure as an example (P6).

The synthesis, and the publications themselves, should lead to answering the following major research questions, which build on one another:

- What are the major methodological challenges in environmental epidemiological studies on SHS exposure?
- What are the implications of an evidence-based approach for public health research?
- What conclusions can be drawn for future research to facilitate evidence-based decision-making in public health?

To provide an answer, or at least a further contribution to the scientific discourse in this area, the following part will focus on selected portions of the publications belonging to this cumulative dissertation. Several challenges will be highlighted and discussed to provide

insight into different aspects that are essential for evidence-based public health derived from environmental epidemiological studies. This synopsis is not intended to repeat or discuss all individual results from the underlying publications. Rather, it aims to highlight those aspects that are important for generating evidence in public health by using environmental epidemiological studies. The public health action cycle (Ruckstuhl et al., 1997) will be used as a framework for describing the results and setting them into the context of an evidence-based public health approach.

5. Methods

The publications rely on different methodological concepts. Overall, only secondary data were used, but differences in the methodological handling exist. The methods of the publications are only described briefly here. A detailed description can be found in the publications themselves (see Appendix).

5.1 Impact of SHS exposure on health

The first paper (P1) is based on a systematic literature review that was conducted in PubMed to identify articles dealing with the association between SHS and three health outcomes (IHD, chronic obstructive pulmonary disease [COPD], and stroke). This review was performed according to the procedure and requirements described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009). All studies identified by the search algorithm and published by 2014 were assessed. All full-text articles were subjected to a quality assessment. Sixteen criteria were used to assess the risk of 1) selection bias and 2) misclassification bias, as well as to judge 3) the adequacy of data analysis. In considering selection bias, criteria differed for case-control and cohort studies, which were the only study designs included in the systematic review (see Table 1).

Table 1: Criteria for quality assessment of studies included in the systematic review of P1

case-control study	*cohort study*
Selection bias	
Cases randomly selected or all cases in a specific population included	Subjects randomly selected or all subjects in a population included
Cases identified without knowledge of exposure status	Subjects identified without knowledge of disease status
Control drawn randomly from the same population of cases	Comparison of persons who did and did not participate
Response rate for identified cases and controls > 70%	Response rate and follow-up rate > 70%
Misclassification bias	
Exposure evaluations made in relation to the time of diagnosis	
Exposure validated by biomarker (and not [only] via self-report)	
Specific disease criteria provided	
Disease validated by histology or other gold standard	
Data analysis	
Adjustment or matching for potential confounders	
Power calculations performed	
Sample size sufficient	
Precise p-values and CIs given	

The systematic literature review formed the basis for a meta-analysis including 24 full-text articles. The main goals of the meta-analysis were: 1) To test whether the study results were homogeneous and, if so, 2) to obtain a combined estimator of the effect magnitude for the association between SHS exposure and the outcomes IHD, COPD, and stroke. Within the meta-analysis, effect sizes stratified for sex and for both sexes combined were calculated for the relationship between SHS and the three selected outcomes (P1).

5.2 Effects of legislation to reduce SHS exposure

The calculated effect sizes were employed in a health impact assessment aimed at estimating the impact of SHS exposure in the German population (P2). For the health impact assessment, a software tool called DYNAMO-HIA (DYNAmic MOdeling for Health Impact Assessment) was used (RIVM, 2010). DYNAMO-HIA is a generic software tool applying a Markov model. It was designed to assist in the quantification of the impact of risk factors on health. Furthermore, it enables the quantification of changes in risk factors owing to interventions for various diseases on overall population health (Boshuizen et al., 2012; Lhachimi et al., 2012). The data for the population living in Germany and for

the disease prevalence of the three outcomes IHD, COPD, and stroke were already included in the software (Lhachimi et al., 2012) and directly used for the simulation. Additionally, the RR values for the association between SHS exposure and the outcomes calculated in the meta-analyses were applied to quantify the health effect of SHS. The RR for each outcome stratified by sex was used for each single age year in the simulation. Furthermore, the prevalence of SHS exposure was included in the analysis based on data from the GEDA 2009 survey (Lampert and List, 2010).

DYNAMO-HIA aims to use an almost real-life population for modeling purposes. Therefore, the analysis is stratified by sex and age in one-year age categories up to the age of 95. To compare the effects of policies designed to reduce SHS exposure on future population health, the reference scenario (no change in SHS exposure) is compared with two other scenarios. In these, the transition probabilities between the risk-factor state of no SHS exposure and SHS exposure are changed. In the first scenario, a success rate of 20% in the reduction of SHS exposure is assumed for all age groups. The second scenario assumes the total eradication of SHS exposure (100% success rate). The simulation began in 2014 and covered 36 years to 2050 (P2).

