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Long-term air pollution exposure from industry and traffic and respiratory health in elderly women from the Ruhr Basin

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‘A handful of patience is worth more than a bushel of brains’

Dutch Proverb

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List of Publications

1) **Schikowski T**, Sugiri D, Ranft U, Gehring U, Heinrich J, Wichmann HE, Krämer U.
Long-term air pollution exposure and living close to busy roads are associated with COPD in women
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2) **Schikowski T**, Sugiri D, Ranft U, Gehring U, Heinrich J, Wichmann HE, Krämer U.
Does respiratory health contribute to the effects of long-term air pollution exposure on cardiovascular mortality?
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3) **Schikowski T**, Sugiri D, Reimann V, Pesch B, Ranft U, Krämer U
Contribution of smoking and air pollution exposure in urban areas to social differences
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Abbreviation

ATS:	American Thoracic Society
BMI:	Body Mass Index
BTS:	British Thoracic Society
CI:	Confidence interval
COPD:	Chronic obstructive pulmonary disease
COLD:	Chronic obstructive lung disease
CRP:	C-reactive protein
DALYS:	Disability-adjusted life's year
DNA:	Desoxyribonucleinacid
EPA:	Environmental Protection Agency
ERS:	European Respiratory Society
FEV_1:	Forced expiratory volume in one second
FVC:	Forced vital capacity
GIS:	Geographic Information system
GOLD:	Global Initiative COLD
IL-8:	Interleukin-8
LTB4:	Leukotriene B4
MD:	Mean difference
NHLBI:	National Heart Lung and Blood Institut
NO_2:	Nitrogen dioxide
NO_3:	Nitrogen tetroxide
O_3:	Ozone
OR:	Odds ratio
PM_{10}:	Particulate matter of size 10µg diameter
$PM_{2.5}$:	Particulate matter of size 2.5 µg diameter
ppm:	Parts per million
RR:	Relative risks
SES:	Socio-economic status
$SO_{2:}$	Sulphur dioxide
TNF-α:	Turmornecrose factor
TSP:	Total suspended solids
VC:	Vital capacity
WHO:	World Health Organisation

CHAPTER 1

Introduction and background

1.1 Demographic changes

The demographic changes in Germany and other western countries are leading to an increase of the aging population. The number of older people in the population is continually growing. A reduction in birth rates and major advances in the medical field have led to a significant increase in life expectancy throughout the 20th century. This demographic transition is dynamic and results in an increased demand on the health sector with questions arising in relation to health care provision and health needs of the elderly population. Current predictions suggest that there will be economic and social disadvantages for the aging population [1]. One major consequence of this demographic transition is the worldwide increase in chronic diseases, which affects older people disproportionately and contributes to quality of life [2]. Therefore, it is important to promote good health among middle age and older people so as to promote health and well being in later life [3].

With the aging of the population came also the possibility of a longer lifetime exposure to various toxic agents, chemical irritants and other environmental pollutants. There is strong evidence that long-term exposure to high levels of air pollution in ambient air can have adverse health effects on morbidity and mortality, especially with respect to vulnerable subgroups such as children and the elderly [4-6]. Epidemiological and experimental studies have shown that the exposure to particles from traffic-related sources can have an effect on the development of chronic respiratory diseases [7,8]. Environmentally-induced respiratory diseases result from inhalation of dusts, allergens, chemical, gases and environmental pollutants.

This dissertation focuses on the epidemiology of air pollution exposure and its effect on respiratory diseases in particular chronic obstructive lung disease in 55-year old women from the Ruhr basin. In addition, it investigates air pollution- associated respiratory health as a risk factor for cardiovascular mortality in this cohort of women, and compares the contribution of smoking and air pollution as competing factors for the association between socioeconomic status (SES) and the development of respiratory symptoms.

1.2 Air Pollution

1.2.1 Definition of air pollutants mainly involved in the exposure and its measurement

In most countries in Europe the quality of ambient air has improved in recent years due to stringent air pollution control programs. However, there is a large body of evidence suggesting that exposure to ambient air pollution levels achieved nowadays can lead to adverse health effects [9]. In particularly exposure to pollutants such as particulate matter

and nitrogen dioxide have found to be associated with increased hospital admission and mortality [10]. Particulate matter can cause inflammation of the airways which may lead to worsening of existing lung disease [11,12]. The effect of air pollution on respiratory health can be substantial at high pollution levels, which can trigger asthma and COPD exacerbation [13-15]. The health burden due to air pollution is one of the biggest environmental health concerns in Europe and around the world [16]. The Global Burden of Disease project has estimated that exposure to fine particles in outdoor air leads to about 100 000 death (and 725 000 years of life lost) annually in Europe [17].

The major components of air pollution in developed countries are nitrogen dioxide (NO_2) from combustion of fossil fuels and suspended solids or liquid particles (TSP or PM_{10}).

Measurements of air pollutions are usually obtained from fixed monitoring stations which are intended to provide information about the quality of air in residential areas (background stations), at major roads or industrial points. This type of measurement takes into account diffuse sources of emission such as traffic emissions from major roads as well as point sources from industry. In Germany the monitoring stations are maintained by the State Environment Agencies (e.g. Landesamt für Natur, Umwelt und Verbraucherschutz in North Rhine Westphalia (LANUV)).

1.2.2 Particulate matter (PM)

Particulate matter (PM) is a term for a mixture of solid particles and liquid droplets found in the air. PM_{10} describes the mass of particles in the atmosphere with a size of less than 10µm diameter. This is the fraction of particles that is most likely to be inhaled in the lung. The less commonly measured $PM_{2.5}$ is defined similarly, but for particles of less than 2.5µm diameter [18]. Particulates are collected on membrane filters using impactors to collect particles of the size less than 10µm per diameter. The current legal threshold value for particulate matter with less than 10µm per diameter is 50µg/m^3 as 24-hour median average. This legal threshold value may be exceeded on 35 days per year [19].

Particulate matter may be classified as either primary or secondary. Primary particles, such as carbon particles from mainly traffic-related combustion, salt from the sea and mineral particles derived from stone abrasion, are released directly into the air.

Secondary particles are not emitted directly from sources. They are formed in the atmosphere as a result of chemical reactions leading to the formation of substances of low volatility, which consequently condense into the solid or liquid phase. Such particles are generally the result of atmospheric oxidation processes.

The smaller particles contain the secondarily formed aerosols (gas-to-particle conversion), particles derived from combustion and re-condensed organic and metal vapours. The larger particles mainly contain earth crust and fugitive dust from roads and traffic [20].

The behavior of the particles in the atmosphere and within the human body is determined mainly by their physical properties, which have a strong dependence on the particle size. The particle size is directly linked to their potential to cause health problems [18]. Small particles with the size of less than 0.1 micrometers can get deeper into the lungs and may even get into the blood system and create greater health problems than larger particles. Exposure to such small particles can affect the lungs and the heart. Exposure to high concentrated ambient air particles can induce pulmonary inflammation [21].

1.2.3 Nitrogen dioxides (NO_2)

Nitrogen dioxide (NO_2) concentrations are measured by means of chemiluminescence. These are continuous half-hourly measurements routinely performed by the LUA NRW. The current EU threshold value for NO_2 is 40 µg/m^3 as yearly-mean measurement and 200 µg/m^3 as hourly-mean measurements. Nitrogen dioxide in low concentrations is colourless and odorless. Nitrogen dioxide exists in equilibrium with nitrogen tetroxide (NO_3). When NO_2 comes in contact with water, nitrous acid and nitric acid are formed. Nitrogen oxides form when fuel is burned at high temperatures, it is the result of an incomplete combustion process [22]. Sources of exposure are diverse, the primary sources of NO_2 are motor vehicles, power plants and other industrial sources. However, also residential homes can produce NO_2, for example heating with fuels, gas stoves and wood may be the source of exposure [18]. The human odor threshold of NO_2 is 0.5ppm, although olfactorily sensitive people can smell as little NO_2 as 0.1ppm.

The primary source of NO_2 emission is from motor vehicles, making it a strong indicator of vehicle emissions. NO_2 is key precursor for a range of secondary pollutants through atmospheric transformation which leads to the formation of O_3 and other strong oxidants, therefore NO_2 can be seen as a pollutant of concern and a surrogate for other pollutants [23]. While power plants and other major industries were the main sources for NO_2 emissions in the early 1970s, the main source of NO_2 emissions nowadays are from motor traffic.

Most health risks result from NO_2 itself or its reaction products including O_3 and secondary particles [23]. It can be an irritant to the mucous membrane and can cause cough, headache and dyspnea. NO_2 can lead to an inflammation of the lung lining and can reduce immunity to lung infections [24]. In particular people with asthma can suffer under high levels of NO_2, because it can cause more frequent and more intense attacks [25].

1.3 Morbidity

Recent studies provided strong evidence for the serious effects of air pollution exposure on morbidity and mortality. These adverse effects on health are not limited to high concentrations, but could also be harmful at low levels and relatively common

concentrations. The most recent evidence on adverse health effects of PM_{10} and NO_2 was summarized by the WHO working group and the Environmental Protection Agency of the US [18,26]. Regulatory agencies in the US and in Europe have considered more stringent air quality standards for airborne particulates, largely based on evidence from epidemiological studies, which showed an association between mortality and respiratory and cardiovascular diseases and short and long-term exposure to high levels of air pollution [27-29]. Our lungs are continually exposed to the external environment and are susceptible to a host of environmental diseases. Respiratory diseases are a major cause of morbidity and mortality both in developed and developing countries. Based on the findings from mortality studies in Europe and the US, particle pollution belongs to the priority topics identified by the European Union, the US Health Effect Institute, the European Science Foundation, the WHO and the US National Research Council [30]. The chronic effects of particle pollution on morbidity especially in vulnerable subgroups have rarely been investigated.

1.3.1 COPD: chronic bronchitis and emphysema

COPD (Chronic Obstructive Pulmonary Disease) is the most common disease of the respiratory tract and hence the most common cause of respiratory insufficiency. The prevalence, morbidity and mortality are worldwide underestimated. Due to the slowing progressing and chronic nature of the disease, COPD represents a massive and growing burden of disease. The Global Burden of Disease project by the WHO and the Worldbank estimated a COPD prevalence of 9.34/1000 men and 7.33/1000 women worldwide [31]. COPD is ranking as the fifth cause of disability-adjusted life's year (DALYS) in 2020 as a worldwide burden of disease [17].

The WHO [16] definition of COPD is as follows:

'Chronic obstructive pulmonary disease is a disease state characterized by airflow limitation that is not fully reversible'

The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases [32]. All diseases known as COPD exhibit lung airway obstruction and are broadly defined. COPD patients usually suffer various degrees of dyspnea (difficulties breathing), wheezing and productive coughing. The major COPD types include chronic bronchitis (according to the WHO) [33] and emphysema [34]. The chronic cough that accompanies COPD is often productive and worse in the morning (early morning cough). The sputum may increase during exacerbation and may be blood-streaked [34-36].

The slow progressing nature of the diseases means that the disease remains undetected for many years, and most patients are first identified when they are present with an exacerbation. COPD is characterized by decreased maximal expiratory flow and delayed lung emptying, which is fairly stable over a period of month. The flow limitation increases in time and is largely irreversible [37].
COPD comprises pathological changes in four compartments of the lungs (central airways, peripheral airways, lung parenchyma, pulmonary vasculature), which are variably present in individuals with the disease.

1.3.2 Chronic Bronchitis

The WHO [9] defines chronic bronchitis as follows:

'Chronic Bronchitis refers to a productive cough for at least 3 months of each successive years for which other causes have been ruled out'

Chronic bronchitis results in hypertrophy of the mucus-secreting glands in the bronchial mucosa which leads to an increased mucus production. This overloads the mucosiliary escalator and is expelled by coughing. The bronchial tree secrets excessive mucus, which leads to chronic, recurrent productive cough.
Chronic mucosal inflammation results in mucosal hypertrophy and narrowing of the smaller airways, which obstructs airflow [33]. The pathologic hallmark of chronic bronchitis is an increase in goblet cell sizes and number that leads to excessive mucus secretion. Airflow obstruction and emphysematous change is a frequent, but universal accompaniment [34,38,39].

1.3.3 Emphysema

The WHO [9] definition for Emphysema is as follow:

'Emphysema describes destruction of the lung architecture with enlargement of the airspaces and loss of alveolar surface area '

Emphysema is an abnormal condition of the pulmonary system, characterized by over inflation and destruction of the alveolar walls, resulting in loss of lung elasticity and decreased gases. Chronic emphysema usually accompanies chronic bronchitis.
There are two major types of emphysema, according to the distribution within the acinus:
Centrolobular, which involves dilatation and destruction of the whole bronchioles and Panlobular emphysema, which involves destruction of the whole of the acinus.

These two major types might be only microscopic lesions during the early stages of the disease. However, during the course of the disease, they may progress to macroscopic lesions or bullae, defined as emphysematous spaces >1cm in diameter [40].

Although these diseases may appear as pure states in their early states, they frequently overlap as they progress. The slow progressing nature of the diseases means that the disease remains undetected for many years, and most patients are first identified when they are present with an exacerbation.

1.4 Lung function testing and respiratory symptoms

1.4.1 Spirometry

The aims of lung function tests are to detect and define abnormal lung function and to allow to monitor the progression of a disease. Normal values are required, because the results vary with age, sex, height and weight, ideally the best result from 4 measurements is recorded and compared with the predicted values [41,42].

The lung function tests provide measures of flow rates, lung volumes, gas exchanges and respiratory muscle function. Flow rate and lung volume measurements can be used to differentiate obstruction from restrictive lung disorders, to characterize disease severity and to measure responses to therapy. Measurements are typically reported as absolute flows and volumes. Figure 1 shows a normal lung function measurement with a successful FEV_1 and FVC measurement.

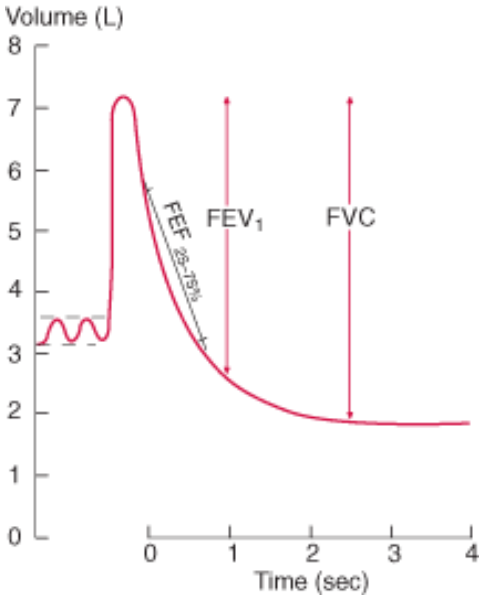

Figure 1 Normal spirogram

For the assessment of the expiratory flow, the patient inhales as deeply as possible, seals his lips around a mouthpiece and exhales as forcefully and completely as possible. The spirometer records the exhaled volume (FVC) and the volume exhaled in the first second (FEV1). Normally the FEV_1 is more than 70% of the FVC. The American Thoracic Society recommends at least 3 acceptable forced expiratory curves. The largest FVC and FEV_1 should be recorded from all acceptable curves [43]. Normal reference values are determined by patient's age, sex and height [44,45].

A person with COPD usually shows a decrease in both, FEV_1 and FEV_1/FVC. The severity of the disease is usually shown in the degree of spirometric abnormality. Figure 2 shows the lung function parameter FEV_1 of a person with COPD and a person without the disease.

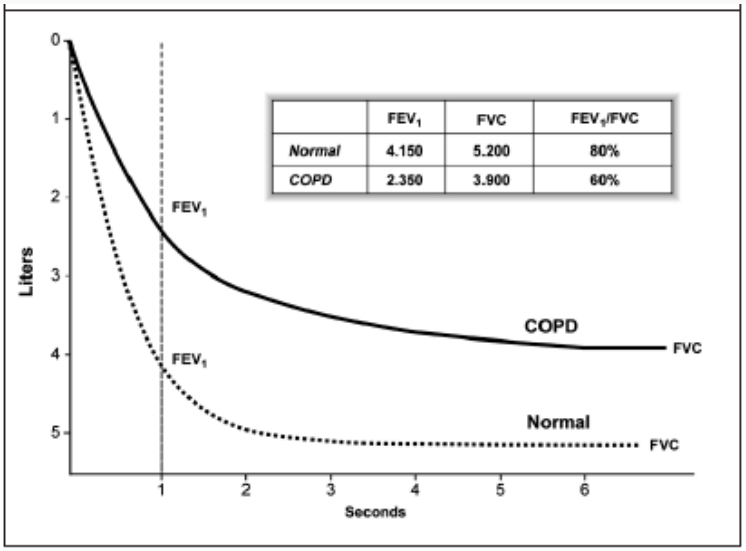

Figure 2 Spirometer of a person with COPD and a person with normal lung function, from Pauwels et al. [46]

The American Thoracic Society and the European Respiratory Society developed spirometric classifications in order to give guidelines in predicting the respiratory health status [47-50]. They recommend to use the FEV_1 /FVC ratio to decide whether there is an airway obstruction or not and to quantify the severity of the disease on the basis of FEV_1. Presented in table 1 below is the staging system for COPD based on the value for FEV_1 % predicted and FEV_1/FVC.

The GOLD guidelines, which were adapted by the ATS and the ETS, introduced a stage 0, which represents absence of airflow obstruction, but presence of chronic symptoms such as cough and phlegm. The aim of this stage was to include persons 'at risk' of developing COPD later in life and to allow intervention while the person has not yet severe respiratory problems [51].

This classification of disease severity into five stages is based on airflow obstruction. The classification into mild, moderate or severe obstruction is based solely on spirometric data [32].

Table 1 General spirometric classification for the diagnosis of COPD according to the ATS and ERS [39]

Severity		Assessment
Stage 0	(at risk)	Patients who: smoke or have exposure to pollutants and have chronic cough and sputum production or have a family history of respiratory diseases
Stage 1	(mild)	$FEV_1 \geq 80\%$; FEV_1 /FVC < 70 %, with or without symptoms
Stage 2	(moderate)	FEV_1 = 50-80%; FEV_1/FVC < 70 %, with or without symptoms
Stage 3	(severe)	FEV_1 = 30-50%; FEV_1/FVC < 70 %, presence or symptoms
Stage 4	(very severe)	FEV_1 < 30% or presence of respiratory failure; FEV_1/FVC < 70 %

In order to be able to distinguish a restrictive lung disease (Asthma) from an obstruction (COPD), it is necessary to do a reversibility test. Two measurements are necessary for this test: a pre-medication measurement and an additional measurement after the use of a bronchiodilator through inhalation. If there is an improvement of the FEV_1 after the use of a bronchiodilator, the patient is suffering from a restrictive lung disease. The FEV_1 should improve by at least 15% [52]. Airflow limitation in COPD is not fully reversible. A high degree in reversibility is usually evidence of the presence of asthma [46].

1.4.2 Respiratory symptoms and diagnosis according to questionnaire

Cough is the most common symptom of lower respiratory tract disease, and can occur in a variety of situations:

- Cigarette smokers often complain of an early morning cough, which usually produces a small amount of sputum.
- Cough at night may be the only symptom of asthma in a child or older adult.

Cough is an expiratory maneuver that is reflexively or deliberately intended to clear the airways. Coughing is a normal response to the presence of mucus or other foreign material in the airway or upper airway, but persistent coughing is annoying and generally indicates irritation of the pulmonary airways [41].

1.5 Mortality

There is strong evidence that long-term exposure to high levels of air pollution can lead to cardiovascular and cardiopulmonary mortality. Studies have linked systemic inflammation, accelerated atherosclerosis and altered cardiac functions to the effect of particle exposure. A recent estimate in Switzerland, France and Austria showed that approximately 40 000 death per year can be attributed to ambient air pollution in particular to PM10 [30]. This reduction in life expectancy is primarily due to increase cardiopulmonary and lung cancer mortality. The knowledge about the underlying biological mechanisms remains limited, however, one hypothized general pathway includes pollution-induced lung damage through oxidative lung damage and inflammation, decline in lung function and cardiovascular disease related to hypoxemia [53,54]. The second hypothesis is that the nervous system may play an important role in the pathophysiologic pathway between particulate exposure and cardiopulmonary disease. Fine particulate may provoke alveolar inflammation which resulting in the release of potentially harmful cytokines and increased blood coagulability [55].

There is also support for a link between respiratory health and cardiovascular mortality [56-58]. It has been shown that the association between respiratory symptoms and mortality are 40% to 60% higher in people who reported persistent cough and phlegm compared to people without symptoms [57].

1.6 Social status

Poor social and economic circumstances affect health throughout life [30]. The social status of a person can influence diseases, exposure and risk factors [59-62]. People with lower social status have a higher risk of serious illness and premature death. The disadvantage of people from lower social status has many forms, from poorer education to living in poor housing and neighbourhoods. These disadvantages tend to concentrate among the same people, the effects on health accumulate during life [63]. The social status of a person has long been known to be associated with the prevalence of COPD and other respiratory diseases [64]. Further, it has been shown that socio-economic differences exists for a number of diseases including ischaemic heart diseases, different types of cancers, respiratory diseases and mortality [65].

Usually, the three core indicators for measuring socio-economic status are: education, income and occupation [60]. Each of these core indicators is a predictor for health [66] as well as a potential confounder or effect modifier in air pollution epidemiology. Information on education emphasizes the difference between people’s knowledge, skills and attitudes [67]. The most common way to measure the educational level is by asking for the highest achieved type of schooling that has successfully completed.

The level of education is widely accepted as a valid measure of socio-economic status in women. It is considered as a good indicator of socio-economic status, in particular, of elderly women, as most of these women were not formally employed [65].

Another important determinant of health is the environment. Increased exposure to air pollution is one of the main contributors for poorer health of people from low SES, especially those that live in deprived urban districts [68]. There is growing evidence that exposures across different stages of life affect adult health outcomes [69,70]. In addition to environmental air pollution, possible SES-related risk factors for respiratory impairment are smoking, occupational exposure, malnutrition, low birth weight or multiple lung infections. These risk factors can be strongly influenced by SES, the level of education influences the type of occupation and income, which in turn influences type and location of housing [71]. Some of these influences associated with SES such as smoking and air pollution are likely to act across the life course to affect respiratory illness later in adult life. The consideration of socio-economic factors is currently gaining more interest in studies on environmental health, because social differences in environmental exposures may help to partly explain the observed inequalities in health [72]. SES may also modify the effect of environmental exposures by changing the susceptibility characteristics.

1.7 Statistical analysis

The aim of the current study was to estimate the effect of exposure or risk factor (explanatory variable) upon a respiratory outcome (outcome variable). This is commonly done by using the regression function. The regression analysis examines a relationship of an outcome variable *y* with one or more explanatory variables *x*.

However, most epidemiological studies have the problems with confounding. A confounder is an extraneous factor that wholly or partially accounts for the observed effect of the risk factor on disease status. The “effect” could be either an apparent relationship or an apparent lack of relationship [73]. All analysis should ideally include the control for all confounding factors.

In our analysis we included age, smoking, exposure to environmental tobacco smoke (ETS), occupational exposure to temperature (heat/cold) and dust and heating with fossil fuels as covariates in all models. FEV_1 and FVC were adjusted for body mass index (BMI) and height additionally. To be able to include other confounding factors into the models, we used a multiple regression approach.

The linear model

$$Y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + ...\beta_k x_k + \varepsilon$$

The linear regression model was used to assess the association between continuous outcome variables (lung function parameters FEV_1 and FVC) and continuous and binary variables (air pollution variables NO_2 and PM_{10} and distance to the nearest road).

In the linear model β_0 is the intercept and β_i are the respective parameters of the independent variables, k is the number of parameters to be estimated in the linear regression with ε representing the error term. The error term is usually normally distributed and picks up the unpredictable part of the response variable y . x_i and y are the data values from the population in question.

The logistic model

$$\log(odds) = \log it(P) = \log\left(\frac{p_i}{1-p_i}\right) = \beta_0 + \beta_1 x_{1,i} + ...\beta_k x_{k,i}$$

In case of a binary outcome variable and when the independent variable includes both, numerical and nominal measure, the logistic regression model is used. In this analysis the logistic regression was used to estimate the association between respiratory symptoms/diseases as binary variables and environmental exposure. The logistic regression is a generalised linear model that uses the logit as its link function.

The logit is a log of the odds and the odds are a function of p. Again, β_0 is the intercept and β_i are the respective parameters of the independent variables. The unknown parameters β are usually estimated by the maximum likelihood method.

To estimate the odds ratio (OR) for exposed ($x_{1,1}$) compared to unexposed ($x_{1,0}$), we could apply the formula:

$$\ln\left(\frac{p_1}{1-p_1}\right) - \ln\left(\frac{p_2}{1-p_2}\right)$$

$$= \ln \frac{\frac{p_1}{1-p_1}}{\frac{p_2}{1-p_2}} = \beta_1$$

$$= \ln oddsratio$$

$$OR = e^{\beta 1}$$

The Cox's proportional hazards function model

$$h(t/x) = h_0(t)\exp(x_1\beta_1 + ... + x_k\beta_k)$$

The association between cardiovascular mortality, air pollution exposure and respiratory health was analyzed with the Cox's proportional hazard model.

In the Cox's regression model $h_0(t)$ defines an unspecific baseline hazard function at the time (t). The predictors, $x_1,\ldots x_2$ are assumed to act additively on log h(t I x) and β the vector of the unknown regression coefficient. The log h(t I x) changes linearly with the βs and the effect of the predictors is the same at all times (t). The estimated value for the regression coefficients β_i, i=1,…,p, can be interpreted as the instantaneous relative risk (or hazard ratios) of an event, at any time, for an individual with the risk factor present compared with an individual with the risk factor absent, given both individuals are the same on all other covariates. The underlying hazard function describes how risk changes over time, and the effect parameters describing how hazards relate to other factors.

1.8 SALIA Study- an environmental health survey on respiratory diseases

SALIA is a cohort of elderly women of now 70-75 years. The cohort of elderly women consist of 4,757 women who were investigated for the first time between 1985 and 1994 by the Medical Institute of Environmental Hygiene (MIU; Düsseldorf) as part of an environmental health survey, which was an element of the Clean Air Plan initiated by the State Environmental Agency of North-Rhine Westphalia [74]. The study was designed as a consecutive cross-sectional survey in different areas of the North-Rhine Westphalia (Appendix 1). These women were an unselected subgroup of 55-year old women mainly from the Ruhr basin (Dortmund, Duisburg, Essen, Gelsenkirchen and Herne) and two reference areas in Münsterland (Borken and Dülmen). These areas were chosen to represent a range of polluted areas with high traffic load and steel and coal industries. The study group was restricted to women, because the main focus was to describe the effects to outdoor air pollution in human health. Most men from these areas were employed in the coal mining and steel industry and therefore were exposed to high levels of occupational exposures. Heavy metals in blood and urine, immune biomarkers (including c-reactive protein (CRP)) and lung function have been measured and respiratory diseases have been investigated by questionnaire. All women aged 54 and 55 residing in the selected areas were asked to participate in the study. 4757 complete a questionnaire addressing respiratory symptoms, medication and other potential confounders, every second responder was invited to have their lung function tested (N= 2593).

In the present thesis, results from the SALIA cohort study are presented. The baseline investigation was conducted in 1985- 1994, using the WIKA I, II and II questionnaire (Appendix 2 (Fragebogen WIKA I, II und III). All WIKA questionnaires included validated questions regarding chronic respiratory symptoms, shortness of breath and cough.

1.9 Aims and outline of the thesis

This dissertation focuses on the epidemiology of air pollution exposure and its effect on respiratory diseases in particular chronic obstructive lung disease in 55-year old women from the Ruhr basin. In addition, it investigates air pollution- associated respiratory health as a risk factor for cardiovascular mortality in this cohort of women, and compares the contribution of smoking and air pollution as competing factors for the association between SES and the development of respiratory symptoms.

In the first publication the association between long-term air pollution exposure and COPD and other respiratory health outcomes is presented. The second publication investigates the questions: a) whether impaired respiratory health is a risk factor for cardiovascular mortality, b) if impaired respiratory health and long-term exposure to air pollution is an independent risk factor for cardiovascular mortality.

In the light of the role of socio-economic status as a determinant of health, in the third publication the contribution of smoking and air pollution exposure as competing factors for socio-economic status and the development of respiratory health were investigated. In last Chapter the results will be discussed and recommendations for future public health actions are made.

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CHAPTER 2

Long-term air pollution exposure and living close to busy roads are associated with COPD in women

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ABSTRACT

Background

Lung function and exacerbations of chronic obstructive pulmonary disease (COPD) have been associated with short-term exposure to air pollution. However, the effect of long-term exposure with particles from industry and traffic on COPD as defined by lung function has not been evaluated so far. Our study was designed to investigate the influence of long-term exposure to air pollution on respiratory symptoms and pulmonary function in 55-year-old women. We especially focused on COPD as defined by GOLD criteria and explored whether this is a sensitive indicator of air pollution health effects.

Methods

In consecutive cross sectional studies conducted between 1985-1994, we investigated 4757 women living in the Rhine-Ruhr Basin of Germany. NO_2 and PM_{10} exposure was assessed by measurements done in an 8 km grid, and traffic exposure by distance from the residential address to the nearest major road using Geographic Information System data. Lung function was determined and COPD was defined by using the GOLD criteria. Chronic respiratory symptoms and possible confounders were defined by questionnaire data. Linear and logistic regressions, including random effects were used to account for confounding and clustering on area level.

Results

The prevalence of COPD (GOLD stages 1-4) was 4.5%. COPD and pulmonary function were strongest affected by PM_{10} and traffic-related exposure. A 7 $\mu g/m^3$ increase in five year means of PM_{10} (interquartile range) was associated with a 5.1% (95% CI 2.5%-7.7%) decrease in FEV_1, a 3.7% (95% CI 1.8%-5.5%) decrease in FVC and an odds ratio (OR) of 1.33 (95% CI 1.03-1.72) for COPD. Women living less than 100m from a busy road also had a significantly decreased lung function and COPD was 1.79 times more likely (95% CI: 1.06-3.02) than for those living farther away. Chronic symptoms as based on questionnaire information showed effects in the same direction, but less pronounced.

Conclusion

Chronic exposure to PM_{10}, NO_2 and living near a major road might increase the risk of developing COPD and can have a detrimental effect on lung function. COPD as defined by the GOLD criteria is a sensitive indicator for air pollution health effects in middle aged women.

BACKGROUND

Acute exacerbations of chronic obstructive pulmonary disease (COPD), chronic bronchitis or emphysema have been associated with short-term exposure to air pollution [1-3]. Studies done in the 1970s found that high levels of particles were related to a high prevalence of chronic bronchitis [4,5]. However, newer studies designed to measure the effects of long-term exposure to air pollution on pulmonary function and respiratory health in adults are rare [6-10]. The studies conducted so far did not use a definition of COPD based on lung function, but focused on respiratory symptoms [11].

Several studies have suggested that lung function decline and respiratory diseases are associated with proximity to roads with heavy traffic, traffic density or exposure to traffic-related air pollution [12-15]. The majority of these studies investigated the influence of air pollution on children's lung function and respiratory health. Only one study has investigated the impact of chronic traffic pollution on pulmonary function exclusively in women [16], however the focus was on FEV1 decline and asthma rather than on COPD.

Our study was done between 1985 and 1994, when sulfur dioxide and particle pollution from industrial sources already had decreased, whereas traffic-related pollution was increasing.

Women are probably more susceptible for COPD and respiratory symptoms caused by environmental factors than men, therefore the study focused on women only [17,18]. We defined COPD by lung function according to the newly developed GOLD criteria [19]. The study was designed to investigate the influence of chronic exposure to air pollution from industrial sources and traffic on respiratory symptoms, pulmonary function with main focus on COPD in 55-year-old women.

METHODS

Study design and population

The study was part of the Environmental Health surveys as an element of the Clean Air Plan introduced by the Government of North-Rhine Westphalia in Germany [20]. Consecutive cross-sectional studies were performed between 1985 and 1994. The study areas (Dortmund (1985, 1990), Duisburg (1990), Essen (1990), Gelsenkirchen (1986, 1990) and Herne (1986)) were chosen to represent a range of polluted areas with high traffic load and steel and coal industries. Two non-industrial small towns, Dülmen (1985) and Borken (1985, 1986, 1987, 1990, 1993, 1994), were chosen as reference areas. Data from similar studies done in 1987, 1993 and 1994 in Cologne, Düsseldorf, Hürth, Dormagen and Wuppertal were not included in this analysis because of a low response, different type of exposure (chemical industry) and no availability of address-coordinates for GIS- based exposure estimation.

All women aged 54 to 55 residing in the selected areas were asked to participate in the study, which took place in March and April in the years specified. 4874 responded (70%). Every second responder was invited to have a lung function testing (N=2593). We restricted the analysis to those 4757 women where addresses were available.

Questionnaire: diagnoses, symptoms and risk factors

As well as the invitation a self-administered questionnaire was sent to the women. The investigating physicians checked the returned questionnaires. We asked whether a physician had ever diagnosed chronic bronchitis and for respiratory symptoms. The questions for respiratory symptoms were in defined answers: chronic cough with: (a) phlegm production, (b) for > 3 month a year, (c) for more than 2 years. We evaluated “chronic cough” and “chronic cough with phlegm production”. The diagnosis of chronic cough with phlegm production was positive, when each of the answers categories (a), (b) or (c) was positive. This symptoms complex classically defines chronic bronchitis. We further asked about risk factors such as single room heating with fossil fuels, occupational exposure (dust and extreme temperatures) and education as indicator for socioeconomic status. We classified socioeconomic status into three categories using the highest school level achieved by either the women or her husband as low (< 10 years), medium (=10 years) or high (> 10 years). Women were grouped according to their smoking habits as never smoker, passive-smoker (home and/or work place), past smoker or current smoker (<15 pack years; 15-30 pack years and >= 30 pack years).

Lung function testing and COPD

Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were measured. Four maneuvers were performed, and the values, where the maximal FEV1 was reached, were used. All measuring instruments were calibrated prior to each testing by using a 3-liter-syringe. All personal were specially trained, the same type of measuring device was used (Vica Test 4 spirometer (Mijnhardt, Rotterdam, Holland)) and all maneuvers were performed in accordance to a standardized protocol [21]. We also used the ratio FEV1/FVC, which is considered a sensitive measure of COPD on its own [22]. A FEV1/FVC ratio <0.7 is the main criterion for COPD according to the newly developed criteria by GOLD [23]. We used this criterion to define the disease. However, we did not use a post-bronchodilator measurement in our epidemiological study, therefore we excluded 168 women with asthma from further analysis of the association between lung function and air pollution, to avoid confounding. Asthma was considered present, when ever diagnosed by a physician or if asthma medication were used.

Air pollution

We used two ways to assess air pollution exposure, first, we used data from the stations maintained by the State Environment Agency. They cover the area in an 8 km grid and are designed to mainly reflect broad scale spatial variations in air quality. Second, we used distance of residential address to the nearest major road, which reflect small-scale spatial variations in traffic related exposure.

All 7 monitoring stations used for this study were located within a distance of not more than 8 km to the women's home address. Given that there was no monitoring station available for Dülmen, the air pollution data from Borken was used, because of its proximity and comparability. Due to the incompleteness of air pollution data from Borken, where continuous measurements started in 1990, the data proceeding this year were imputed by using measurements (1981-2000) from 15 monitoring stations in the Ruhr area assuming similar trends. Between 1985 and 1987 discontinuous measurements were performed in Borken and Dülmen (four days per month). These discontinuous measurements agreed well with the imputed values. Mean measured TSP between 1984-1987 was 70µg/m^3 and the imputed value for 1985 was 66µg/m^3.

The concentrations of nitrogen dioxide (NO_2) was measured half-hourly by means of chemiluminescence. Total suspended particles (TSP) were gathered with a low volume sampler (air flow: 1m^3/h) and measured using beta-ray absorption. For the assessment of individual medium term air pollution exposure we used annual mean concentrations in the year of the investigation and for long-term air pollution exposure we used five-year means of measurements done before the investigation. To estimate the exposure of particulate matter of less then 10 µm dynamic diameters (PM_{10}), we multiplied TSP measurements with a conversion factor of 0.71. This conversion factor was calculated from 7 monitoring sites in the Ruhr area, where parallel measurements of TSP and PM_{10} were performed between 1998 and 2004.

We further assessed the exposure to motor vehicle exhaust by the distance (< 100m and >=100m) from each residential address to the nearest major road (> 10 000 cars per day) by using geographic information system (GIS) software Arc GIS 9.0 (ESRI Redlands, CA). Average daily traffic counts for the year 1997 and mean traffic load per square kilometer for the year 1987 (without Borken and Dülmen) were obtained from the North Rhine Westphalia State Environment Agency (LUA NRW).

Statistical Method

The association of symptoms and diagnoses with ambient air pollution exposure was analyzed by logistic regression. Odds ratios (OR) with 95% confidence intervals (CI) are presented for an interquartile range increase in PM_{10} and NO_2 exposure and for living nearer

than 100m respectively >=100m from a road with heavy traffic. FEV1, FVC and the ratio FEV1/FVC were approximately normally distributed and multiple linear regressions were used for analysis. The regression coefficients b were transformed to relative mean differences (MD) MD=1+b/mean (lung function). We included a random area effect in the logistic as well as the linear regression analysis to account for possible clustering within areas.

Age, socioeconomic status, smoking, exposure to environmental tobacco smoke (ETS), occupational exposure to temperature (heat/cold) and dust and heating with fossil fuels were included as covariates in all models. FEV1 and FVC were adjusted for body mass index (BMI) and height additionally.

All statistical analysis was done with SAS for windows release 9.1 (SAS Institute, Cary, NC).

Table 1: Characteristics of study participants

Participants (N=4757)	**n/N**	**%**	
Time of residency ≥ 5 years under current address	4255/4749	89.6	
Smoking status			
Never –smoker without ETS	1762/4396	40.1	
Never-smoking with ETS	1472/4396	33.5	
Ex-smoker	384/4396	8.7	
Current smoker			
<15 pack years	269/4396	6.1	
15-30 pack years	282/4396	6.4	
>30 pack years	227/4396	5.7	
Single room heating with fossil fuels	1039/4653	21.8	
Occupational exposure to dust/fumes	552/4757	11.6	
Occupational exposure to extreme Temperatures	469/4757	9.9	
Social status			
Low	1401/4702	29.8	
Medium	2248/4702	47.8	
High	1051/4702	22.4	
	N	**mean**	**SD**
Age [years]	4755	54.5	0.6
Body Mass Index [kg/m^2]	3844	27.7	4.7
Height [cm]	3846	162.1	5.8

RESULTS

Description of the study population

The characteristics of the 4757 women are shown in table 1. According to the study design, the age range was very narrow and the mean age of the women was identical 54.5 years in each year and area. The majority of women reported to be never smokers: 40.1% without exposure to environmental tobacco smoke (ETS) and 33.5 % with ETS exposure at home or at work. Occupational exposure to dust or extreme temperatures at work was reported by 11.6 % respectively 9.9%. According to our definition, 47.8% of the women or their partners had an education of at least 10 years of schooling, a medium socio-economic status (SES).
The prevalence of doctor's diagnosed chronic bronchitis was 9.5% and frequent cough was reported by 22.5% of the women and chronic cough with phlegm production was reported by 4.6% (table 2). The diagnosis of bronchitis was less frequently reported from women who participated in the spirometric measurements compared to women who did not participate. Differences in symptom prevalence between these groups could not be detected. The prevalence of COPD defined by the criterion FEV1/FVC <0.7 was 4.5%.

Table 2: Prevalence of airway diseases, symptoms and lung function in 55 year old women

	all		**With spirometry (N=2593)**	
	n/N	**%**	**N/N**	**%**
Chronic bronchitis by physician diagnosis	442/4649	9.5	211/2537	8.4
Chronic cough with phlegm production	225/4701	4.8	116/2563	4.6
Frequent cough	1065/4731	22.5	561/2581	21.8
COPD $FEV_1/FVC<0.7$			116/2581	4.5
			n	**Mean** **SD**
FEV_1 [L]			2590	2.55 0.46
FVC [L]			2584	3.09 0.51
FEV_1/FVC			2581	0.83 0.07

Air pollution exposure

18.5% of all women lived in a distance of less than 100 m from a road with more than 10 000 cars a day (major road). Medium distance was 494 m (Table 3). Correlation (Pearson's r) of mean traffic load per km^2 between 1987 and 1997 was r=0.7. The distributions of medium-term and long-term air pollution exposure are also presented in Table 2. The range of PM_{10} was smaller than that of NO_2 and, the ranges of the five-year means were smaller than those

of the annual means. The five year means were somewhat higher than the annual means, but highly correlated (Pearson r > 0.9). Living near a major road was associated with mean values of NO_2 but not with the other pollutants. There were considerable correlations between the single air pollutants. Pearson's r for the five year means of PM_{10} and NO_2 was r=0.7.

Table 3: Distribution of air pollution exposure

N=4757	**Min**	**P 25**	**Median**	**Mean**	**P 75**	**Max**
Medium term						
NO_2 [µg/m^3]	20	29	41	39	45	60
PM_{10}[µg/m^3]	35	40	43	44	47	53
Distance to Road [m] with >10,000 cars/ Day	6	424	494	519	556	6374
Long-term						
NO_2[µg/m^3]	22	25	46	39	49	55
PM_{10} [µg/m^3]	39	43	47	48	53	56

Association between small scale ambient air pollution exposure and respiratory morbidity and lung function

Table 4 shows the results of the logistic regression analysis for the association of living near a major road and respiratory diagnoses, symptoms and lung function. Women living within a radius of 100m to a major road reported more frequent cough (adj. OR= 1.24; 95% CI 1.03-1.49). Cough with phlegm production was marginally associated (OR 1. 07, 95% CI 0.83-1.37)). The odds ratio for the association of COPD and traffic related pollution was higher (OR 1.79, 95%CI 1.06-3.02).