5.3 Factors associated with SHS exposure

Three other studies were conducted to assess the factors associated with SHS exposure. These studies are based on secondary data from Germany (P3), the United States (P4), and Bangladesh (P5). For Germany, the data from the public use file of the German Health Update 2012 were taken (n = 13,933). Only non-smoking adults were included in the analysis (P3). The analysis in P4 is based on data from the National Youth Tobacco Survey 2014, which provides a nationally representative sample of middle- and high-school students in the United States (n = 20,007). Women of reproductive age (n = 17,749) were included in the analysis of P5, which uses Bangladesh Demographic and Health Survey 2011 as the data source. Therefore, regional and intercultural differences in the factors associated with SHS can be described. Furthermore, the various study populations were considered in the analyses.

Factors potentially associated with SHS exposure were selected based on previous literature reviews. Only factors significantly associated in the bivariate analysis were included in the multivariable analyses—either multinomial logistic regression (P3, P5) or binary logistic regression (P4) models. The outcome parameter was always SHS exposure. This was either divided by exposed vs. not exposed (P4) or distinguished between different

categories of exposure (P3, P5). A stratification by the SHS exposure setting, such as workplaces, bars/discotheques, restaurants, at home or at the house of a friend, was conducted in P3. Furthermore, P4 also focused on different types of SHS exposure, such as 1) overall SHS exposure, 2) SHS exposure from cigarettes, or 3) SHS exposure from electronic cigarettes.

5.4 Evidence in environmental health risk assessments

The last publication (P6) is based on a narrative literature review. In this review, the similarities in the approaches of evidence-based medicine and evidence-based public health are described. A focus is set on factors that are important to consider in conducting an adequate study in environmental epidemiology. Therefore, the selection of study designs, the assessment of key sources of exposure, and aspects regarding stratification of results, bias, and confounding are described.

6. Results

The public health action cycle provides a systematic and comprehensible way to highlight the stages in public health decision-making and implement public health interventions. It may serve as an instrument for developing adequate strategies to reduce risk factors, foster healthy behaviors or settings, and, therefore, promote population health. Overall, different aspects of quality at the levels of structure, process, and outcomes (Donabedian, 1966, 1988) must be ensured during the development, implementation, and evaluation of public health activities (Ruckstuhl et al., 1997). The idea of the public health action cycle goes back to the plan-do-check-act (PDCA) cycle, also known as the Deming cycle, which is an iterative four-step management method used in business for the control and continual improvement of processes and products (Deming, 1989). In addition, the Institute of Medicine had described the functions of governments in public health in a paper called “The Future of Public Health” (Institute of Medicine, 1988) in 1988, at a time when academization by implementation of national initiatives for research and training in public health was in the early stage of development in Germany (Nationale Akademie der Wissenschaften Leopoldina et al., 2015; von Troschke, 2001).

The public health action cycle distinguishes between four categories or phases which may be used for strategic planning for all activities taking place in public health. Therefore, it is not restricted to only individual interventions, but rather allows a broader view of measures

to improve populations' health. These phases within a circular process are 1) assessment, 2) policy formulation, 3) implementation, and 4) evaluation (see Figure 1).