Women living within a radius of 100m to a major road had a significantly decreased FVC and FVC Although COPD as defined by FEV1/FVC < 0.7 was associated with distance to a major road FEV1/FVC showed no association.

Since smoking is the strongest risk factor for the development of respiratory symptoms and COPD, we repeated the analysis separately for smokers and non-smokers. The relationship between distance to major road and the development of respiratory symptoms including COPD did not change substantially (data not shown).

Table 4: Distance to major roads and medium term exposure to air pollutants (annual means and five year means) as predictors for respiratory symptoms and pulmonary function

		Annual means		**Five year means**	
	<100m from major road with 10,000 cars/day compared to > 100m	**NO_2 [16µg/m^3]**	**PM_{10} [7µg/m^3]**	**NO_2 [16µg/m^3]**	**PM_{10} [7µg/m^3]**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Chronic bronchitis by physician diagnosis (n_1=4205, n_5=3761)	1.15 (0.89-1.50)	1.25(*) (1.00-1.58)	1.00 (0.85-1.18)	1.37** (1.16-1.62)	1.13 (0.95-1.34)
Chronic cough with phlegm production (n_1=4237, n_5=3792)	1.07 (0.83-1.37)	1.11 (0.85-1.45)	1.03 (0.87-1.23)	1.22 (0.90-1.64)	1.11 (0.93-1.31)
Frequent cough (n_1=4262, n_5=3813)	1.24* (1.03-1.49)	1.13* (1.01-1.27)	1.01 (0.93-1.10)	1.15(*) (0.99-1.33)	1.05 (0.94-1.17)
COPD FEV_1/FVC<0.7 (n_1=2314, n_5=2096)	1.79* (1.06-3.02)	1.39** (1.20-1. 63)	1.37(*) (0.98-1.92)	1.43** (1.23-1.66)	1.33* (1.03-1.72)
	MD (95% CI)	**MD (95% CI)**	**MD (95% CI)**	**MD (95% CI)**	**MD (95% CI)**
FEV_1 (n_1=2315, n_5=2095)	0.987* (0.962-0.997)	0.961** (0.939-0.984)	0.953* (0.916-0.989)	0.951** (0.925-0.977)	0.949** (0.923-0.975)
FVC (n_1=2310, n_5=2092)	0.982* (0.966-0.998)	0.974** (0.954-0.993)	0.966* (0.940-0.992)	0.966** (0.945-0.987)	0.963** (0.945-0.982)
FEV_1/FVC (n_1=2314, n_5=2096)	0.999 (0.990-1.007)	0.989** (0.985-0.993)	0.989(*) (0.978-1.000)	0.988** (0.982-0.993)	0.989* (0.980-0.997)

Effect estimates adjusted for are age, smoking, SES, occupational exposure and form of heating
FEV_1 and FVC were additionally adjusted for BMI a height
women living less than five years at their residence were excluded in the analyses of five year means of air pollutants
n_1 sample size of all women, n_5 sample size of women living at least five years at their residence (*) p<0. 1; * p< 0.05; ** p<0.01

Association between broad scale ambient air pollution exposure and respiratory morbidity and lung function

The associations with medium-term exposure (annual means) were evaluated for all women, the associations with long-term exposure for women living at least 5 years at their place of residence (N=4255). The odds ratios for the association between annual respectively five year means of air pollution and respiratory morbidity were all above one and significantly different from one for chronic bronchitis, frequent cough and NO_2 and COPD and all pollutants investigated (table 4, fig. 4). All odds ratios for long-term exposure were stronger than those for medium term exposure (table 4).

This was not due to the selection of women with living more than 5 years at their residence, because the odds ratios for annual means did not change when including women with a residency > 5 years.

Linear regression revealed significant negative associations of all air pollutants with FEV1, FVC and FEV1/FVC (table 4). Again the effects were stronger for the five-year means than for the annual means (table 4). Figures 1-4 demonstrate the steady decrease of lung function with increasing PM_{10}.

We repeated the analysis separately for smokers and non-smokers to assess whether the effect of long term exposure to air pollutants was modified by smoking. However, no signs of interaction could be detected (data not shown).

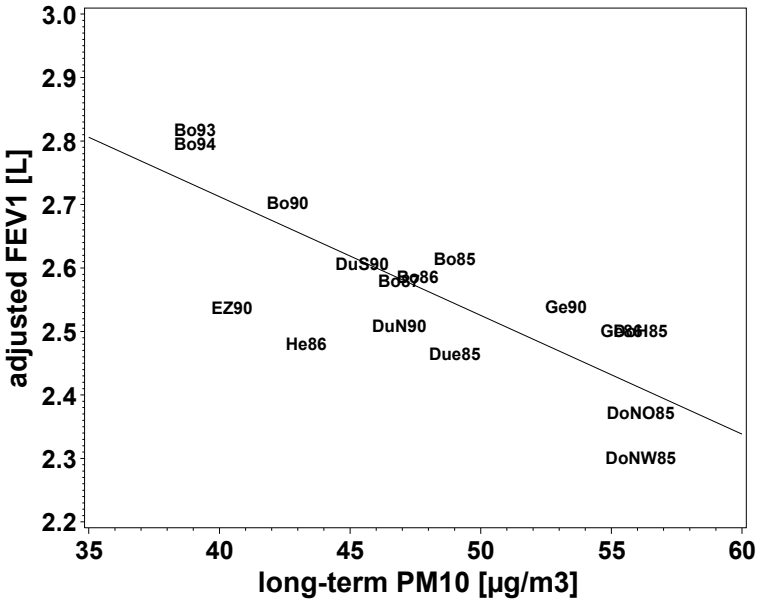

Figure 1:

Association between FEV1 and long-term PM10 exposure (five-year mean), adjusted for age, height, BMI, SES, heating with fossil fuels, occupational exposure (Dust/ temperature) and smoking for women who lived at least five years at their place of residence. Means of each place and year of study: Bo= Borken, DoH= Dortmund Hörde, DoNO= Dortmund North-East, Due= Dülmen, DuS= Duisburg South, DuN= Duisburg North, EZ= Essen Centre, Ge= Gelsenkirchen, He=Herne

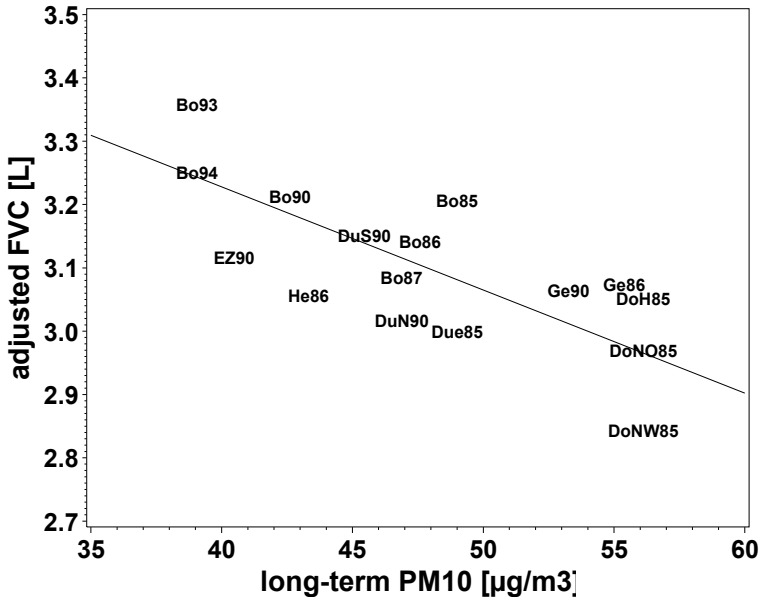

Figure 2:

Association between FVC and long-term PM10 exposure (five-year mean), adjusted for age, height, BMI, SES, heating with fossil fuels, occupational exposure (Dust/ temperature) and smoking for women who lived at least five years at their place of residence. Means of each place and year of study: Bo= Borken, DoH= Dortmund Hörde, DoNO= Dortmund North-East, Due= Dülmen, DuS= Duisburg South, DuN= Duisburg North, EZ= Essen Centre, Ge= Gelsenkirchen, He=Herne

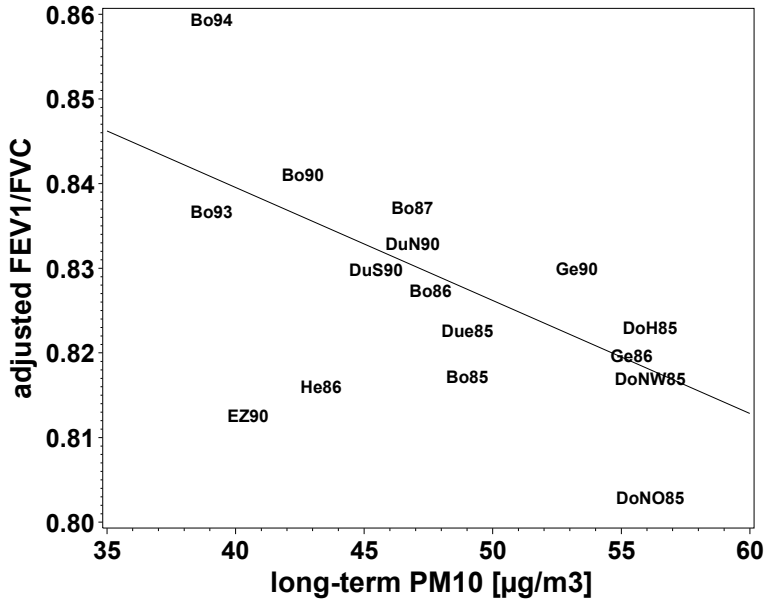

Figure 3:

Association between FEV1/FVC and long-term PM10 exposure (five-year mean), adjusted for age, SES, heating with fossil fuels, occupational exposure (Dust/ temperature) and smoking for women who lived at least five years at their place of residence. Means of each place and year of study: Bo= Borken, DoH= Dortmund Hörde, DoNO= Dortmund North-East, Due= Dülmen, DuS= Duisburg South, DuN= Duisburg North, EZ= Essen Centre, Ge= Gelsenkirchen, He=Herne

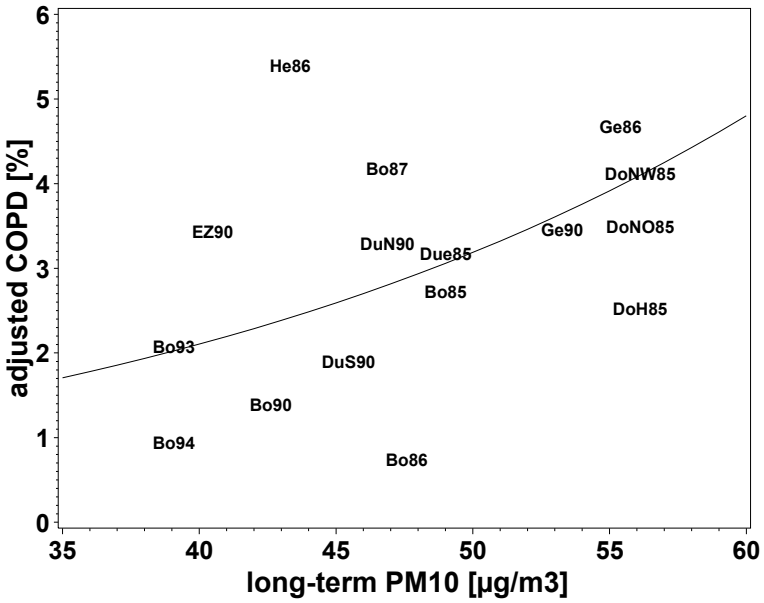

Figure 4:

Association between COPD and long-term PM10 exposure (five-year mean), adjusted for age, SES, heating with fossil fuels, occupational exposure (Dust/ temperature) and smoking for women who lived at least five years at their place of residence. Means of each place and year of study: Bo= Borken, DoH= Dortmund Hörde, DoNO= Dortmund North-East, Due= Dülmen, DuS= Duisburg South, DuN= Duisburg North, EZ= Essen Centre, Ge= Gelsenkirchen, He=Herne

DISCUSSION

In this cross sectional study on 55-year-old women we found, that long-term exposure with air pollution from industrial sources and traffic had an adverse effect on pulmonary function, COPD and respiratory health. The effects on respiratory health symptoms were strongest for NO_2 and traffic exposures whereas PM_{10} effects on these symptoms could only be detected in non-smoking women. COPD as defined by FEV_1/FVC and pulmonary function were strongest affected by PM_{10}. The effects of air pollutants were substantial: a 7 µg/m^3 change in five year means of PM_{10} was associated with a 5.1% decrease in FEV_1, a 3.7% decrease in FVC and a 33% increase in prevalence of COPD. We found stronger effects associated with five-year means than with annual means, which is probably due to their greater stability.

COPD and chronic cough with phlegm production (symptoms of chronic bronchitis) were not very common in this group of 55 year old women (prevalence 4.5% and 4.6%), but for this age group similar prevalence have been found in other studies [24,25].

The pollutant results can be compared with the findings from the Swiss SAPALDIA study, which investigated the association between air pollution and respiratory health in 20-60 years old adults[26,27]. A 10µg/m^3 increase of annual mean PM_{10} was associated with a 3.4% decrease in FVC and a 1.6% decrease in FEV_1 [6]. These results point in the same direction as our results, although we found stronger effects.

Contrary to us, the results presented for the SAPALDIA study were restricted to the group of healthy non-smokers. However, in the Swiss study as well as in our study the PM_{10} effect as defined by lung function was equally pronounced in smokers and in non-smokers. We explored whether the higher mean concentrations of PM_{10} in our study were a reason for this. Yet in our study the effect estimates did not depend on the absolute level of air pollution. An analysis done for the years 1985-1987 when air pollution was higher yielded similar results as an analysis with the 1988-1994 values (data not shown).

The stronger effects in our study can probably be explained by differences in the study population. We investigated 55 year old women (age range 51.9-56.3). It has already been demonstrated that the effect of smoking on lung function and COPD are stronger in women than in men [16], and this may also apply for PM_{10} effects.

A qualitative comparison can be made with a Japanese study. Sekine et al reported a reduction in lung function parameters in females living near trunk roads [16]. In our study, we found that women living less than 100m from a major road had an elevated risk of developing chronic cough and COPD. Living <100m away was significantly associated with a decline in lung functions parameters and the development of COPD compared to women who lived >100 away.

Several limitations of this study must be considered. One limitation is the incompleteness of air pollution measurements. Values for Borken before 1990 were imputed assuming similar trends as in the other areas. This assumption seems plausible because similar trends in Borken and the other areas have been shown for the years after 1990 and the discontinuous measurements of TSP in 1984-1987 agreed well with the imputed values. Further on the location of major roads may have changed between 1985-1994 and 1997. However the correlation of mean traffic load per km^2 in 1987, a measure available for the big cities, with the same measure in 1997 is 0.7, demonstrating proportionality of traffic over time. A further limitation is the cross sectional design of our study, where migration may cause a problem. However, this does not apply to our study, since only 10% of women moved in the last 5 years before the investigation. It is also possible, although unlikely, that some women already died from COPD or other Particle related diseases before the age of 55. This could have led to an underestimation of the true effect.

The advantage of this study is the wide number of cross-sections with a large range of exposure that was included. This makes the results less susceptible to random variation in one area and year. Another advantage is the objective exposure assessment on individual level by using the GIS model.

CONCLUSION

Our study showed that COPD defined by lung function is a sensitive marker for air pollution health effects in the definition of an obstructive disease compared to the definition by symptoms only. The GOLD criteria proofed to be a useful tool in the detection of air pollution effects on respiratory health. To our knowledge this is the first study assessing long-term effects of air pollution on COPD and lung function by combining broad and small-scale spatial exposure. The results of this study suggest that chronic exposure to air pollution from PM_{10}, NO_2 and living near a major road might increase the risk of developing COPD and can have a detrimental effect on lung function.

Competing interests

The authors have no competing interests.

Contributors

T Schikowski performed the epidemiological analysis, drafted and wrote the paper, giving final approval to the version to be published. D Sugiri was co-investigator of the repeated cross-sectional studies, performed Geographical Information System analysis and was responsible for the data management and statistical analysis, giving final approval to the version to be published. U Krämer was main investigator of the repeated cross-sectional studies, commented and advised on exposure assessment statistical analysis and commented on the manuscript, giving final approval to the version to be published.
U Ranft was co-investigator of the repeated cross-sectional studies and commented on the draft, giving final approval to the version to be published. HE Wichmann commented on the draft. J Heinrich commented on the draft. U Gehring provided assistance with the data management, imputed air pollution data for Borken and commented on the draft.

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CHAPTER 3

Does respiratory health contribute to the effects of long-term air pollution exposure on cardiovascular mortality?

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ABSTRACT

Background

There is growing epidemiological evidence that short-term and long-term exposure to high levels of air pollution may increase cardiovascular morbidity and mortality. In addition, epidemiological studies have shown an association between air pollution exposure and respiratory health. To what extent the association between cardiovascular mortality and air pollution is driven by the impact of air pollution on respiratory health is unknown. The aim of this study was to investigate whether respiratory health at baseline contributes to the effects of long-term exposure to high levels of air pollution on cardiovascular mortality in a cohort of elderly women.

Methods

We analyzed data from 4750 women, aged 55 at the baseline investigation in the years 1985-1994. 2593 of these women had their lung function tested by spirometry. Respiratory diseases and symptoms were asked by questionnaire. Ambient air pollution exposure was assessed by the concentrations of NO_2 and total suspended particles at fixed monitoring sites and by the distance of residency to a major road. A mortality follow-up of these women was conducted between 2001 and 2003. For the statistical analysis, Cox' regression was used.

Results

Women with impaired lung function or pre-existing respiratory diseases had a higher risk of dying from cardiovascular causes. The impact of impaired lung function declined over time. The risk ratio (RR) of women with forced expiratory volume in one second (FEV_1) of less than 80% predicted to die from cardiovascular causes was RR=3.79 (95%CI: 1.64-8.74) at 5 years survival time and RR=1.35 (95%CI: 0.66-2.77) at 12 years. The association between air pollution levels and cardiovascular death rate was strong and statistically significant. However, this association did only change marginally when including indicators of respiratory health into the regression analysis. Furthermore, no interaction between air pollution and respiratory health on cardiovascular mortality indicating a higher risk of those with impaired respiratory health could be detected.

Conclusion

Respiratory health is a predictor for cardiovascular mortality. In women followed about 15 years after the baseline investigation at age 55 years long-term air pollution exposure and

impaired respiratory health were independently associated with increased cardiovascular mortality.

BACKGROUND

There is growing evidence that short and long-term exposure to high levels of air pollution may increase cardiovascular morbidity and mortality [1-5]. In addition, epidemiological studies have shown an association between increased levels of air pollution and exacerbations of airways diseases [6] or impairments of lung function [7]. There is also support for a link between respiratory health and cardiovascular mortality [8-10].To what extent the association between cardiovascular mortality and air pollution is driven by the impact of air pollution on respiratory health is unknown. It is hypothesised that pulmonary inflammation induced through harmful particles may cause the release of mediators that increase blood coagulation [11,12]. Other studies have shown that increased blood coagulability or viscosity is a risk factor for cardiovascular mortality [13]. However, other mechanisms not related to respiratory health including systemic inflammation, accelerated atherosclerosis and altered cardiac autonomic function may also be responsible for the effect of particle exposure on cardiovascular mortality [4].

Studies have shown that people with pre-existing respiratory disease have a higher risk of dying from cardiovascular causes due to short-time variations in air pollution exposure [14-17]. Whether people with pre-existing respiratory disease have a higher risk of dying from cardiovascular disease after long-term air pollution exposure is not clear. We have shown that high levels of air pollution were associated with a reduction in lung function, impaired respiratory health and chronic obstructive lung disease [18] in women aged 55 years from the Ruhr Area in 1985-1994. We also showed that these levels of air pollution increased the risk of mortality in the same group of women during a follow-up until 2002/2003 [19].

In this presented study, we investigated whether respiratory health at baseline contributes to the effects of long-term exposure to high levels of air pollution on cardiovascular mortality in this cohort of elderly women. Indicators of respiratory health at baseline investigation were chronic bronchitis and respiratory symptoms as well as lung function measures. In compliance with the study objective, the following questions were to be answered:

(1) Is impaired respiratory health a risk factor for cardiovascular mortality?
(2) Alongside long-term air pollution exposure, is impaired respiratory health an independent risk factor for cardiovascular mortality?
(3) Is there a difference in pollution induced cardiovascular mortality in people with and without impaired respiratory health?