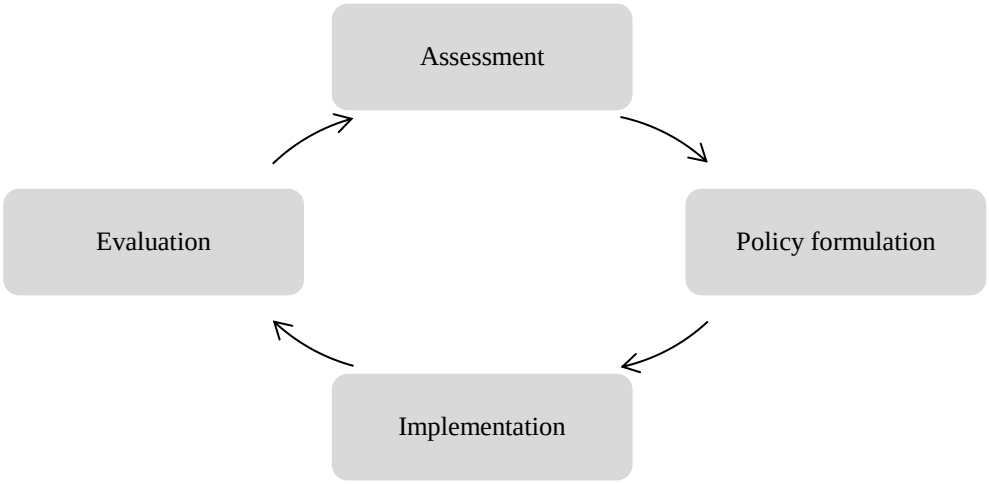

Figure 1: The public health action cycle (Institute of Medicine, 1988; Ruckstuhl et al., 1997)

Keeping in mind the need for evidence-based public health, the four stages will now be used as a framework to briefly name the most important aspects to consider in environmental epidemiological studies using the example of SHS exposure. It should be noted that not all aspects can be strictly divided between the stages. The argument for the requirements regarding evidence is overarching and, therefore, sometimes overlaps the stages. Evidence is the fundamental basis for the first two stages (assessment and policy formulation), but also highly important for the implementation stage. The evaluation stage is required to create more evidence.

6.1 Assessment

All actions in public health should be based on current research evidence, because knowledge about cause and effect is a decisive element in public health practice. As mentioned by the Institute of Medicine (1988), it is essential to "regularly and systematically collect, assemble, analyze, and make available information on the health of the community, including statistics on health status, community health needs, and epidemiologic and other studies of health problems" (Institute of Medicine, 1988, p. 7). This study adds information on the effect sizes for the association between SHS exposure and three outcomes (IHD, COPD, and stroke). This is the first study to calculate effect sizes for the association between SHS exposure and the disease outcomes IHD, COPD, and stroke at once. The results of the meta-analysis (P1) indicate the high relevance of SHS

exposure, because positive, and mostly significant, results were found for the association between SHS exposure and the three outcomes for both sexes.

A major added value in terms of evidence is the fact that the same methods were used for calculating the effect sizes. Otherwise, it would be somehow difficult to compare results from other primary studies or systematic reviews. This is another finding from P1, that there is quite a large heterogeneity in the quality and reported effects between studies. This is mainly attributable to the fact that study designs differ greatly. In particular, the measurement of exposure is crucial in the field of SHS exposure. Many studies rely on self-reports, and the definitions or ways to request SHS exposure information differ (P6). In addition, many studies assess both the exposure and the outcome by self-reports (P3–P5), which may lead to biased results. These biases make a health impact assessment (P2) difficult, because a lack of knowledge about actual exposure (P3–P5) or dose-response relationship (P6) will lead to inadequate or highly uncertain results. Nevertheless, these kinds of data are necessary to provide adequate information on population health and the factors associated either with adverse health effects or—as in the case of SHS exposure—the risk factors impacting health.

6.2 Policy formulation

Furthermore, it must be considered that the factors associated with SHS exposure may differ on a small-scale level between individual characteristics of the people within a population (such as age, sex, or socioeconomic status) or on a large-scale level between various countries or regions (P3–P6). These differences should be taken into account when developing target-specific interventions. Therefore, studies that focus on subgroups and their particular SHS exposure, as well as their needs, are necessary.

P3, based on data from Germany, notes that the factors associated with SHS exposure vary between locations of SHS exposure. For example, males were more likely to be exposed to SHS in the workplace and in bars or discotheques than women. In comparison, women were more likely than men to be exposed to SHS at home or at the house of a friend. This indicates the relevance of target-specific interventions that take into account the setting of SHS exposure and other characteristics of the risk groups. Within the publications included in this analysis, two particularly vulnerable subgroups for SHS exposure and related adverse health effects have been included. These are women (P5) and children (P4). In addition, P4 found that the factors associated with SHS exposure may differ if the results are stratified by the type of exposure (overall, cigarette, or electronic cigarette exposure).

Therefore, the characteristics of exposure and exposed subpopulations should be considered during the development of adequate public health policies and interventions.

6.3 Implementation

This study did not focus on any specific type of public health intervention implemented to reduce SHS exposure. Nevertheless, an evidence-based strategy is not only necessary in the preceding stages, where the problem is defined and the intervention is planned; the implementation also plays a major role. It can be referred to another publication by the author of this dissertation, which focuses on aspects of guideline implementation (Fischer et al., 2016). Successful interventions should also focus on what was done well in other contexts or other settings, or what can be learned from the international perspective (P3–P5).