METHODS

Study population

The SALIA cohort (**S**tudy on the influence of **A**ir pollution on **L**ung function, **I**nflammation and **A**ging) was initiated as part of the Environmental Health Surveys introduced by the North Rhine Westphalia government in the mid 1980s, focusing on the effect of air pollution on respiratory health in women and children. Consecutive cross-sectional studies were performed between 1985 and 1994 in the Ruhr area and two rural towns as reference areas. The study population comprised 4874 women aged 55 at the time of entering the study who were living in pre-defined residential areas and willing to participate. In the years specified, the study areas included Dortmund (1985, 1990), Duisburg (1990), Essen (1990), Gelsenkirchen (1986, 1990) and Herne (1986) which represent a range of high-polluted areas. The two rural towns, Borken (1985, 1986, 1987, 1990, 1993 and 1994) and Dülmen (1986) were chosen as reference areas. About every second responder was invited to have her pulmonary function tested, exceptions were Dortmund in 1990 where no lung function measurements were performed and Borken in 1993/94 where all women were invited to participate (N=2593).

Follow-up study

The follow-up study was conducted by the Institute of Epidemiology (GSF Munich) between January 2002 and May 2003. All women were followed for the cause of specific mortality. Causes of death were obtained from official death certificates and were coded according to the International Classification of Diseases, Ninth Revision (ICD-9). Mortality for all causes of death and cardiovascular (ICD9-400-440) causes were recorded. The analysis was restricted to 4750 from the 4874 women whose complete information was available from the baseline investigation and who could be followed-up in 2002-2003. Women who moved during the follow-up period and who were lost for the follow-up after moving were judged censored at the time of movement. Otherwise, survival time was censored at the time of follow-up or the time of death from causes other than cardiovascular. The cause of death is known for 399 women. The analysis presented focuses on cardiovascular mortality.

Assessment of risk factors for respiratory health and cardiovascular mortality

Baseline co-morbidities and potential risk factors such as smoking and the level of education were assessed by a self-administered questionnaire. All returned questionnaires were checked by the investigating physician. We grouped the women according to their reported smoking habits: never smoker without environmental tobacco smoke (ETS), passive-smoker

(ETS at home and/or work place), past smoker and current smoker (<15 pack years; 15-30 pack years and >= 30 pack years). Current smokers with missing information about the numbers of cigarettes smoked were assigned to smokers with >=30 pack years. These variables were used to control for confounding. Their socio-economic status was determined by categorizing the women into three levels of education using the highest school level completed by either the women or her husband as low (< 10 years), medium (=10 years) or high (> 10 years).

Assessment of respiratory health by questionnaire

Identical standardized self-administered questions were used during the entire screening period from 1985-1994. The questionnaire included questions about impaired respiratory health. The following questions were used to describe frequent cough with or without phlegm production:

Do you usually cough in the morning, when you get up or during the day?

If yes: Do you produce phlegm when you have this cough?

These questions are part of the classical definition of chronic bronchitis [20]. We further asked: Do you have a physician's diagnosis of chronic bronchitis?

Assessment of respiratory health by pulmonary function

Spirometry was conducted using a Vica Test 4 spirometer (Mijhardt, Rotterdam, The Netherlands). All measuring instruments were calibrated prior to each session. At least two acceptable spirograms were obtained from a minimum of four forced expirations. A trained technician identified the best single spirogram. All staff was specifically trained and the same measuring device was used throughout the study. In our analysis, we used the forced expiratory volume in one-second (FEV_1) and the forced vital capacity (FVC). Linear regression models were used to predict the lung function parameter FEV_1 and FVC based on age, height, race and sex. We used the equations which are recommended by the American Thoracic Society [21]. The prediction equations for creating reference values for these women were:

$$FEV_1^{predicted} = 0.433-0.0036*age-0.00019*age^2+0.000115*height^2$$

$$FVC^{predicted} = -0.356+0.0187*age*0.00038*age^2*0.000148*height^2$$

We defined impaired lung function by using FEV_1 < 80% and FVC < 80% of the predicted value of each parameter. These cut-offs were also used in the re-analysis of the Harvard Six City Study [5]. To verify that these reference equations were suitable for our study collective, we applied them to the women living in the rural areas (reference areas). It turned out that

the reference equations fitted very well the lung function values of these women, i.e. 5% of these women had lung function values below the 80% cut-offs.

Assessment of air pollution exposure

We obtained the air pollution measurements data from 8 monitoring stations maintained by the State Environment Agency of North-Rhine Westphalia. In each city concentrations of ambient air pollutants were measured at fixed monitoring sites representing urban background levels. The monitoring stations are located in an 8 km grid throughout the women's residential areas. However, the air pollution data from Borken and Dülmen are incomplete, because continuous measurements in this region started in 1990. For the years proceeding 1990, the data were imputed by using measurements (1981-2000) from 15 monitoring stations in the Ruhr area assuming similar trends. Estimated 'average' differences were added to the levels measured in 1990 to 1991 for the imputation of air pollution concentrations in the years before 1990. The estimated average differences were 1.02 $\mu g/m^3$ per year for NO_2 and 1.36 $\mu g/m^3$per year for $PM_{10.}$ More details can be found elsewhere [19]. To estimate the long-term air pollution exposure we used five-year means of measurements done before the investigation. The concentrations of nitrogen dioxide (NO_2) were measured half-hourly by means of chemo-luminescence. Total suspended particles (TSP) were gathered with a low volume sampler (air flow: $1m^3/h$) and measured using beta-ray absorption. For reasons of comparability with studies based on PM_{10} measurements (particulate matter with aerodynamic diameters less than 10µm), we estimated the corresponding PM_{10} values by multiplying the TSP measurements with a conversion factor of 0.71. Details for justification of this conversion factor can be found elsewhere [19]. We further used geographic information system (GIS) software Arc GIS 9.0 (ESRI Redlands, Cato) to calculate the distance of the residential address to the nearest major road with more than 10,000 cars /day. A distance of 50 m to the nearest major road was used as cut-off to reflect small-scale spatial variations in traffic related exposure. Traffic counts were provided by the North Rhine Westphalia State Environment Agency (LUA NRW).

Statistical methods

Cox' proportional hazard regression model was used to analyze the association between cardiovascular mortality, air pollution exposure and respiratory health. Following the study questions, three analysis steps were done:

First, we investigated whether cardiovascular death was associated with impaired respiratory health. The assumption of proportional hazard was tested by introducing a time-dependent

covariate into the Cox' model [22]. This new variable was defined as the product of the logarithm of survival time with the binary variable characterising impaired respiratory health. The proportionality assumption was rejected when the regression coefficient of this covariate was significantly ($p < 0.1$) different from the null value. We presented relative risks of cardiovascular death due to respiratory health impairment at two survival times (5 years (60 month) and 12 years (144 month)) which correspond roughly to the 25th and 75th percentile of the survival time distribution of those who died in the study group.

Second, the risk ratios of cardiovascular mortality for each air pollution indicator were estimated adjusted for potential confounders (model (a)). Educational level and smoking behaviour had already been identified as relevant confounders in our previous paper [19]. Then, respiratory health indicators were additionally considered in the Cox' regression analysis (model (b)). If the assumption of hazard proportionality for the respiratory health strata was not met (result of step one) then a stratified analysis was done and, if no interaction between respiratory health and air pollution exposure had to be taken into account (if otherwise see step three), common risk ratio estimates of the strata were given. No or negligible differences between the estimated risk ratios for air pollution exposure between model (a) and model (b) indicate that respiratory health is an independent risk factor for cardiovascular mortality alongside air pollution exposure.

Third, it was determined whether the relative risks for air pollution associated cardiovascular mortality were different in strata defined by respiratory health. Because of the small power of interaction tests a p-value of 0.3 or less was chosen as indication for interaction. If the p-value was less, then no combined estimates but estimates for both strata are given separately.

Risk ratio estimates of continuous exposure measures refer to unit steps as chosen in [18,19], i.e. 16µg/m^3 and 7µg/m^3 for NO_2 and PM_{10}, respectively.

Survival times in subgroups defined by respiratory health indicators were graphically depicted by Kaplan-Meier curves with 95 percent confidence limits.

All analyses were conducted with the statistical software SAS. For Cox' regression analysis, we used the procedure PHREG of SAS version 9.1 for windows (SAS Institute Cary, NC).

RESULTS

Description of the study participants

In total, 4750 women were in the study, and a percentage of 54.5% underwent lung function testing. Distribution characteristics of the whole study group and, separately, of the sub-group with lung function measures are summarised with respect to respiratory health,

mortality and other socio-demographic indicators in table 1. Due to the study design the women who had their lung function tested lived to a larger extent in rural areas and related to that they were to some extent healthier and smoked less than those in the whole study group. Again, because of the design, air pollution exposure in the sub-group with spirometry was slightly lower than in the whole study group (table 2).

Table 1: Characteristics of impaired respiratory health, mortality and socio-demographics of a cohort of women aged 55 years at baseline investigation

	Whole study group N=4750		**Study group with spirometry N=2580**	
	n/N	**%**	**n/N**	**%**
FEV_1 <80% of predicted value	--	--	409/2577	15.9
FVC <80% of predicted value	--	--	526/2571	20.5
Chronic Bronchitis by physician diagnose	442/4642	9.5	211/2525	8.4
Frequent cough with phlegm production	518/4700	11.0	266/2554	10.4
Frequent cough	1063/4724	22.5	560/2568	21.8
All cause death	399/4750	8.4	183/2580	7.1
Cardiovascular death	127/4750	2.7	53/2580	2.1
Never smoker without ETS	1779/4750	37.5	1191/2577	46.2
Never smoker with ETS	1494/4750	31.5	829/2577	32.2
Ex-smoker	377/4750	7.9	201/2577	7.8
Current smoker with < 15 pack years	270/4750	5.7	136/2577	5.3
Current smoker with 15-30 pack years	284/4755	6.0	137/2577	5.3
Current smoker > 30 pack years	224/4755	4.7	83/2577	3.2
Smoking behaviour unknown	322/4750	6.8	143/2577	5.5
Living in rural area	1681/4750	35.4	1315/2580	51.0
Less then 10 y school	1400/4695	29.8	685/2574	26.6
At least 10 y school	2243/4695	47.8	1253/2574	48.7
More then 10 y school	1052/4695	22.4	636/2574	24.7
	N	**Mean / SD**	**N**	**Mean / SD**
Age [years]	4748	54.5 / 0.6	2576	54.5 / 0.7

Abbreviations:
FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; SD: Standard deviation

Table 2: Distribution of women depending on their ambient air pollution exposure (5 year mean values prior to baseline investigation) and traffic exposure indicated as percentiles

	Mean / Percentage	P0	P25	P50	P75	P100
Whole study group (N=4750)						
NO_2 [µg/m³]	39	22	25	46	49	55
PM_{10} [µg/m³]	48	39	43	47	53	56
<50m distance to major road (>10,000 cars/day)	8.5 %	--	--	--	--	--
Study group with spirometry (N=2580)						
NO_2 [µg/m³]	36	22	24	27	50	53
PM_{10} [µg/m³]	47	39	43	47	52	54
<50m distance to major road (>10,000 cars/day)	7.6 %	--	--	--	--	--

Abbreviations:
Px: x^{th} percentile; NO_2: Nitrogen dioxide; PM_{10}: Particulate matter with aerodynamic diameter of ≤ 10 µm, calculated as PM_{10} = 0.71*TSP; TSP: Total suspended particles

Respiratory health and cardiovascular mortality

In table 3, crude risk ratios (RR_c) demonstrate that cardiovascular death was associated with impaired respiratory health and unfavourable lung function values. The association between cardiovascular mortality and impaired respiratory health defined by diagnosis and symptoms demonstrated a different time pattern than that defined by lung function measurements. The association of the diagnosis of chronic bronchitis with cardiovascular mortality did not change over time: Women with the diagnosis of chronic bronchitis had an increased risk ratio of dying from cardiovascular causes at 60 months survival time (RR_c=1.53; 95% CI: 0.83-2.79) and at 144 months survival time (RR_c=1.65; 95% CI: 0.93-2.95). Similar results were found for frequent cough with phlegm production. The impact of impaired lung function at age 55 years on cardiovascular mortality however declined over time. Figure 1 and 2 show the survival curves of women with and without impaired FEV_1 and FVC. The proportionality assumption is not valid. Interaction with survival time was significant for both lung function indicators (table 3). The risk of women with impaired lung function at age 55 years to die from cardiovascular causes at the age of 60 years, was 3.8 to 5.0 times higher than the risk of women without pathological findings of the lung function. The risk ratio at the age of 67 years declined near the null value (table 3).

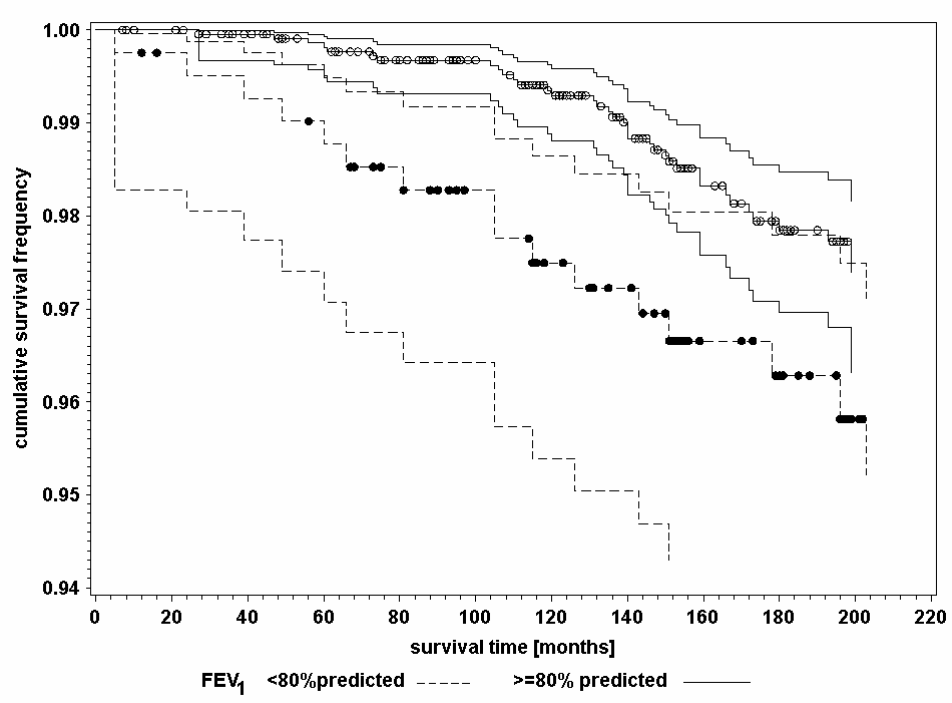

Figure 1:

Kaplan–Meier survival curves with 95 percent confidence limits of cardiovascular mortality for women aged 55 years at baseline investigation with FEV_1 < 80% predicted and FEV_1 ≥ 80% predicted; dots indicating censored events. *Abbreviations:* FEV_1: Forced expiratory volume in 1 second

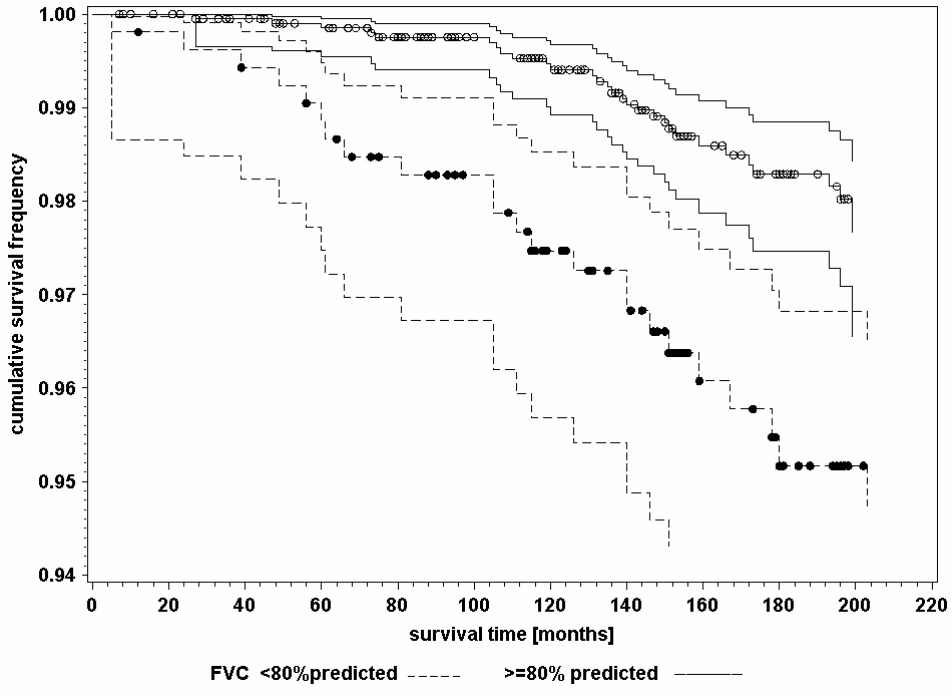

Figure 2:

Kaplan–Meier survival curves with 95 percent confidence limits of cardiovascular mortality for women aged 55 years at baseline investigation with FVC < 80% predicted and FVC ≥ 80% predicted; dots indicating censored events. *Abbreviations:* FVC: Forced vital capacity

Table 3: Crude risk ratios (RR_c) and 95% confidence interval (95% CI) of cardiovascular mortality for impaired respiratory health and lung function indicators at 5 and at 12 years of survival time and p-value for interaction with baseline, results of Cox' regression analysis.

Respiratory symptoms and lung function	RR_c, 95% CI at 5 years	RR_c, 95% CI at 12 years	p-value for interaction with baseline
Chronic Bronchitis by physician diagnose	1.53 0.83-2.79	1.65 0.93-2.95	0.7986
Frequent cough with phlegm production	1.34 0.71-2.51	1.65 0.94-2.89	0.5377
Frequent cough	1.17 0.73-1.89	1.21 0.76-1.93	0.9006
FEV_1 < 80% of predicted value	3.79 1.64-8.74	1.35 0.66-2.77	0.0303
FVC <80% of predicted value	5.03 2.10-12.02	1.89 1.01-3.57	0.0445

Abbreviations:
FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity;

Respiratory health indicators as additional covariates for the association between air pollution exposure and cardiovascular mortality

In a previous paper we could provide evidence that an increase of exposure to PM_{10} was strongly associated with a reduction of lung function (FEV_1: 5.1% (95% CI 2.5%-7.7%), FVC: 3.7% (95% CI 1.8%-5.5%)) as well as with increased frequency of respiratory symptoms [18]. In a further paper we have shown [19], that the association between air pollution levels and cardiopulmonary death rate was strong and statistically significant. This was also true for cardiovascular death, which we focused on in this paper (table 4). Table 4 shows the results of the Cox' regression analysis for the impact of air pollution exposure on cardiovascular mortality adjusted for confounders (model (a)) and additionally for respiratory disease or symptoms (model (b)). The risk ratios for the association between air pollution and cardiovascular mortality differed only marginally (<10%) between model (a) and model (b). We also tested all interactions between respiratory diagnosis and symptoms and air pollution on cardiovascular mortality. All p-values were above 0.3. Therefore no separate estimates in strata defined by respiratory health are given.

For both lung function indicators the assumption of hazard proportionality over time was not valid. We therefore applied stratified Cox' regression analysis for model (b). The results are

presented in table 5. In this sub-group of women with lung function measurements, the associations between traffic related pollution (NO_2 and small distance to mayor road) and cardiovascular death were particularly strong. This again might be due to the study design which led to more pronounced contrasts in traffic related pollution. The associations between traffic related air pollution exposure (distance to major road and ambient NO_2) and cardiovascular mortality were modified by impaired lung function. However, this modification was contrary to the meaningful expectation that impaired lung function would increase the risk ratio of air pollution exposure.

Table 4: The influence of respiratory health indicators (diagnoses and symptoms), assessed at baseline investigation, on the association between air pollution exposure (traffic, NO_2, PM_{10}) and cardiovascular mortality in a cohort of women aged 55 years at baseline investigation; results of a Cox' regression analysis.