6.4 Evaluation

The last but not least important step of the public health action cycle is the evaluation. This evaluation should focus primarily on the effectiveness but also on the efficiency of the chosen intervention, to create more evidence. In P2, a health impact assessment was performed which was actually not the evaluation of an intervention, but rather an estimation of the effects of legislation to reduce SHS exposure on population health. Again, such estimates may be prone to bias, because interventions in public health are complex processes involving several interacting components, with a lack of linear, well-evidenced causal pathways linking the intervention and health outcomes. This should be taken into account when designing and interpreting studies in the field of environmental epidemiology or evaluations of public health interventions.

After the evaluation, the process of the public health action cycle can start again. That means evidence-based public health is a process with ongoing iterations, necessary for identifying the most effective and efficient measures to reduce health risks such as SHS exposure and their adverse health outcomes. A reiteration of this process is required because of social transformations and other developments, along with innovations in research and policy which lead to changes in attitudes and behaviors among the population. To evaluate certain interventions, methodological shortcomings in previous studies (such as potential misclassification, bias, or confounding) must be respected to allow the creation of evidence.

7. Discussion

Activities in public health are characterized by complexity and indeterminacy, which pose a strong limitation, or at least a challenge, to evidence-based public health (Attena, 2014). This is also shown by the results presented within the publications included in this dissertation. This synopsis aimed to highlight the most important methodological considerations relevant for assessing the impact of SHS exposure on human health. Furthermore, where environmental epidemiological studies correspond with evidence-based approaches and where the pitfalls are should be noted.

Using the public health action cycle to describe results already indicates that evidence plays a crucial role in many, if not all, aspects of public health. Although there are similarities between evidence-based public health and evidence-based medicine, there are also some relevant differences. For example, the gold standard for inferences about causal relationships is an experimental study. This would typically be a double-blind RCT in clinical research. In public health, particularly in environmental epidemiology, this concept cannot be applied to all types of research. This aspect was referred to in an article published in the Christmas issue 2003 of the British Medical Journal. This humorous article presented the results of a systematic review of the effects of using a parachute during free-fall. The conclusion was that no RCTs that covered this research question existed (Smith and Pell, 2003). It does not have to be pointed out that the idea of an RCT is unethical and not feasible, but this illustrates once more the fact that an RCT as a gold standard is not applicable in all cases (Black, 1996; Hatt et al., 2015; Shelton, 2014).

Environmental epidemiological researchers mainly rely on observational studies (Thomas, 2009). This is linked to a risk for different types of biases and increasing uncertainties. Therefore, there are three basic requirements for addressing these uncertainties: 1) Identification and evaluation of the sources of uncertainties, 2) evaluation of their combined effect on the outcome of the assessment, and 3) communication of these uncertainties to policymakers and the public (Brownson et al., 2009b; LaKind et al., 2015).

For applying an evidence-based approach in public health using epidemiological studies as the fundamental basis, major attention should be paid to the assessment of exposure and risk. Therefore, the Bradford Hill postulates for causality are of major relevance, because they include the strength of association, consistency, specificity, temporality, biologic gradient, plausibility, coherence, data based on experiments, and analogy (Hill, 1965). As mentioned, not all of these criteria can be applied in the field of public health, but it is worth considering these factors.

One of the most challenging tasks in environmental epidemiology deals with the estimation of health effects associated with past patterns of exposure and the prediction of effects that may occur in the future as a result of continued or projected exposure. Therefore, exposure assessment is an essential aspect of a study's quality. A more accurate assessment of exposure can increase the power of an environmental epidemiological study by reducing misclassification of confounders and modifiers. The results of the meta-analysis (P1) and also of the other studies using secondary data (P3–P5) highlight the need for focusing on adequate methods to assess and report the exposure thoroughly, because several major differences exist regarding the definition and measurement of SHS exposure. For example, studies included in the meta-analysis (P1) used various definitions of SHS exposure, focusing either on certain settings, such as the home or workplace, or relied only on information such as "spousal smoking", without any further assessment of the frequency, duration, or intensity of exposure (Avila-Tang et al., 2013; Bentayeb et al., 2013). For this reason, information on SHS exposure may be inexact or poorly reported (Barnoya and Glantz, 2005; He et al., 1999). Using spousal smoking, for example, as the sole marker of SHS exposure, may lead to a downward bias resulting from exposure misclassification (Ahijevych and Wewers, 2003; Pron et al., 1988).