	<50m distance to major road			**NO_2 [16µg/m^3] (five-year mean) [1]**			**PM_{10} [7µg/m^3] (five-year mean) [1]**		
	RR	**95%-CI**	**p-value**	**RR**	**95%-CI**	**p-value**	**RR**	**95%-CI**	**p-value**
n/**N**		120/4457			97/4198			97/4198	
Model (a), adjusted for potential confounders[3]	1.67	0.98-2.83	0.0573	1.72	1.24-2.39	0.0011	1.64	1.15-2.33	0.0056
Model (b), additionally adjusted for									
Chronic Bronchitis by physician diagnose	1.63	0.96-2.76	0.0693	1.69	1.22-2.35	0.0017	1.62	1.14-2.30	0.0073
Frequent cough with phlegm production	1.71	1.01-2.88	0.0478	1.70	1.22-2.36	0.0015	1.62	1.14-2.31	0.0071
Frequent cough	1.71	1.01-2.88	0.0469	1.71	1.23-2.37	0.0013	1.63	1.15-2.32	0.0067

[1] Analyses on long term exposure to air pollution were made on subjects who were living longer than five years under their current address.
[2] Current smoking at the time of entering the study, no further adjustment for exposure to tobacco smoking
[3] Educational level and smoking *Abbreviations:*
RR: Risk ratio; CI: Confidence interval; n/N: number of dead and sample size; Model (a) / (b): see text

Table 5: The influence of lung function indicators, measured at baseline investigation, on the association between air pollution exposure (traffic, NO_2, PM_{10}) and cardiovascular mortality in a cohort of women aged 55 years at baseline investigation; results of a Cox' regression analysis.

	<50m distance to major road			**NO_2 [16µg/m²] (five-year mean) [1]**			**PM_{10} [7µg/m²] (five-year mean) [1]**		
	RR	**95%-CI**	**p-value**	**RR**	**95%-CI**	**p-value**	**RR**	**95%-CI**	**p-value**
n/N		52/2478			42/2328			42/2328	
Model (a), adjusted for potential confounders[2]	2.33	1.09-4.95	0.0288	1.91	1.22-2.98	0.0048	1.26	0.75-2.14	0.3882
Model (b), additionally estimated in strata defined by or adjusted[3] for:									
FEV_1 < 80%	2.27[4]	1.06-4.85	0.0339	1.12	0.52-2.41	0.7683	1.14[4]	0.67-1.95	0.6352
FEV_1 ≥ 80%				2.23	1.27-3.89	0.0049			
FVC < 80%	1.21	0.28-5.25	0.7951	1.13	0.57-2.22	0.7329	1.13[4]	0.66-1.93	0.6621
FVC ≥ 80%	3.20	1.30-7.85	0.0112	2.38	1.30-4.34	0.0047			

[1] Analyses on long term exposure to air pollution were made on subjects who were living longer than five years under their current address.
[2] Educational level and smoking
[3] if p-value of interaction between air pollution exposure and lung function indicator was greater 0.3
[4] Common estimation for both strata because of no interaction between lung function indicator and air pollution exposure
Abbreviations:
RR: Risk ratio; CI: Confidence interval; n/N: number of dead and sample size; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity
Model (a) / (b): see text

DISCUSSION

Our study demonstrates that impaired respiratory health at the age of 55 is a risk factor for cardiovascular mortality. Women with impaired lung function had a higher cardiovascular mortality risk especially in the first years after the investigation. The impact of air pollution however was even less strong in these women than in those with normal lung function. We could not find an indication that women with impaired respiratory health would have an increased risk of suffering cardiovascular death associated with increased long-term exposure to air pollution. Therefore, long-term air pollution exposure and impaired respiratory health are independently associated with cardiovascular mortality.

Our findings in regards to the positive association between respiratory impairment and cardiovascular mortality are consistent with other published studies [23] [8-10]. The studies from Schunemann et al. and Sin et al. also showed that decreased pulmonary function is a

risk factor for cardiovascular mortality [8,10]. Yet, these studies did not investigate the relation between impaired respiratory health and air pollution-associated cardiovascular mortality. In contrast to these studies we found that the risk associated with impaired lung function declined over time.

There are several hypotheses about the general pathways of cardiovascular effects due to increased levels of air pollution [24,25]. One hypothesised that a biological pathway for cardiovascular mortality associated with long-term exposure to air pollution is pollution-induced lung damage. It suggests that in individuals who are susceptible, exposure to air pollution especially to ultrafine particles can induce alveolar inflammation, which subsequently result in respiratory illness and then in cardiovascular death [11,12]. The second hypothesis indicates that lung inflammation induced by air pollution not only leads to lung diseases, but independently can also cause vascular and heart diseases [25,26]. Alveolar macrophages and lung epithelial cells process inhaled particles or other air pollutants, this pro-inflammatory mediators not only promote a local inflammatory response in the lungs, but can also translocate into the circulation and induce a systemic inflammatory response[27]. Consequently, the possible biological pathway for this association is systemic inflammation and the progression of atherosclerosis [28]. Further, air pollution can lead to altered cardiac function due to a change in heart rate and blood pressure and finally lead to death [29-32].

The results of our study are more consistent with the second hypothesis. In fact, in our cohort study we could show that air pollution and impaired respiratory health are independently associated with cardiovascular death. Indeed women with already impaired lung function had a higher cardiovascular mortality risk especially in the first years after the investigation compared to those with normal lung function. But, increased levels of air pollution did not influence the mortality of these women. On the contrary, the relative risk of cardiovascular mortality associated with air pollution appeared to be higher in women without impaired lung function. In some women possibly, impaired lung function might be a sign for a still unknown but manifest cardiovascular disease which subsequently leads to early death not related to air pollution. However because of the relative small subgroups we chose a p-value of 0.3 to indicate an interaction. Therefore, the evidence for the variation in risk between the sub-groups is still not strong.

This observed result is in accordance with findings from the re-analysis of the Harvard Six City Study [4,5]. In their study, Krewski et al. reported about the risk of death associated with exposure to fine particles in different sub-groups among them those defined by lung function. In their study subjects with compromised lung function had a slightly greater risk of death.

However, none of these interactions achieved statistical significance. The results of this re-analysis did not provide evidence of variation in risks among population sub-groups [5].

In a previous time series study, DeLeon et al. [14] observed that individuals with contributing respiratory conditions whose primary cause of death was circulatory were more affected by elevated levels of air pollution This role of respiratory disease in air pollution related cardiovascular mortality could not be confirmed in our study. There are two major differences to our study. First, the DeLeon-study focused primarily on daily mortality counts and the listing of the contributing respiratory causes on the death certificates. However, time-series studies can only investigate associations with the most recent exposure compared to cohort studies, which are able to show acute and chronic effects of air pollution on diseases and mortality. Second, DeLeon et al. demonstrated that the effect was only visible in older individuals (aged 75 and older) with underlying respiratory diseases. Older individuals were more susceptible to adverse effects of air pollution. The women followed up in our study were at most 73 years old. Therefore, the lack of effect in our study might be due to the younger age range.

Our study has certain limitations. The respiratory symptoms and the chronic bronchitis were self-reported, which might lead to some reporting bias. Furthermore, the women received only one lung function measurement, and we relied on cause-of-death data from death certificates which has the potential of bias for specific cause of death. As in most studies dealing with influences of covariates on survival of population groups, we chose Cox' Regression for analysis. This is basically a multiplicative approach. Therefore, our result of an independent association of air pollution and respiratory health on cardio vascular mortality can only be interpreted in this multiplicative context. The number of women with reduced lung function, respiratory diseases and cardiovascular mortality was low with respect to the statistical power of the study and was further reduced by stratification. Another limitation is the incompleteness of air pollution measurements. Values for the reference areas Borken and Dülmen before 1990 were imputed assuming similar trends as in the high-polluted areas. The estimation of ambient air PM_{10} concentrations by using TSP measurements may add another limitation to the study and may result into a bias of our risk ratio estimates. Indeed, assuming a smaller conversion factor for the rural area, for instance 0.65, which means greater fraction of coarse particles in TSP compared to the urban areas, the inconsistency of the results between table 4 and table 5 diminished. In tables 4 and 5, the risk ratios for PM_{10} using model (a) increased and showed similar results to the risk ratio for the influence of traffic and NO_2 (data not shown). However, this modification of the TSP/PM_{10} conversion factor did not influence our main results, namely, the association between lung function and respiratory health indicators and cardiovascular mortality.

The strength of our analysis is the long follow-up of our cohort with multiple exposure assessments of air pollution levels and different respiratory health assessments (respiratory symptoms and lung function measurements).

In conclusion, the results from our analysis show that impaired respiratory health as measured by diagnoses, symptoms and lung function is related to an increased subsequent cardiovascular mortality. Women with impaired lung function had a higher cardiovascular mortality risk, especially in the first years after the investigation. We observed some indications that the impact of air pollution however was weaker in these women than in those with normal lung function. We therefore concluded that long-term exposure to high levels of air pollution affects respiratory health and cardiovascular death independently in a group of middle aged women. However, due to the short follow-up period of these women, we might have underestimated the long-term air pollution effects on less pronounced respiratory damage. A further follow-up study of these women is needed to provide more information about cardiovascular mortality in this group when they become older.

Competing interests

The authors have no competing interests.

Contributors

TS performed the statistical and epidemiological analysis, drafted and wrote the paper. DS was co-investigator of the repeated cross-sectional studies, performed the Geographical Information System analysis, performed the statistical analysis and was responsible for the data management. UK was main investigator of the repeated cross-sectional studies, commented and advised on the statistical analysis and commented on the manuscript. UR was co-investigator of the repeated cross-sectional studies, commented and advised on the statistical analysis and commented on the manuscript. HEW commented on the manuscript. UG was co-investigator of the mortality follow-up and commented on the manuscript. JH was main investigator of the mortality follow-up and commented on the manuscript. All authors read and approved the final manuscript.

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CHAPTER 4

Contribution of smoking and air pollution exposure in urban areas to social differences

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ABSTRACT

Background

Socio-economic status, smoking, and exposure to increased levels of environmental air pollution are associated with adverse effects on respiratory health. We assessed the contribution of occupational exposures, smoking and outdoor air pollution as competing factors for the association between socio-economic status and respiratory health indicators in a cohort of women from the Ruhr area aged 55 at the time of investigation between 1985 and 1990.

Methods

Data of 1251 women with spirometry and complete questionnaire information about respiratory diseases, smoking and potential confounders were used in the analyses. Exposure to large-scale air pollution was assessed with data from monitoring stations. Exposure to small-scale air pollution was assessed as traffic-related exposure by distance to the nearest major road. Socio-economic status was defined by educational level. Multiple regression models were used to estimate the contribution of occupational exposures, smoking and outdoor air pollution to social differences in respiratory health.

Results

Women with less than 10 years of school education in comparison to more than 10 years of school education were more often occupationally exposed (16.4% vs. 10.1%), smoked more often (20.3% vs. 13.9%), and lived more often close to major roads (26.0% vs. 22.9%). Long-term exposure to increased levels of PM_{10} was significantly associated with lower school education. Women with low school education were more likely to suffer from respiratory symptoms and had reduced lung function. In the multivariate analysis the associations between education and respiratory health attenuated after adjusting for occupational exposure, smoking and outdoor air pollution. The crude odds ratio for the association between the lung function indicator FEV_1 less than 80% of predicted value and educational level (<10 years vs. >10 years of school education) was 1.83 (95% CI: 1.22-2.74). This changed to 1.56 (95% CI: 1.03-2.37) after adjusting for occupational exposure, smoking and outdoor air pollution.

Conclusions

We found an association between socio-economic status and respiratory health. This can partly be explained by living conditions indicated by occupational exposure, smoking behaviour and ambient air pollution. A relevant part of the social differences in respiratory health, however, remained unexplained.

BACKGROUND

Socio-economic status (SES) and exposure to increased levels of environmental air pollution are key issues in the discussion about social differences and health. Both have been linked to adverse health effects in recent years [1-3]. Socio-economic status is a determinant of health and is well known to play an important role in the development of several diseases, respiratory diseases among them [4-6]. There have been a number of studies regarding SES that have focused on respiratory symptoms and lung function decline [4,7,8]. At the same time, long-term exposure to air pollution has also been connected with a broad range of health effects, including respiratory impairments and lung diseases [9-12]. Because SES is considered as one of many important determinants of health, it has been included as a potential confounder or effect modifier in most epidemiological studies about adverse health effects of increased levels of air pollution [3,13,14]. Some recent studies have shown support for effect modification, with SES and air pollution-associated respiratory death [2,15,16].

In addition to environmental air pollution, possible SES-related risk factors for respiratory impairment are smoking, occupational exposure, malnutrition, low birth weight or multiple lung infections. These risk factors can be strongly influenced by SES: the level of education influences the type of occupation and income, which in turn influences the home living conditions[6]. The consideration of socio-economic factors is currently gaining greater interest in studies on environmental health, as social differences in environmental exposure may help to partly explain the observed differences in health [17]. SES may also modify the effect of environmental exposures by changing the susceptibility characteristics [18,19].

The aim of our analysis was to investigate the association between SES and respiratory impairment and whether or not this association could be ascribed to smoking or air pollution exposure that are associated with SES levels themselves. The present analysis was performed in order to determine the contribution of smoking and air pollution as explanatory factors for the relationship between SES and the development of respiratory symptoms. SES was taken as a function of the educational level, as education is the main determinant for occupational development and income in Germany. According to our knowledge this is the first study that analyses data of a German cohort of women with a focus on environmental differences and respiratory health.

METHODS

Study population

We used data of a large cohort with detailed information regarding respiratory health, SES, and other risk factors. Details of that cohort study have been described previously [9,20]. Briefly, the baseline investigation of the SALIA (Study on the influence of Air pollution on Lung function, Inflammation and Aging) study group has been carried out between 1985 and 1994. These cross-sectional studies were part of the Environmental Health Surveys of the government of North-Rhine Westphalia, Germany, to obtain information regarding the effect of air pollution on respiratory health and allergies in women from the highly industrialized Ruhr district and two rural reference towns. These areas were chosen to represent a variety of environmental and socio-economic conditions. All women from predefined areas were asked to participate in the study. The study population comprised 4874 women aged 54-55 years at the time of baseline investigation and of German nationality. All participants gave informed consent for the interview, the health examination and the blood analysis. The response rate was stable throughout the consecutive cross-sections and was between 66% and 74%. Due to capacity reasons, only a subgroup, was invited to have their lung function measured (n = 2593). To avoid heterogeneity caused by specific social differences between rural and urban areas, only women from areas in the Ruhr district were included in the analysis (n = 3072) . Additionally, we used only data from women with successful spirometry and with complete questionnaire data about education and covariates in the current analysis (n = 1251). The reason for this exclusion criterion was to be able to compare effects on lung function with effects on respiratory symptoms in the same study group.
The SALIA cohort study complies with the Helsinki Declaration and has received approval of the Ethics Committee of the Ruhr University in Bochum /Germany.

Lung function measurements and COPD

Lung function was assessed by spirometry using VICATEST (VICATEST 4, Mijnhardt, Odijk, The Netherlands) by trained technicians. Identical protocols were used for all lung function measurements. The measuring instruments were calibrated prior to each session. At least two acceptable spirometric measurements were obtained from a minimum of four forced expirations. This procedure is in accordance with the ATS criteria [21]. In our analysis, we used the forced expiratory volume in one-second (FEV_1) and the forced vital capacity (FVC). Linear regression models were used to predict the lung function parameter FEV_1 and FVC based on age, height, race and sex. We used the equations which are recommended by the American Thoracic Society [22].

The prediction equations for creating reference values for these women were:

$$FEV_1^{predicted} = 0.433-0.0036*age-0.00019*age^2+0.000115*height^2$$

$$FVC^{predicted} = -0.356+0.0187*age*0.00038*age^2*0.000148*height^2$$

We considered lung function to be impaired if FEV_1 < 80% or FVC < 80% of the predicted value of the respective parameter. These cut-offs were also applied in the re-analysis of the Harvard Six City Study [13]. Furthermore, we applied the GOLD criterion [23] to identify chronic obstructive pulmonary disease (COPD). According to the GOLD criterion, a post-bronchodilator measurement of FEV_1/FVC <0.7 defines COPD, at least stage one.

However, a post-bronchodilator measurement was not used in our study. Therefore, we excluded 44 women with bronchial asthma from further analysis of the association between COPD and SES and respiratory health risk factors, to avoid confounding of COPD with bronchial asthma. Bronchial asthma was considered present when diagnosed by a physician or if asthma medication was used.

Respiratory symptoms and diagnoses, SES, and respiratory health risk factors

Symptoms and diagnoses were assessed by a self-administered standardised questionnaire. For the respiratory health status, the questionnaire included questions regarding chronic bronchitis and bronchial asthma diagnosed by a physician, frequent cough, and frequent cough with phlegm production as well as medication. Furthermore, relevant potential respiratory health risk factors such as occupational exposure to dust, gases, vapours, wet conditions or extreme temperatures, smoking, environmental tobacco smoke (ETS) and level of education were included in the questionnaire. All returned questionnaires were checked by the investigating physician. We grouped the women into three categories according to their reported current smoking habits: non-smoker (including ex-smoker), passive smoker (ETS at home and/or work place), and current smoker. We determined the SES by categorizing the women into three levels of education using the highest school level completed by either the women or her husband as low (< 10 years), medium (=10 years), high (> 10 years).

Air pollution data

We used ambient air concentration of particulate matter of less then 10 µm dynamic diameters (PM_{10}) and nitrogen dioxide (NO_2) to assess environmental pollution for our analysis. Total suspended particles (TSP) and NO_2 are routinely measured by the State Environmental Agency of North Rhine Westphalia. The concentrations of NO_2 are measured half-hourly by means of chemiluminescence. TSP were gathered with a low-volume sampler (air flow: 1 m^3/h) and continuously measured using beta-ray absorption. To be able to compare our results with other air pollution studies where PM_{10}, measurements were used, we multiplied the TSP measurements with a conversion factor of 0.71.

This conversion factor was calculated from seven monitoring sites in the Ruhr area, where parallel measurements of TSP and PM_{10} were performed between 1998 and 2004 [20]. Across the Ruhr district, concentrations of ambient air pollutants were measured at stationary monitoring sites representing urban background levels. The monitoring stations are approximately located on an 8 km grid in the women's residential areas. Individual ambient air pollution exposure of the women was assessed by the measurements of the monitoring station nearest to the women's home addresses and by using 5-year-mean concentrations before the baseline investigations. We used 8 mean values from 6 monitoring stations. Furthermore, we used geographic information system (GIS) (Arc GIS 9.0, ESRI Redlands, Cato, U.S.A.) to calculate the distance of a woman's residential address to the nearest major road with more than 10.000 cars/day. A distance of less than 100 metres to the nearest major road was considered to indicate an increased exposure to local traffic-related air pollution. The daily traffic counts were obtained from the State Environmental Agency of North Rhine Westphalia.

Statistical Analysis

The statistical analysis was performed by using SAS® statistical software package, version 9.1.3 (SAS Institute, Cary, NC). The statistical description of respiratory health indicators and risk factors were provided per level of SES. We used the Cochran-Mantel-Haenszel test and linear regression for binary and continuous variables, respectively, to test a linear association of health outcomes and risk factors with the levels of SES. In order to test for a linear trend, SES was coded as follows:

One if educational level was less than 10 years school education, 0.5 if equal to 10 years and 0 if more than 10 years school education. An undirected association was assessed by chi-square test. The bivariate unadjusted associations between respiratory health indicators and risk factors were assessed by logistic regression. A stepwise procedure of multiple logistic regressions with pre-specified steps was used to analyse alterations of the associations between respiratory health indicators and SES (model I) by consecutively additional inclusion of occupational exposure (model II), tobacco smoke (model III) and environmental air pollution exposure (model IV) into the regression models. The results of the regression analyses are presented as odds ratios with 95% confidence limits and their p-values. The alteration of the crude SES effect by additional allowance of other risk factors in the model was assessed by the percentage reduction in the 'excess odds', i.e. OR-1, due to adjustment for the other risk factors. This percentage change can be taken as a measure of explained SES effect by other risk factors. Odds ratios of the continuous risk factors PM_{10} and NO_2 were calculated for an interquartile range increase of 7 $\mu g/m^3$ and 16 $\mu g/m^3$, respectively. The odds ratios presented for the SES factor indicate the risk ratios of the lowest versus the highest SES level. Interaction terms were included into the regression

models to evaluate whether the risk factors modified the effect of the SES. Outcome variables which showed no association (p>0.05) with SES were not analyzed. Likewise, risk factors, which showed no univariate association with SES, were not included in the analysis of alterations of the associations between respiratory health indicators and SES. If the association between SES and respiratory health was not homogeneous for different strata of the risk factors, the analysis was restricted to the stratum, where the association between SES and respiratory health indicator was highest.

Table 1: Distribution of SES (educational level) in the study group and the prevalence of women with impaired respiratory health by SES

	SES: all grades		**<10 years**		**=10 years of school education**		**>10 years**		
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
SES	1251	100	318	25.4	637	50.9	296	23.7	
Indicators of impaired respiratory health									**p-value[1] of linear trend effect of SES**
Frequent cough	1247	26.3	316	30.1	636	26.7	295	21.4	0.0152
Frequent cough with phlegm production	1240	12.9	312	16.0	633	12.3	295	10.9	0.0561
Chronic bronchitis diagnosed by a physician	1245	11.2	317	10.1	635	12.9	293	8.5	0.5785
Bronchial asthma	1238	3.6	312	4.8	632	3.6	294	2.0	0.0683
COPD	1207	4.1	303	5.3	614	4.9	290	1.4	0.0193
FEV_1 <80% predicted	1251	20.5	318	24.5	637	20.9	296	15.2	0.0045
FVC <80% predicted	1251	26.8	318	33.3	637	26.2	296	21.0	0.0005

[1] Cochran-Mantel-Haenszel test
Abbreviations:
FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; COPD: Chronic obstructive pulmonary disease

RESULTS

Prevalence of respiratory health impairment and SES

The cohort has been previously described in detail [9,20]. In brief, lung function measurements and complete information were obtained from 1251 women in the urban areas of the Ruhr district. In particular, information was available on school education of either the women or their husbands. The average age of the participants was 55 years

(mean: 54.5, SD 0.6). Table 1 shows the distribution of SES expressed as educational levels. The prevalence of women with impaired respiratory health and a reduction in lung function according to their educational level are also presented in Table 1.

The results show clearly the differences in prevalence of respiratory impairment in women with different school education. Respiratory symptoms were more frequently reported in women with less than 10 years of school education. However, chronic bronchitis by a physician's diagnose was more common in women with 10 years of school education. The percentage of women with impaired lung function (FVC and FEV1 <80%) was higher in the group with less than 10 years of school education. A similar result can be seen for COPD. The prevalence of impaired respiratory health decreased with increased education. A linear trend was seen for all respiratory health indicators with the exception of chronic bronchitis by a physician's diagnose. For chronic bronchitis, no significant association of any kind with the educational level could be assessed using chi-square test. We therefore excluded chronic bronchitis from the further analysis. The association between respiratory health indicators and SES was stronger for the indicators based on lung function measurements than for those based on questionnaire variables. The percentage of women with reduced lung-function who, however, did not report symptoms was lower in better educated women (Table 2). This might be due to selective underreporting of these women. For instance, 81% of women with more than 10 years of education and reduced lung function (FVC < 80%) reported frequent cough in comparison to only 67% of women with less than 10 years of education.

Prevalence of respiratory health risk factors and SES

The distributions of respiratory health risk factors in the study group are presented in Table 2. Unfavourable occupational exposure to dust, gases, vapours, wet conditions or extreme temperatures concerned 14.2% of the study group. Current smoking on entry to the study was in 17.5%, 36.6% were never smokers but did report environmental tobacco smoke (ETS) exposure, 45.9% were never smokers without environmental tobacco smoke, and 9.6% were ex-smokers. The mean distance to the nearest road with more than 10.000 cars per day was 519 m. 22.1% of all women lived in a distance of less than 100 m from a road with more than 10.000 cars a day (major road). The mean values for exposure to PM_{10} and NO_2 were 49.4 µg/m^3 and 49.2 µg/m^3, respectively. Women with less than 10 years of school education had a higher prevalence of occupational exposure. Women with lower SES had a higher exposure to ETS and were more likely to be current smokers. Further, women with less than 10 years of school education lived closer to major roads than women with higher education, but traffic exposure was not linearly associated with SES. Long-term exposure to increased levels of PM_{10} was significantly associated with lower school education. Women with less than 10 years of school education were exposed to higher levels of PM_{10} compared

to women with higher education. The prevalence of occupational exposure and current smoking status and the long-term average concentration of PM_{10} were significantly increased with decreased level of education. NO_2 exposure did not exhibit any association with SES. We therefore excluded the risk factor NO_2 exposure from further analysis.

Table 2: Respiratory health risk factors by SES (educational level)

Respiratory health risk factors	SES: all grades		<10 years		=10 years of school education		>10 years		P-value[1] of linear trend effect of SES
	N	%	N	%	N	%	N	%	
Occupational exposure[2]	1251	14.2	318	16.4	637	15.1	296	10.1	0.0296
Current smoker		17.5		20.3		17.9		13.9	0.0368
Non-smoker with ETS	1243	36.6	315	38.4	632	37.3	296	33.1	0.1780
Non-smoker without ETS		45.9		41.3		44.8		53.0	0.0038
Distance to major road with >10.000 cars/day 0-100m	1216	22.1	304	26.0	624	19.9	288	22.9	0.3490
	N	**AM SD**	**N**	**AM SD**	**N**	**AM SD**	**N**	**AM SD**	
PM_{10} 5-years mean	1254	49.4 4.6	318	50.0 4.3	637	49.7 4.4	296	48.2 5.2	<0.0001
NO_2 5-years mean	1254	49.2 4.3	318	49.1 4.6	637	49.3 4.1	296	49.4 4.2	0.3941

[1] p-value of the logistic regression
[2] Dust, gases, vapours, wet conditions or extreme temperature
Abbreviations:
NO_2: Nitrogen dioxide; PM_{10}: Particulate matter with aerodynamic diameter of ≤ 10 µm, calculated as PM_{10} = 0.71*TSP; TSP: Total suspended particles; AM: Arithmetic mean; SD: Standard deviation

Associations between respiratory health risk factors and respiratory health indicators

We tested all associations of risk factors with health outcomes in separate bivariate models (Table 3). Current smoking exhibited a significant adverse effect with all respiratory health indicators, whereas ETS did not. Likewise, occupational exposure was a significant respiratory health risk factor, but not significant for bronchial asthma. A reduction in FVC and FEV_1 (<80% predicted) was significantly associated with exposure of high levels of PM_{10}. An elevated prevalence of COPD and reduced FEV_1 (<80% predicted) with women exposed to high traffic was indicated. The parameter estimates were similar but slightly smaller compared to those in our previous publication [9], where we included women from urban and rural areas. As exposure of ETS was not a risk factor for respiratory impairment in this study group we excluded ETS from further statistical analysis.

Table 3: Bivariate associations of respiratory health risk factors with respiratory health indicators by logistic regression

		Frequent cough N=1212	Frequent cough with phlegm production N=1205	Bronchial asthma N=1203	COPD N=1172	FEV_1 <80 N=1216	FVC <80 N=1216
Occupational exposure[1]	OR 95%CI p-value	2.01 (1.44-2.82) <0.001	1.94 (1.28-2.95) 0.002	1.59 (0.75-3.38) 0.224	1.94 (0.97-3.90) 0.062	1.86 (1.30-2.66) 0.001	1.69 (1.20-2.37) 0.002
Current smoker	OR 95%CI p-value	2.03 (1.48-2.78) <0.001	1.99 (1.34-2.94) 0.001	2.34 (1.22-4.49) 0.011	3.32 (1.81-6.12) <0.001	2.22 (1.59-3.09) <0.001	1.47 (1.07-2.03) 0.018
Non-smoker with ETS[2]	OR 95%CI p-value	1.05 (0.78-1.41) 0.740	1.06 (0.71-1.58) 0.772	0.76 (0.36-1.63) 0.479	1.15 (0.55-2.42) 0.706	1.07 (0.78-1.49) 0.674	0.99 (0.75-1.32) 0.966
PM_{10} 5-year mean [7µg/m^3]	OR 95%CI p-value	1.06 (0.87-1.28) 0.565	1.09 (0.85-1.41) 0.489	0.94 (0.60-1.46) 0.771	1.25 (0.79-1.99) 0.340	1.46 (1.17-1.82) 0.001	1.44 (1.18-1.76) <0.001
Distance to major road (<= 100 m) with >10.000 cars/day	OR 95%CI p-value	1.13 (0.83-1.53) 0.431	1.02 (0.68-1.53) 0.929	1.04 (0.51-2.13) 0.920	1.69 (0.90-3.18) 0.101	1.30 (0.94-1.79) 0.118	1.07 0.79-1.45 0.678

[1] Dust, gases, vapours, wet conditions or extreme temperature
[2] 300 current smokers were excluded from the analysis
Abbreviations:
OR: Odds ratio; 95%CI: 95% Confidence interval; NO_2: Nitrogen dioxide; PM_{10}: Particulate matter with aerodynamic diameter of ≤ 10 µm, calculated as PM_{10} = 0.71*TSP; TSP: Total suspended particles; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; COPD: Chronic obstructive pulmonary disease

Table 4: Association between SES (educational level) and respiratory health indicators and its alteration by respiratory health risk factors
Stepwise logistic regression analysis

		Frequent cough[1] N=944	Frequent cough with phlegm production[1] N=938	Bronchial asthma N=1203	COPD FEV_1/FVC <0.7 N=1172	FEV_1 <80% N=1216	FVC <80% N=1216
Model I	OR	2.01	2.02	2.33	2.46	1.83	1.99
SES (educational level)	95%CI	(1.31-3.10)	(1.15-3.56)	(0.96-5.65)	(1.04-5.78)	(1.22-2.74)	(1.38-2.88)
unadjusted, 3 categories	p-value	0.001	0.015	0.061	0.040	0.003	<0.001
as continuous variables							
	OR	1.95	1.97	2.28	2.40	1.78	1.95
Model II	95%CI	(1.26-3.00)	(1.11-3.48)	(0.94-5.56)	(1.01-5.68)	(1.18-2.68)	(1.35-2.83)
SES adjusted for	p-value	0.003	0.020	0.068	0.046	0.005	<0.001
occupational exposure[2]	%-change	6%	5%	4%	4%	6%	4%
Model III	OR	1.91	1.95	2.18	2.26	1.71	1.92
SES additionally adjusted	95%CI	(1.23-2.97)	(1.10-3.46)	(0.89-5.32)	(0.94-5.41)	(1.13-2.58)	(1.32-2.79)
for current smoking	p-value	0.004	0.023	0.088	0.068	0.011	0.001
	%-change	10%	7%	11%	14%	14%	7%
Model IV	OR	1.92	1.92	2.27	2.20	1.59	1.79
SES additionally adjusted	95%CI	(1.23-2.99)	(1.07-3.41)	(0.92-5.59)	(0.91-5.32)	(1.05-2.42)	(1.23-2.61)
for 5-year mean PM_{10}	P-value	0.004	0.028	0.074	0.080	0.029	0.002
	%-change	9%	10%	5%	18%	29%	20%
Model V	OR			2.28	2.12	1.56	1.78
SES additionally adjusted	95%CI	not applicable	not applicable	(0.92-5.62)	(0.88-5.10)	(1.03-2.37)	(1.22-2.60)
for distance to major road	P-value			0.074	0.095	0.037	0.003
with >10.000 cars/day ≤	%-change			4%	23%	33%	21%
100 m							

[1] Only women living in a distance more than 100 m to the nearest major road with heavy traffic
[2] Dust, gases, vapours, wet conditions or extreme temperature
Abbreviations:
OR: Odds ratio for <10 years education versus >10 years education; 95%CI: 95% Confidence interval; PM_{10}: Particulate matter with aerodynamic diameter of ≤ 10 µm, calculated as PM_{10} = 0.71*TSP; TSP: Total suspended particles; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; COPD: Chronic obstructive pulmonary disease; %-change: Calculated as the percentage reduction in the 'excess odds' due to adjustment for that factor

Association between SES and respiratory health indicators and its alteration by respiratory health risk factors

Before assessing the contribution of respiratory health risk factors to the association between SES and respirators health indicators, we checked whether the effect between educational level and respiratory health risk factors was homogeneous. For chronic cough with and without phlegm production a significant ($p < 0.1$) modification of the SES effect by the distance to a major road was observed. The association was stronger in better educated women and stronger for women living in a distance of more than 100 m to the nearest major road. Therefore for the symptoms of chronic cough with and without phlegm production, we only considered the stratum of low traffic exposure, i.e. women living in a distance of more than 100 m to the nearest major road, in the following step-wise regression analysis. Table 5 shows the results of the step-wise regression analysis of the association between respiratory health indicators and SES adjusted by additionally including other risk factors (occupational, current smoking and air pollution exposure). These results indicate that a low level of education was associated with a reduction in lung function, i.e. an increased prevalence of FEV_1 or FVC less than 80% of the predicted value, as well as an increased prevalence of COPD, chronic cough with and without phlegm production, and bronchial asthma. The associations remained stable when adjusting for occupational exposure. However, the association was attenuated after additionally adjusting for smoking. After further adjustment for the environmental risk factors exposure of PM_{10} and distance to major road an additional attenuation of the SES effect was observed for COPD, FEV1 < 80% and FVC <80%. The alteration of the crude SES effect by additional allowance of other risk factors in the model was assessed by the relative change of the odds ratios which can be taken as a measure of explained SES effect by the other risk factors. This measure of explanation showed a range between 5% to 10% attributable risk for the self-reported respiratory health indicators and 21% to 33% change for the measured lung function indicators. The smallest change was observed for bronchial asthma with current smoking showing the best explanation of the SES effect.

DISCUSSION

Our study is the first to analyze data of a cohort of women with the focus on environmental differences and respiratory health in Germany by including measurements of large- and small-scale air pollution. The results showed that women of lower educational level had a higher prevalence of respiratory impairment including a reduced lung function. We could

observe that a reduction in lung functions (FEV_1 and FVC < 80% of predicted value) was significantly associated with long-term exposure to high levels of PM_{10}.

Adjusting for smoking and outdoor air pollution decreased the relevance of SES for acquiring chronic respiratory symptoms or lung function impairment. The investigated respiratory health risk factors taken together, explained a relative portion of the social differences in the prevalence of self-reported chronic respiratory health indicators by 4% to 10% and for the measured respiratory health outcomes by 21% to 33%. The weaker explanatory potency of respiratory health risk factors for self-reported symptoms might partly be explained by a SES-dependent underreporting behaviour. Indeed, if the lung function measurements were taken as gold standard, we observed an increasing underreporting with decreasing educational level. Our findings are probably not only true for the Ruhr area, but can also be transferred to regions of other industrialized regions, as they might show similar social structures and patterns of behaviour. Our analysis is a contribution to the German environmental inequalities discussion by investigating the associations between air pollution exposure, including PM_{10} in ambient air, heavy traffic, occupational exposure, smoking behaviour, SES indicated by educational level, and respiratory health indicators including lung function measurements.

We used level of education, as it is widely accepted as a valid measure of SES [24] in particular in women. It is considered a good indicator of SES in women, because most women of this generation were not formally employed and had less occupational exposure [4]. Besides, social class, level of education and occupation are closely correlated and only some of the respiratory diseases may be caused by occupational exposure, however, women generally do not hold jobs with high levels of exposure to dust, such as miners, or extreme temperatures that are the potential causes of respiratory diseases [25].

It has been recognized that both air pollution and SES are priority areas for public health interventions [26]. At the same time, evidence showed that air pollution is a serious health concern [11,12]. A small number of studies in Germany showed that people with lower SES lived closer to major roads with high traffic exposure and had more adverse housing conditions and higher concentrations of indoor air pollution [27-30].

In our study we could show that impaired respiratory health was associated with low levels of education. This association however, attenuated after adjusting for smoking and ambient air pollution. Similar results were found in studies that focused on effect modification by SES of air pollution-associated mortality [2,4,16,31]. We observed effect modification by SES only for reported symptoms and traffic exposure, which might be related to differences in reporting behaviour. Several European studies revealed that low SES was not necessarily related to high exposure of air pollution [31,32]. It is possible that in different regions the social-group distribution varies.

We have to consider the following limitations when interpreting these results. The cross-sectional studies were designed to investigate the effect of high levels of air pollution on respiratory health. However, a cross-sectional study cannot address longitudinal issues.

Data on school education, lifestyle and other individual living conditions of these women were collected to control for potential confounders. Information on other attributes such as neighbourhood and income was not available. Another important limitation is that information regarding SES in early life, this was not available, therefore, it is possible when considering the total SES effect, then adjusting for height, and using a reference equation for FEV_1 and FVC, there might be "adjusting out" an important intermediary process in the form of lung growth.

Clustering might play a role, when assessing SES effects. However, the Ruhr area is a very homogeneous area with respect to SES. In this study, controlling for clustering by area did not change standard deviations.

The assessment of SES was restricted to the highest achieved educational level by either the woman or her husband. 33.5% of husbands had higher educational levels than their spouses. We repeated the regression analysis by using only the educational level of the women (data not shown), however, the relevance of the education on respiratory health was weaker and the attenuation was less pronounced by the covariates for exposure.

Information bias might also have influenced the results for the reported respiratory diseases such as chronic bronchitis and frequent cough. Women with lower education might differently respond to questions regarding their respiratory health than people with a higher education. It is possible that women from low social status visit the physician less frequently compare to women of higher social status, so underreporting might have taken place. These could be the reasons for the missing association between chronic bronchitis by physician's diagnose and social status.

Small inequalities that might exist in exposure are likely to be the results of long-term socioeconomic processes whereby property values become depressed in areas of higher pollution and poorer people live in areas of low rent.

However, only small differences were detected in air pollution exposures between the groups, therefore it was difficult for the air variables to explain differences in SES effects. The coverage of the monitoring stations is probably inadequate to capture the spatial variations especially in NO_2. This usually requires a very dense network. This may have contributed to the homogeneous exposures in NO_2, but we included distance to a major road to capture smaller spatial variations.

We put together non-smokers and ex-smoker in the reference groups for the effect of current smoking with the potential consequence of confounding. However, in a separate analysis

with ex-smoking as an additional risk factor, we did not see any substantial alterations of the association between SES and respiratory health indicators.

However, there are also several other strengths to our study. Firstly, we were able to differentiate between large- and small-scale measures of air pollution by using long-term exposure measures (5-year means) from stationary monitoring stations and the distance of the residential address to the nearest major road. Secondly, we only included women, men were excluded from this highly industrialized area, to avoid bias due to occupational exposures from mining and steel industry. The majority of these women were not in the work force and had no occupational exposures. Thirdly, the Ruhr district was historically the base of the coal mining and steel industry and had very high levels of ambient air pollution until the recent past, when this study was conducted. The decline in these industries was proportional throughout the area and homogeneously distributed across the whole study region.

CONCLUSION

These findings demonstrate that the situation of women in Germany with regards to environmental differences is similar to conditions in other industrialized regions. There was a significant association between the low SES and the impaired respiratory health, which was indicated by increased prevalence of respiratory symptoms and diagnoses as well as reduced lung function. The effect of SES on respiratory symptoms and impaired lung function could partly be explained by known unfavourable living conditions, as were smoking and ambient air pollution, in these women with less school education. A considerable part of the social differences, however, remained still unexplained. Our results add to the environmental inequity discussion that low social status represents an important risk factor for developing respiratory diseases and that these women are prone to live in higher polluted areas. High priority should be placed on reducing these risk factors for populations in less advantaged areas to promote environmental equity. Further follow-up of the cohort, currently being conducted, will provide additional information on these long-term effects of exposure to air pollution and the association with socioeconomic status and adverse health.

Competing interests

The authors have no competing interests.

Authors' contributions

TS performed the epidemiological analysis, drafted and wrote the paper. DS was co-investigator of the repeated cross-sectional studies, performed Geographical Information System analysis and was responsible for the data management and statistical analysis. VR helped to draft the manuscript. BP participated in the design of the study and helped to draft

the paper. UR was co-investigator of the repeated cross-sectional studies, advised on exposure assessment, and commended on the statistical analysis and helped to draft the manuscript. UK was main investigator of the repeated cross-sectional studies, advised on exposure assessment, and commented on the statistical analysis and helped to draft the manuscript. All authors read and approved the final manuscript.

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CHAPTER 5

General Discussion

5.1 Main findings

The effects of exposure to high levels of air pollution on respiratory health have been debated for a long time, but only a few studies have focused on long-term exposure. Data from the presented analysis indicate that long-term exposure to high levels of ambient air pollution can have a detrimental effect on lung function and respiratory symptoms and diseases.

This thesis describes the prevalence of respiratory symptoms and diseases measured by lung function and questionnaire, as well as long-term air pollution as risk factors for the development of respiratory diseases in a cohort of middle-aged women from the Ruhr area. It further investigates the association between air pollution induced respiratory health outcomes and cardiovascular mortality. In the final analysis it takes a look at the contribution of risk factors such as smoking and air pollution exposure to social differences in respiratory health outcomes.

The prevalence of impaired lung function was higher in women living in urban areas compared to women from the rural areas. The prevalence of COPD according to the GOLD classification $FEV_1/FVC < 0.7$ was 4.5%, which can be expected in this age group. A large survey on COPD in the United States showed a prevalence of moderate COPD in 7.2% of 45-54 age old [1]. The disease is more prevalent in older people, so one can expect an age-related increase of COPD in these women.

High levels of air pollution were associated with a reduction in lung function, as well as impairment in respiratory health and the development of COPD.

Further, respiratory health was identified as risk factor for cardiovascular mortality in this cohort, as was air pollution. However, no evidence could be found to support the hypothesis that air pollution induced respiratory impairment was a risk factor for cardiovascular mortality. We observed some indications that the impact of air pollution was even weaker in women with impaired lung function compared to women with normal lung function. Therefore, we concluded that long-term exposure to high levels of air pollution affects respiratory health and cardiovascular death independently in this group of middle aged women.