Since many studies focused on SHS exposure at home irrespective exposure that may take place outside home, groups of people described as "unexposed" may include a not negligible proportion of persons with SHS exposure in other settings, such as the workplace (Hill et al., 2007). A review of nine epidemiological studies published before 1992 noted that the lack of data on SHS exposure outside the home was one of the major weaknesses in the epidemiological evidence (Steenland, 1992). Therefore, studies may underestimate the risk from SHS exposure, because exposures at home may be smaller than exposures at the workplace (Glantz and Parmley, 1991). Although this argument may have changed following the implementation of smoke-free laws, which led to the greatest source of SHS exposure being the home (Enstrom and Kabat, 2006), it still highlights the importance of including different settings in calculating SHS exposure, which P3 did. Furthermore, the differences in the type of SHS exposure studied in P4 are relevant. This is confirmed by a study focusing on different cigarette sizes and brands, which indicated significant type-specific differences for emitted particulate matter concentrations (Kant et al., 2016). Overall, difficulties in ascertaining SHS exposure may explain the lack of precision in several estimates (Bonita et al., 1999).

Epidemiological studies must measure the intensity and duration of SHS exposure by using adequate study designs—preferably cohort studies—to support causal associations. This is also needed to identify dose-response relationships. Until now, the meta-analysis could only compare exposed vs. not exposed people to calculate effect sizes (P1), and the studies focusing on the factors associated with SHS exposure (P3, P5) relied on very crude information regarding exposure. Furthermore, a disease may require a minimal level of exposure and increase in probability with a longer exposure period. A further limitation is that many studies reasonably desire to focus on the isolated association between a given exposure and an adverse health effect. Nevertheless, assessing combined effects of multiple exposures is important in the field of public health, because interventions often target an overall exposure scenario (Hertz-Picciotto, 2008; Merrill, 2008).

Information on past exposures may either not be available or of poor quality because self-report assessments are prone to recall bias or other types of information bias (Thomas, 2009). For that reason, it is expected that biological markers of exposure may improve current estimates of exposure in environmental epidemiologic research. A more accurate assessment of SHS exposure may improve the sensitivity of epidemiologic studies to detect associations (especially weak associations) between exposures and adverse health outcomes. Furthermore, misclassification of exposure measures can be reduced. In general, non-differential misclassification causes measures of effect to be biased toward the null value, whereas differential misclassification can result in bias either toward or away from the null value (Rothmann et al., 2008).

Although some earlier studies found that the reliability of self-classification of SHS exposure is moderate to very good (Brownson et al., 1993; Coultas et al., 1989; Eisner et al., 2005; Emmons et al., 1994; Hammond and Leaderer, 1987; Pron et al., 1988), nowadays the evidence indicates that self-reported information is an imprecise measure to assess SHS exposure (Jefferis et al., 2010; Lightwood et al., 2009). The sensitivity of SHS exposure assessment by self-reports may vary between the domestic setting and work-related settings or public places (Iribarren et al., 2004). Furthermore, subjective reports of SHS exposure are subject to recall and reporting biases (Bentayeb et al., 2013).

In the case of SHS exposure, there are some objective markers that can be used, although they vary regarding their suitability to detect dose-response relationships. Despite a missing gold standard for measuring SHS exposure (Kaur et al., 2004), one of the most frequently used biomarkers to assess SHS exposure is cotinine. Cotinine, which is a metabolite of nicotine, is commonly used as a biomarker for measuring SHS exposure

(Avila-Tang et al., 2013; Jefferis et al., 2010; Misailidi et al., 2014). It can be measured in blood, urine, and saliva (Bernert et al., 2000; Jarvis et al., 1984), and has a half-life of approximately 15–20 hours (Benowitz et al., 1983), which is much longer than the half-life of nicotine (2 hours) (Hawamdeh et al., 2003; Jarvis et al., 1988; Jarvis et al., 1987; Nondahl et al., 2005). Therefore, cotinine reflects SHS exposure during the previous 1–2 days (Eisner et al., 2005; Hammond and Leaderer, 1987; Nondahl et al., 2005). An advantage of cotinine assessment is its ability to detect low quantities of serum cotinine, allowing the identification of low levels of SHS exposure among non-smokers (Nondahl et al., 2005).