As for the environmental inequity analysis, it could be demonstrated that the situation of women in Germany is similar to conditions in other western countries. There was a significant association between low socio-economic background and impaired respiratory health outcomes. This effect could be partly explained by known unfavorable living conditions such as smoking and living in areas with higher levels of air pollution. Low socio-economic background was positively associated with respiratory health as well as with air pollution exposure. Women from low socio-economic background appeared to have a higher risk of developing respiratory diseases measured by lung function and were prone to live in areas with higher pollution levels.

5.2 Methodological considerations

5.2.1 Data collection

The SALIA study on the influence of long-term air pollution exposure on respiratory health is based on consecutive cross-sectional surveys from the Ruhr areas. It existed of two parts, in the first part, information regarding respiratory symptoms and diseases was collected with aid of a self-administered questionnaire. The second part consisted of examination by a physician and a lung function test for which every second participant was invited.

The main goal of the participating Municipal Health Services was to study the effect of air pollution on respiratory symptoms for their region in women and children (prevalence). These so-called “Wirkungskatasteruntersuchung” were part of the Clean Air initiative by the ‘Ministerium für Umwelt, Raumordung, und Landwirtschaft’ of Northrhine-Westphalia. The main reason for these studies was to give an insight into the health situation of women and children in these high polluted areas. Further the identification of preventable risk factors such as high levels of SO_2 and NO_2 from industrial sources, which were modifiable by the State Environment Agency, was an important aspect for the North Rhine Westphalia government. The third reason was to study the prevalence of and risk factors for respiratory symptoms and diseases and to implement or improve preventative measures.

The survey included all women who were 55 years old at the time of the baseline investigation, German nationality and who lived in the study areas i.e. Dortmund, Duisburg, Essen, Gelsenkirchen, Herne in the Ruhr area and Borken and Dülmen in Münsterland. Names and addresses of all women were provided through the Municipal Registration Office of each city (Einwohnermeldeamt). All Municipal health departments were responsible for contacting the women and also for mailing out the questionnaires. The analyzing institute had no access to the addresses to maintain privacy laws.

Table 2 Overview on the number of women studied in each area and each year

Participation	Borken	Dülmen	Essen	Dort-mund	Duis-burg	Gelsen-kirchen	Herne	Gesamt
1985/86	267	148	-	803	-	209	136	1558
1987	301	-	-	-	-	-	-	301
1990	267	-	291	632	685	316	-	2191
1993/94	717	-	-	-	-	-	-	717
Died till 2003	76	15	23	180	56	39	10	399

Data from similar studies in other areas of the Ruhr Basin were excluded from the analysis due to the low response rate in these areas, different type of exposure mainly due to chemical industry and no availability of address geo-coordinates for GIS-based exposure estimates. Women were lost to follow-up, because they had moved out of the area and the forwarding address was unknown. The mortality follow-up was conducted between January 2002 and May 2003 by the Institute of Epidemiology in Munich (GSF). All women were followed for their cause specific mortality. The analysis was restricted to 4757 women whose complete information was available from the baseline investigation and who could be followed-up in 2001 and 2003. By May 2003 the cause of death was known for 399 women. The present analysis focused on cardiovascular mortality.

5.2.2 Study design

Consecutive cross-sectional surveys have certain advantages when studying risk factors for respiratory health in different study regions. They are a relatively inexpensive way of determining whether an association worthy of further study is present in a given population. The information obtained in cross-sectional surveys are valuable for public health research as well as environmental research. They give a snapshot of the effect of air pollution in the general population [2]. The biggest advantage is the ability to perform these questionnaire surveys time effective and large number of people can be investigated. They document the concurrence of disease and suspected causative factors, both in a population and in individuals or subgroup within populations [2].

However, a cross-sectional study cannot address longitudinal issues. Measuring potential risk factors and disease outcomes at the same point in time provides information on associations, but these associations may not be biological plausible [2,3]. Unless one can show a temporal association between cause and effect, cross-sectional studies can only assume causation.

5.2.3 Validity of assessment of respiratory health outcomes and confounding

Two methods of assessing respiratory health were used, lung function measurement and self-administered questionnaires. Various definitions for respiratory symptoms were used: chronic cough with (a) phlegm production, (b) for more than 3 month a year, (c) for more than two consecutive years. In this analysis chronic cough and cough with phlegm production was evaluated. Further, the women were asked, whether a physician had ever diagnosed chronic bronchitis. To support the case definition lung function tests without provocation were performed. It is well known that lung function tests are the reliable diagnostic criteria for the assessment of chronic obstructive pulmonary disease. The definition of chronic obstructive

pulmonary disease was based on the GOLD classification [1]. The definition of chronic bronchitis was based on the definition and classification of chronic bronchitis by the Committee on the aetiology of chronic bronchitis [4]. Chronic cough with and without phlegm production were purely based on reporting by the women, which could be subject of information bias.

In chapter 4 we could show that self-reported respiratory health outcomes had weaker explanatory potency, which might be due to SES-dependent reporting behavior. If the lung function measurements were taken as gold standard, an increase in underreporting with educational level could be observed. The reason for this could be a difference in health consciousness in women with higher educational background compare to women with less education.

Relevant potential risk factors such as occupational exposure to dust, gases, vapours, wet or extreme conditions, smoking, environmental tobacco smoke and level of education by either the women or her husband were included into the questionnaire. These potential confounders were included in the regression models. The women were grouped according their smoking habits in three categories: never smoker, passive smoker at home or work place and current smoker. The SES was determined by categorizing the women in three levels of education using the highest school level achieved by either the women or her husband as low (< 10 years), medium (=10 years) and high (>10years). It is common practice to use education as a proxy for SES, but it can lead to the lumping together of different causal phenomena. While it is true that in some society's education is predictive of income and wealth, education may have more direct effects on health through access to and interpretation of health information and the ability to make better use of health care. Several other studies support the levels of education as a valid measure for SES in women [5-7]. This categorization is considered a good indicator of SES in women, since most women of this generation were not formally employed or stopped working after the birth of their first child and had therefore less or no occupational exposure. Also, social class, level of education and occupation are closely correlated and only some of the respiratory diseases may be caused by occupational exposure. Women generally did not hold jobs with high levels of exposure to dust such as coal mining or extreme temperature (steel industry) that are the potential cause of respiratory diseases. It is plausible that there is a change in the effects of covariates during the observation period.

5.2.4 Assessment of air pollution

As presented in all three papers, the assessment of air pollution exposure was done in two ways: by using data from monitoring stations and the distance of the residential address to the nearest major road. Data from monitoring station was used, because it is not feasible to

do personal exposure measure for large populations. The use of data from existing monitoring stations is commonly used in epidemiological studies [8,9]. These monitoring stations cover the area in an 8 km grid and they are designed to mainly reflect broad scale spatial variations in air quality. The main objective of these monitoring stations are to determine the general background levels in residential areas as well as to determine the concentrations of air pollution in highly polluted areas. We included data from 7 monitoring stations in the analysis of the study, which were located within a distance of not more than 8 km to the women's home address. The air pollution data from Borken was used for the air pollution assessment of Dülmen, because of its proximity and comparability. The air pollution data of Borken were incomplete, because continuous measurements started in 1990. The data preceding this year were imputed by using measurements (1981-2000) from 15 monitoring stations in the Ruhr area assuming similar trends. Between 1985 and 1987 discontinuous measurements were performed in Borken and Dülmen (four days per month). These discontinuous measurements agreed well with the imputed values.

Traditionally, the Ruhr area has been a highly industrialized area with extremely high pollution levels from the steel and mining industry. However, since the 1990s some of these industries have been closed down and vehicular traffic has been the main source of pollution in this area. Vehicular traffic is one of the main source for ultrafine particles and very high numbers have been observed near busy roads, with steep gradients in concentrations at distances increasing up to several hundred meters from such roads [10,11]. Various studies have shown that these particles are the main cause for cardiovascular morbidity and mortality [12,13].

5.2.5 Potential source of bias

Our study has the advantage of being population-based, with a large number of cross-sections and a large range of exposure. In each study year identical questions regarding respiratory symptoms and diseases were used, with the questions regarding respiratory symptoms derived from the WHO questionnaire [14]. These questions have been reported to have good reproducibility in regards of defining chronic bronchitis and asthma. However, the potential problem of subjective recognition or recall of symptoms is integral to the use of questionnaires. Only questions about recent respiratory symptoms are less prone to recall bias. We included an objectively measured respiratory outcome variable namely COPD defined by lung function measurements, to avoid the problem with recall bias as much as possible.

Women with lower school education might respond differently to questions regarding their respiratory health status compared to women with higher education. It is possible that women from lower SES have different health awareness than women of higher educational

level and therefore visit the physician less frequently. An example for underreporting was discussed in the third paper, where a similar number of women from lower and from the highest social status reported chronic bronchitis diagnosed by a physician.
To avoid misclassification of exposure status, we combined exposure assessment on traffic – related air pollution exposure by means of GIS, which takes within study area variability of exposure into account. Most women spent large part of their time indoors, however, we estimated the outdoor air pollution levels from road traffic, which might make the exposure assessment less precise. Since this error is probably non-differential in relation to the studied outcomes, it would be inclined to attenuate any true association.

5.2.6 Aspects of effect modification (interactions) in this thesis

Effect modification occurs, when the measure depends on the level of another factor [15].
If effect modification is present, a stratified analysis can be used. This approach is sufficient to evaluate possible effect modification between a limited numbers of factors. However, it has to be taking into consideration that respiratory symptoms and diseases are the result of multiple factors. Different approaches to test for possible effect modification were used in this thesis:
In paper 1 “Long-term exposure to traffic related pollutants and living close to busy roads are associated with COPD in women”, we generally used stratification to test effect modification between smokers and non-smokers as well as SES and smokers. For both analyses no change of effect could be observed.
For the second paper “Does respiratory health contribute to the effects of long-term air pollution exposure on cardiovascular mortality?”, we used the Cox’ Regression for the analysis, which is based on a multiplicative approach. Therefore, the result of an independent association of air pollution and respiratory health on cardiovascular mortality can only be interpreted in this multiplicative context. Both lung function indicators showed that the assumption of hazard proportionality over time was not valid. Therefore, we used a stratified Cox’ regression analysis. The associations between traffic-related air pollution exposure (distance to major road and ambient NO_2) and cardiovascular mortality showed effect modification by impaired lung function. However, this modification was contrary to the expectation that impaired lung function would increase the risk of air pollution exposure.
In the third paper “Contribution of smoking and air pollution exposure in urban areas to social differences in respiratory health”, a step-wise regression approach was used. We assessed potential effect modification by including interaction terms into the regression models to evaluate, whether the risk factors modified the effect of the SES. For chronic cough, with and without phlegm production, a significant modification of SES effects by distance to major road was observed. The SES/symptom association was stronger in women living further

away from major roads. This problem with effect modification between SES and location of residency with respect of proximity to traffic was also observed by several other European studies [16,17], the possible explanation for this is that in different regions the social-group distribution differs in urban and rural areas.

5.3 Implications of the study results for practice and research

Respiratory health problems represent a large social and economic burden not only in industrialized countries. Especially COPD is a serious public health problem in many countries. The disease is currently irreversible and can cause high levels of disability, in particular, in the elderly [18]. In this thesis it has been shown that prevalence rates of chronic respiratory diseases as a result of exposure to high levels of environmental pollution from either smoking or air pollution are of particular concern. However, little is known about the long-term effects of exposure to environmental pollutants on respiratory outcomes and cardiovascular diseases. Although this analysis focused on the association of air pollution and respiratory health in the Ruhr area, the issues described are likely to be common in most western countries and with growing concern also in developing countries. The health consequences of high levels of air pollution may results in a range of chronic conditions for the aging population worldwide.

With the view on the demographic changes occurring in Germany and worldwide, the future of public and environmental health will be more likely to become involved in serving the needs of the older population. The shift from infectious disease prevention to chronic diseases as the most prevalent reason for morbidity and mortality as well as the increase of the aging population is an important step for public health research, which also demands to focus on health in early and mid-life and to provide a healthy environment [19]. We examined the women at the age of 55 years, which was fairly young, however, already 4.5% had COPD and 2.7 % had died of cardiovascular causes by 2003, which means that these women are a particularly high risk group for air pollution associated health effects. Several studies have shown that exposures across different stages of life can affect adult outcomes and most studies on social inequalities use a life course approach [19,20]. This life course approach investigates, how biological and social factors affecting people at different stages in life and can contribute to the development of social inequalities in adult health and diseases. In particular respiratory diseases and cardiovascular health are affected by risk factors across the life course, which also have an affect on health in later life [19].

When considering the role of air pollution as a risk factor for respiratory and cardiovascular health, several issues should be kept in mind. Sustainable air pollution reduction should be an interdisciplinary approach, which includes social and scientific research. The combination of both, the study of air pollution effects and the effects of education on health implies that

better educational opportunities may also mitigate adverse effects of air pollution as well as minimize health disparities [3]. With respect to environmental inequality we could show that the situation of women in Germany is similar to conditions in other countries. The effect of SES on respiratory health outcomes could partly be explained by known unfavorable living conditions, which also included smoking and ambient air pollution, in women with low school education. These results add to the environmental inequity debate that low socioeconomic status represents an important risk factor for the development of respiratory diseases and that women with less education are also prone to live in areas with high air pollution levels. It is important to give high priorities on the reduction of these risk factors for populations in disadvantaged areas.

Furthermore, health promotion should also be considered, in particular for people from lower educational level. People from lower SES suffer more from multiple exposures not only environmental hazards, but also poverty, a lack of social cohesion and chronic health problems [16]. An important objective of environmental health promotion is to integrate all partners concerned with improving health and wellbeing of populations [21,22].

The impact of socioeconomic status on respiratory symptoms, lung function and cardiovascular health is second only to smoking [7]. However, in contrast to smoking, where prevention targets the individual, air pollution reduction requires policy decisions, regulations as well as technological and structural changes [23]. It is evident that involuntary exposure of the entire population to high levels of air pollution has adverse effects on the health of the population. Therefore, reduction of air pollution and environmental tobacco smoke should have similar preventative measures.

From the results of the present analysis some modifiable risk factors emerged, that were of importance for respiratory symptoms and diseases in women. Environmental factors which proved to be of high significance were the distance of the residency to the nearest major road with traffic volume of more than 10,000 cars per day as well as high levels of PM10. Both risk factors could be reduced by implementing strategies to promote low or no-emission cars. Implementation of comprehensive traffic policies will be more effective than traditional selective policy approaches [24].

5.4 Recommendations and future public health research

To be able to provide successful aging among older adults more large-scale longitudinal studies are needed, in which the effects of chronic exposure to high levels of air pollution are studied. It is important to develop strategies to reduce the risk of developing chronic respiratory diseases and further to reduce the risk of dying prematurely of cardiovascular diseases caused by long-term exposure to ambient air pollution. As the life span of older adults continue to increase, the number of people with chronic conditions and functional

limitations are also likely to increase [25]. Special attention should be paid to susceptible subgroups in the general population, common thresholds of air pollution exposure might not be useful to protect these populations and their needs. Another major issue is the protection of people from less advantaged areas. High priority should also be given to reducing the risk for less advantaged population who live in higher polluted areas to promote environmental equity as well as healthy aging. Identifying factors that promote and help successful aging among people with chronic conditions and for disadvantaged populations will not only enhance the quality of their life, but also the quantity of their life.

Long-term follow-ups of studies like the SALIA study are necessary to investigate the long-term effects of chronic exposure to air pollution on general health including the lungs, the heart and the brain. A longer follow-up would confirm the long-term impact of exposure to ambient air pollution and to entangle the association between pollutants and the confounding variables. Currently a follow-up of 400 women from this cohort is conducted in co-operation with the Technical University of Berlin and BGFA in Bochum. The main aims of this follow-up are to investigate:

- The role of biomarkers in the association between fine particle exposure and health impairment of the respiratory system and the brain
- Association between fine particle exposure and mild cognitive impairment
- Association between fine particle exposure and biomarkers of DNA impairment
- Identification of subgroups, which are susceptible to adverse health effects of ultra-fine particle pollution.

5.5 Conclusions

Based on the presented analyses in this thesis, the following conclusion can be drawn:

- *Chronic exposure to high levels of PM_{10}, NO_2 and living near a major road can have detrimental effect on lung function and chronic respiratory symptoms*
- *Further, chronic exposure to ambient levels of PM_{10} and NO_2 increases the risk of developing COPD*
- *Respiratory health is a predictor for cardiovascular mortality*
- *Chronic exposure to air pollution and respiratory health are independently associated with increased cardiovascular mortality in women*
- *Living conditions of these women indicated by occupational exposure, smoking behavior and ambient air pollution can only partly explain the association between SES and respiratory health outcomes*

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Summary

The health effects of long-term exposure to high levels of ambient air pollution are a major public health problem. In the 1980s and 1990s the government of North Rhine-Westphalia identified chronic respiratory diseases associated with exposure to high levels of air pollution as an important health issue in their region. Between 1985 and 1994 the Medical Institute of Environmental Hygiene (MIU) investigated 4757 women in cross-sectional studies from the Ruhr area. These women were an unselected subgroup of 55-year-old women from the Ruhr basin and two reference areas in Münsterland. The data from these investigations are the basis for this dissertation.

This dissertation focused on the epidemiology of air pollution exposure and its effect on respiratory diseases in particular chronic obstructive lung disease (COPD) in these women. In addition, it investigated air pollution- associated respiratory health as a risk factor for cardiovascular mortality in this cohort of women, and compared the contribution of smoking and air pollution as competing factors for the association between socioeconomic status (SES) and the development of respiratory symptoms. The results of this dissertation are presented in three publications.

In the first publication, the prevalence of respiratory symptoms/diseases and their association with long-term exposure to high levels of air pollution were investigated. The prevalence of COPD was 4.5% and COPD and lung function were strongest affected by particles (PM_{10}) and traffic exposure. A 7µg/m^3 increase in five-year means of PM_{10} was associated with a 5.1% (95% CI: 2.5%-7.7%) decrease in forced expiratory volume in one second (FEV_1) and a 3.7% (95%CI: 1.8%-5.5%) decrease in forced vital capacity (FVC). Further it could be shown that this increase was also associated with an odds ratio of 1.33 (95%CI: 1.03-1.72) for COPD. Similar results could be seen for women living less than 100m from a busy road with 10,000 cars/day. These women had a significantly decreased lung function and COPD was 1.79 (95%CI: 1.06-3.02) more likely than for those living farther away. Chronic symptoms showed a less pronounced association. Long-term exposure to high levels of PM_{10} and NO_2 as well as living near a major road increases the risk of developing COPD and can also have detrimental effects on lung function.

The second publication describes to what extent the association between cardiovascular mortality and air pollution is driven by the impact of air pollution on respiratory health. The study investigated, whether respiratory health at baseline contributed to the effects of long-term exposure to high levels of ambient air pollution on cardiovascular mortality.

The analysis showed that women with impaired lung function or pre-existing respiratory diseases had a higher risk of dying from cardiovascular causes than women without. The impact of impairment in lung function declined over time. The risk ratio of women with FEV_1 of less than 80% predicted to die from cardiovascular causes was 3.79 (95% CI: 1.64-8.74) at 5 year survival time and 1.35 (95% CI: 0.66-2.77) at 12 year survival time. Further it could be shown that the association between air pollution levels and cardiovascular death was strong and statistical significant.

However, when including indicators of respiratory health into the regression analysis, the association did only change marginally. This investigation showed that respiratory health is a predictor for cardiovascular mortality. In women followed for about 15 years after the baseline investigation, long-term exposure and impaired respiratory health were independently associated with increased cardiovascular mortality.

In the third publication we investigated the contribution of occupational exposures, smoking and outdoor air pollution as competing factors for the association between socio-economic status and respiratory health indicators.

For this analysis was restricted to women from urban areas and with successful spirometry (n= 1251).

Socio-economic status was defined by educational level. Women with less than 10 years of school education in comparison to more than 10 years of school education were more often occupationally exposured (16.4% vs. 10.1%), they also smoked more often (20.3% vs. 13.9%). Further is could be shown that women with less education lived more often close to major roads (26.0% vs. 22.9%). Long-term exposure to increased levels of PM_{10} was significantly associated with lower school education. Women with low school education were more likely to suffer from respiratory symptoms and had reduced lung function.

Noticeably, in the multivariate analysis the associations between education and respiratory health attenuated after adjusting for occupational exposure, smoking and outdoor air pollution. The crude odds ratio for the association between the lung function indicator FEV_1 less than 80% of predicted value and educational level (<10 years vs. >10 years of school education) was 1.83 (95% CI: 1.22-2.74). This changed to 1.56 (95% CI: 1.03-2.37) after adjusting for occupational exposure, smoking and outdoor air pollution.

There was an association between socio-economic status and respiratory health. This can partly be explained by living conditions indicated by occupational exposure, smoking behaviour and ambient air pollution partly explained the association between socio-economic status and respiratory health. A relevant part of the social differences in respiratory health, however, remained unexplained.