These challenges, among others, are discussed in P6. Evidence-based public health needs to take into account several aspects related to study design in environmental epidemiology. Overall, the aim of all these studies should be freedom from biases (Thomas, 2009) and confounding in study results. Within the quality assessment of the primary studies in the meta-analysis published in P1, controlling for possible effects of confounding was used as one criterion for the quality scale. Studies have used various determinants as potential confounders, such as age, gender, smoking status (if not only non-smokers were included), health status, and disease history. A recommendation for future epidemiological studies is to consider possible effects of confounding. This can be done by adjustment, matching, or more restrictive exclusion criteria for study participants (Chen et al., 2004; Dunbar et al., 2013; McElduff et al., 1998). Confounding may be related both to the assessment of exposure and the outcome of interest (Iribarren et al., 2001). For example, smoking at some point during life may confound the effect of SHS exposure (Johannessen et al., 2012). The potential for misclassifying the smoking status of former or even current smokers as passive smokers is a longstanding concern in studies using self-reports for assessing SHS exposure (Coultas, 1998). Therefore, the association between SHS exposure and adverse health effects should only be evaluated among never-smokers (Enstrom and Kabat, 2003), which most of the primary studies included in P1 already did.

Whereas in evidence-based medicine, RCTs as the gold standard are particularly important, evidence-based public health should also focus on study design, but here it is crucial to select the right option and assess exposure and outcomes, as well as confounding factors, as accurately as possible.

For the evidence-based public health approach, however, it is not enough to create evidence by methodologically sound scientific studies. The translation of the evidence into practice is at least equally important (Mitton et al., 2007). This matter of course is also

depicted in a definition of evidence-based health care, which "is characterized by decision-making in which the decision is based on a systematic appraisal of the best evidence available" (Gray, 1997, p. 65). Alberg et al. (2014) called the last step of their framework for evidence-based public health "action", and described it as the process in which steps are taken to protect society from harmful exposures, if a causal hypothesis was confirmed and public health action is warranted. Therefore, (environmental) epidemiological studies provide a foundation for decisions based on evidence. A large variation in the use of evidence-based decision-making practices has been shown (Bambra, 2013; Brownson et al., 2009a; Lovelace et al., 2015). For that reason, the gap between research and policy and practice must be bridged (Rychetnik et al., 2012), to accelerate the integration of scientific discoveries into routine public health practice (Fielding and Briss, 2006).

8. Conclusion

The entire dissertation project highlighted several intersections between evidence-based approaches and environmental epidemiology. The aim of this synopsis was not to add evidence to the already-growing body of literature regarding the association between SHS exposure and adverse health outcomes. Rather, it aimed to reflect on some methodological issues that should be considered in studies in the field of environmental epidemiology (as a subdiscipline of public health) in general and in effects of SHS exposure in particular. This should open the floor for further discussion in the scientific community. This exchange is important, because evidence-based public health is still considered underdeveloped (Brownson et al., 2009b; Latham et al., 2013).

Environmental epidemiology and other scientific disciplines have much to contribute to facilitate population health (Aldrich et al., 2015). Although there may be several shortcomings in environmental epidemiological studies dealing with SHS exposure, this type of observational research is necessary. Evidence can also be derived from multiple—well-conducted—studies to assess the impact of public health interventions, when the conduct of RCTs is difficult or impossible (Black, 1996; Heller and Page, 2002; LaKind et al., 2015). Therefore, the methodological constraints must be resolved. Although standardized approaches in public health are needed, particularly for the assessment of exposure and outcome in (environmental) epidemiological studies, a focus on only one gold standard is not justified. Since public health acts on several levels, an interdisciplinary approach that uses the most appropriate methods from the respective disciplines of

research traditions to create evidence is necessary. All decisions in public health should be evidence-based, irrespective of the area of interest. Therefore, public health researchers must succeed in using the most appropriate methods. Perhaps an approach termed “evidence-based environmental epidemiology” will be formulated in the future. However, all types of research conducted in public health must use sound methods. That, besides the inclusion of patient values and expertise, is the main prerequisite to calling the concept “evidence-based”.

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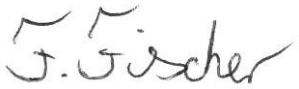
Declaration of originality

I hereby declare that this thesis represents my original work and that I have used no other sources except as noted by citations. All data, tables, figures and text citations which have been reproduced from any other source have been explicitly acknowledged as such. This thesis has not been accepted in substance for any other degree, nor is it currently being submitted in candidature or achievement of any other degree at any other university. I further declare that I have not previously made attempts to do a doctorate at any national or international university.

Bielefeld, September 6, 2016



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