In last chapter the methodological aspects of theses studies are discussed and the public health relevance of the findings are described. From the results of the present thesis some modifiable risk factors emerged, that were of importance for respiratory symptoms and diseases in women. Environmental factors which proved to be of high significance were the distance of the residency to the nearest major road with traffic volume of more than 10,000 cars per day as well as high levels of PM10. Both risk factors could be reduced by implementing strategies to promote low or no-emission cars. Implementation of comprehensive traffic policies will be more effective than traditional selective policy approaches.

To be able to provide successful aging among older adults more large-scale longitudinal studies are needed, in which the effects of chronic exposure to high levels of air pollution are studied. It is important to develop strategies to reduce the risk of developing chronic respiratory diseases and further to reduce the risk of dying prematurely of cardiovascular caused by long-term exposure to ambient air pollution.

Long-term follow-ups of studies like the SALIA study are necessary to investigate the long-term effects of chronic exposure to air pollution on general health including the lungs, the heart and the brain. A longer follow-up would confirm the long-term impact of exposure to ambient air pollution and to entangle the association between pollutants and the confounding variables.

Deutsche Zusammenfassung

Der Langzeiteffekt von Luftschadstoffen aus der Umwelt auf die Gesundheit ist ein wichtiges Untersuchungsgebiet von Public Health. In den 80er und 90er Jahren wurden in Nordrhein-Westfalen so genannte Wirkungskatasteruntersuchungen mit dem Ziel durchgeführt, den Zusammenhang zwischen chronischen Atemwegserkrankungen und der Belastung durch Luftschadstoffe zu untersuchen.

Zwischen 1985 und 1994 untersuchte das Medizinische Institut für Umwelthygiene (MIU) ungefähr 4800 Frauen in Querschnittsuntersuchungen in ausgewählten Arealen des Ruhrgebietes und des südlichen Münsterlandes. Alle Frauen waren zum Zeitpunkt der Erstuntersuchung 55 Jahre alt.

Die Untersuchungsdaten dieser Wirkungskatasteruntersuchungen bilden die Datenbasis dieser Dissertation. Das Ziel dieser Dissertation war es, die Epidemiologie einer Luftschadstoffbelastung auf Atemwegserkrankungen insbesondere Chronisch Obstruktive Lungenerkrankungen (COPD) in diesen Frauen zu untersuchen. Zusätzlich wurden die Zusammenhänge zwischen Atemwegserkrankungen und Symptomen, reduzierter Lungenfunktion sowie die Exposition mit Luftschadstoffen auf das kardio-vaskuläre Mortalitätsrisiko untersucht. Des Weiteren wurde untersucht, ob der Sozialstatus einen Einfluss auf Atemwegserkrankungen als auch auf die Lungenfunktion hat und ob dieser durch schlechte Lebensweise und Lebensbedingungen, wie etwa Rauchen oder erhöhte Luftschadstoffbelastung, erklärbar ist.

Die Dissertation setzt sich aus drei Publikationen zusammen.

In der ersten Publikation wird der Zusammenhang zwischen Prävalenzen von Atemwegserkrankungen und einer Langzeitbelastung durch Luftschadstoffe untersucht. Nach den GOLD Kriterien zur Definition einer COPD litten 4,5 % dieser Frauen an einer COPD. Lungenfunktion und Prävalenzen von Atemwegserkrankungen waren signifikant mit einer Belastung durch Feinstaub und verkehrsbedingten Luftschadstoffen assoziiert. Eine Zunahme um 7 mg/m^3 in Feinstaub (PM_{10}) in der Außenluft führt zu einer Einschränkung der Lungenfunktion hinsichtlich des forcierten exspiratorischen Volumens in einer Sekunde (FEV_1) um 5,1% (95% CI: 2,5% - 7,7%) sowie der forcierten exspiratorischen Vitalkapazität (FVC) um 3,7% (95 %CI: 1,8 %- 5,5 %). Des Weiteren konnte gezeigt werden, dass mit zunehmender Belastung durch Luftschadstoffe die Prävalenz von COPD anstieg.

Ähnliche Ergebnisse zeigten sich bei Frauen die in der Nähe einer verkehrsreichen Straße lebten. Diese Frauen hatten eine signifikante reduzierte Lungenfunktion und das Risiko eine COPD zu entwickeln war erhöht (Odds Ratio: 1,79, 95% CI: 1,06 -3,02). Für die Prävalenz

von chronischen Atemwegssymptomen war ein entsprechender Zusammenhang mit einer verkehrsbedingten Schadstoffbelastung gering ausgeprägt. Grundsätzlich bestätigt sich in dieser Untersuchung, dass Langzeitbelastung mit den Luftschadstoffen PM_{10} und NO_2 sowie die Nähe der Wohnung zur verkehrsreichen Straße das Risiko einer Entstehung von COPD erhöhen und zu einer Reduzierung der Lungenfunktion führen kann.

In der zweiten Publikation wird untersucht, ob Atemwegserkrankungen und Symptome, reduzierte Lungenfunktion sowie die Exposition mit Luftschadstoffen das kardio-vaskuläre Mortalitätsrisiko erhöhen. Diese Untersuchung zeigte, dass Frauen mit einer reduzierten Lungenfunktion oder einer schon bestehenden Atemwegserkrankung ein höheres Risiko hatten an einer kardio-vaskuläre Todesursache zu sterben. Der Zusammenhang zwischen kardio-vaskulären Mortalität und einer Reduzierung der Lungenfunktion nahm über die Zeit ab. Das Risiko von Frauen mit einer Reduzierung in $FEV_1 < 80$ % an einer kardio-vaskuläre Todesursache zu sterben war (relatives Risiko pro Interquartilsabstand) 3,79 (95% CI: 1,64-8,74) nach 5 Jahren Überlebenszeit und 1,35 (95% CI: 0,66- 2,77) nach 12 Jahren Überlebenszeit. Des Weitern konnte gezeigt werden, dass der Zusammenhang zwischen einer Exposition gegenüber Luftschadstoffen und der kardio-vaskuläre Mortalität statistisch signifikant war. Wenn jedoch die Atemwegskrankungen in die Regression Analyse aufgenommen wurden, zeigten sich nur marginale Veränderungen. Diese Untersuchung deutet daraufhin, dass der Zusammenhang zwischen kardio-vaskulärer Mortalität und PM_{10} unabhängig von einer vorangegangen Atemwegsbeeinträchtigung ist.

In der dritten Publikation wurde untersucht, ob ein Effekt des Sozialstatus auf die Häufigkeit von Atemwegserkrankungen sowie auf eine Reduzierung der Lungenfunktion durch ungünstige Lebensweise und Lebensbedingungen, wie etwa Rauchen oder erhöhte Luftschadstoffbelastung, erklärbar ist. Diese Analyse beschränkt sich auf Frauen, die in Ballungsräumen leben.

Der Sozialstatus der Frauen wurde durch die Schulbildung definiert. Frauen mit weniger als 10 Jahren Schulbildung zeigten eine höhere Belastung mit Staub am Arbeitsplatz als Frauen mit einer längeren Schulbildung (16,4 % vs. 10,1 %). Frauen mit geringer Bildung waren häufiger Raucherinnen (20,3 % vs. 13,9%) und wohnten häufiger in der Nähe einer verkehrsreichen Straße (26,0 %vs. 22,9%). Eine erhöhte Langzeitexposition mit PM_{10} war signifikant mit geringem Sozialstatus assoziiert. Frauen mit niedrigem Sozialstatus zeigten mehr Atemwegssymptome und hatten eine reduzierte Lungenfunktion.

Mittels multivariaten Regressionsanalysen konnte gezeigt werden, dass ein Teil des Sozialstatuseffektes auf die Prävalenz von Atemwegserkrankungen und die Lungenfunktion durch individuelle Lebensstilfaktoren wir Arbeitsplatzbelastung, Rauch und Belastung durch Luftschadstoffe erklärt werden kann.

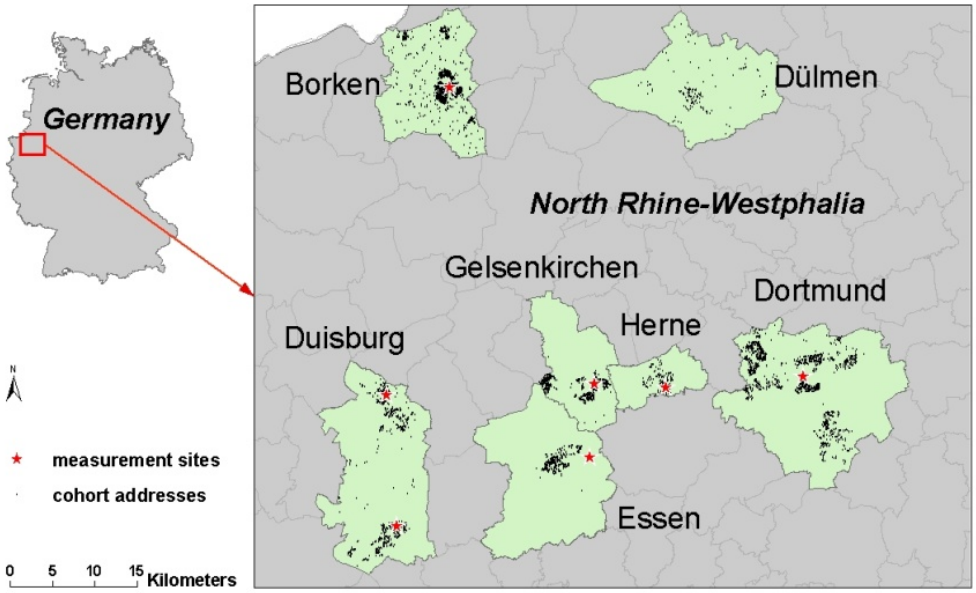
Im letzten Kapitel werden die methodischen Aspekte dieser Dissertation diskutiert und der Bezug der Untersuchung zur Public Health aufgezeigt. Die Ergebnisse weisen auf modifizierbare Risikofaktoren hin, welche wichtig für die Entstehung von Atemwegserkrankungen bei Frauen hin. Umweltbedingte Faktoren, welche einen Einfluss auf den Gesundheitszustand dieser Frauen haben, waren die Nähe zur nächsten verkehrsreichen Straße sowie hohe Außenluftkonzentrationen von PM_{10}.

Um Bedingungen für gesundes Altern zu ermöglichen, ist es wichtig in weiteren Langzeitstudien den Langzeiteffekt von Luftschadstoffen auf die Gesundheit von älteren Menschen zu untersuchen. Von besonderer Bedeutung ist dabei die Aufklärung des Einflusses einer lang andauernden Belastung mit Feinpartikeln auf inflammatorische Erkrankungen und die Entstehung chronischer Erkrankungen der Lunge und des Herzens im Alter.

Appendices

Appendix 1

Study area



Appendix 2

2.1 Example of Key Variables 1985-86

Tabelle 3.3/4 Zielvariable mit zugehörigen Maßeinheiten und Meß- bzw. Erhebungsmethoden

Name	Maßeinheit	Methode, Gerät
a) Frauen		
1. Chronische Bronchitis nach WHO-Symptomatik		Fragebogen
2. Chronische Bronchitis nach Arztdiagnose		Fragebogen
3. Erkältungshäufigkeiten in den letzten 12 Monaten		Fragebogen
4. Nasennebenhöhlenentzündung nach Arztdiagnose		Fragebogen
5. Bronchialasthma nach Arztdiagnose		Fragebogen
6. Heuschnupfen nach Arztdiagnose		Fragebogen
7. Anhusten		Klassifizierung durch den beurteilenden Arzt
8. Bleigehalt im Blut	µg/100 ml	Atomabsorption
9. Cadmiumgehalt im Blut	µg/1000 ml	Atomabsorption
10. Cadmiumgehalt im Urin	µg/24 Std.	Atomabsorption
11. Phenolgehalt im Urin	mg/24 Std.	Gaschromatographie
12. Arsengehalt im Urin	µg/24 Std.	Atomabsorption
13. Fluoridgehalt im Urin	mg/24 Std.	Ionenselektive Elektrode
14. Komplementkonzentration C3c im Serum (nach früherer Nomenklatur C'3)	mg/100 ml	Immundiffusion
15. Ruhe-Vitalkapazität (VC)	L	Spirometer
16. Forcierte Vitalkapazität (FVC)	L	Spirometer
17. Forciert-expiratorisches Lungenvolumen in der 1. Sekunde (FEV_1)	L	Spirometer
18. Maximale Strömung bei 50% FVC (MEF_{50})	L/sec	Spirometer
19. Maximale Strömung bei 25% FVC (MEF_{25})	L/sec	Spirometer
b) „Kinder allgemein"		
1. Häufiges Husten		Fragebogen
2. Bronchitis nach Arztdiagnose		Fragebogen
3. Erkältungshäufigkeit in den letzten 12 Monaten		Fragebogen
4. Nasennebenhöhlenentzündung nach Arztdiagnose		Fragebogen
5. Heuschnupfen nach Arztdiagnose		Fragebogen
6. Pseudokrupp nach Arztdiagnose		Fragebogen
7. Tonsillitis in den letzten 12 Monaten		Fragebogen
8. Anhusten		Klassifizierung durch den beurteilenden Arzt
9. Tonsillenzustand am Untersuchungstag		Klassifizierung durch den beurteilenden Arzt
10. Lymphknotenzustand am Untersuchungstag		Klassifizierung durch den beurteilenden Arzt
11. Bleigehalt im Zahn	µg/g	Atomabsorption
c) „Kinder speziell"		
1.–11. siehe entsprechende Ziffern unter b)		
12. Bleigehalt im Blut	µg/100 ml	Atomabsorption
13. Cadmiumgehalt im Blut	µg/1000 ml	Atomabsorption
14. Cadmiumgehalt im Urin	µg/24 Std.	Atomabsorption
15. Phenolgehalt im Urin	mg/24 Std.	Gaschromatographie
16. Arsengehalt im Urin	µg/24 Std.	Atomabsorption
17. Fluoridgehalt im Urin	mg/24 Std.	Ionenselektive Elektrode
18. Komplementkonzentration C3c im Serum (nach früherer Nomenklatur C'3)	mg/100 ml	Immundiffusion

2.2 Example of Questionnaire 1985-86

Erwachsenenfragebogen Teil A

Bitte nur in diesem stark umrandeten Feld das Zutreffende eintragen oder ankreuzen.

1 2 3 / 1 2 0 — 4 5 6 7 8 9 / 8 6 — 10 11 12 13 — 14 15 16 17

1. Wann sind Sie geboren?	Tag Monat Jahr	18 19 20 21 22 23
2. Wohnen Sie unter Ihrer jetzigen Anschrift länger als 5 Jahre?	Ja ☐ Nein ☐	24
Wenn nein: **2.1** Lag Ihre vorige Wohnung weiter als eine halbe Stunde Fußweg von der jetzigen Wohnung entfernt?	Ja ☐ Nein ☐	25
3. Wie oft waren Sie im Laufe der letzten 12 Monate erkältet?	ungefähr _____ mal garnicht ☐	28
4. Husten Sie gewöhnlich beim Aufstehen oder sonst im Laufe des Tages?	Ja ☐ Nein ☐	29
Wenn ja: **4.1** Haben Sie bei diesem Husten Auswurf?	Ja ☐ Nein ☐	30
4.2 Besteht der Husten während eines Jahres insgesamt länger als 3 Monate?	Ja ☐ Nein ☐	31
4.3 Leiden Sie unter diesem Husten schon länger als 2 Jahre?	Ja ☐ Nein ☐	32
5. Woran leiden Sie zur Zeit nach ärztlichem Urteil?		
An chronischer Bronchitis	Ja ☐ Nein ☐	33
Nasennebenhöhlenentzündung	Ja ☐ Nein ☐	34
Heuschnupfen	Ja ☐ Nein ☐	35
Bronchialasthma	Ja ☐ Nein ☐	36
Silikose	Ja ☐ Nein ☐	37
einer Nierenerkrankung	Ja ☐ Nein ☐	38
Gicht	Ja ☐ Nein ☐	39
Bluthochdruck	Ja ☐ Nein ☐	40
6. Nehmen Sie gegenwärtig Medikamente oder bekommen Sie Medikamente gespritzt?	Ja ☐ Nein ☐	41
Wenn ja: **6.1** Bitte nennen Sie die Namen der Medikamente		
_____		42 43 44 45 46 47
_____		48 49 50 51 52 53
_____		

Luftreinhalteplan Ruhrgebiet Mitte 1987–1991

Bitte nur hier antworten

7. Sind Sie Raucher ?	Ja ☐ Nein ☐	54 ☐
Wenn ja:		
7.1 Seit wann rauchen Sie ?	seit 19 ____	55 56 ☐☐
7.2 Was und durchschnittlich wie viel rauchen Sie ?		
Zigaretten	____ Stück tgl.	57 58 ☐☐
Zigarren	____ Stück tgl.	59 60 ☐☐
Pfeifen	____ Stück tgl.	61 62 ☐☐
Wenn nein:		
7.3 Wielange sind Sie Nichtraucher ?		
Schon immer	☐ 1	63 ☐
Mehr als ein halbes Jahr	☐ 2	
Weniger als ein halbes Jahr	☐ 3	
8. Wird in Ihrer Umgebung (Haushalt, Arbeitsplatz) geraucht ?	Ja ☐ Nein ☐	64 ☐
9. Waren Sie am Arbeitsplatz über längere Zeit folgenden Stoffen ausgesetzt ?		
Arsen	Ja ☐ Nein ☐	65 ☐
Benzol	Ja ☐ Nein ☐	66 ☐
Blei	Ja ☐ Nein ☐	67 ☐
Cadmium	Ja ☐ Nein ☐	68 ☐
Fluor, Fluoriden	Ja ☐ Nein ☐	69 ☐
10. Waren Sie am Arbeitsplatz über längere Zeit folgenden Einflüssen ausgesetzt ?		
Stäuben, Gasen, Dämpfen	Ja ☐ Nein ☐	70 ☐
Hitze, Kälte, Nässe	Ja ☐ Nein ☐	71 ☐
Wind und Wetter	Ja ☐ Nein ☐	72 ☐
11. Etwa wie lange sind Sie im Straßenverkehr Autoabgasen ausgesetzt ?		
Weniger als 1 Stunde täglich	☐ 1	73 ☐
Mehr als 1 Stunde täglich	☐ 2	
12. Wie wird Ihre jetzige Wohnung beheizt ?		74 ☐
Durch Fernheizung	☐ 1	
Zentralheizung	☐ 2	
Etagen- oder Einzelraumheizung	☐ 3	
Bei Etagen- oder Einzelraumheizung		
12.1 Womit heizen Sie ?		75 ☐
Mit Koks / Kohle	☐ 1	
Gas	☐ 2	
Öl	☐ 3	
Strom	☐ 4	
13. Benutzen Sie Gas zum Kochen oder Warmwasserbereiten ?	Ja ☐ Nein ☐	76 ☐
14. Essen Sie regelmäßig Gemüse aus Ihrem oder einem anderen privaten Garten ?	Ja ☐ Nein ☐	77 ☐

ERWACHSENENFRAGEBOGEN Teil B

Bitte nur hier antworten

1 2 3: 2 9 9

4 5 6 7 8 9: 8 6

15. Untersuchungsdatum	Tag . Monat . Jahr	1o 11 12 13 14 15
16. Körpergröße	____ cm	16 17 18
17. Körpergewicht	____ kg	19 2o 21
18. Fischgenuß in den letzten 48 Stunden	Ja ☐ Nein ☐	22 ☐
19. Erkältung mit Husten am Untersuchungstag	Ja ☐ Nein ☐	23 ☐
2o. Fieber in der letzten Woche	Ja ☐ Nein ☐	24 ☐
21. Anhusten	Normal ☐ 1 Auffällig ☐ 2 Unbewertbar ☐ 9	25 ☐
22. Welche Ausbildung haben Sie oder Ihr Ehepartner (auch falls verstorben)?	Ich selbst / Mein Ehepartner	26 27 ☐☐
Volksschule	☐ 1 / ☐ 1	
Lehre, Berufs- oder Mittelschule	☐ 2 / ☐ 2	
Handels-, Fach- oder Höhere Schule	☐ 3 / ☐ 3	
Fachhochschule oder Universität	☐ 4 / ☐ 4	
23. Blutprobe	Ja ☐ Nein ☐	
24. Urinprobe	Ja ☐ Nein ☐	

2.3 Key Variables 1990

Zielvariable der Querschnittstudie Frauen 1990 (Z-FR)

Interne Schadstoffbelastung (Blut)	
01	Blei [µg/dl]
02	Cadmium [µg/l]
03	COHb [%]
04	Benzol [µg/l]
05	Toluol [µg/l]
06	Trichlorethen [µg/l]
07	Tetrachlorethen [µg/l]
Interne Schadstoffbelastung (Urin)	
08	Arsen [µg/24h]
09	Cadmium [µg/24h]
10	Quecksilber [µg/24h]
11	Nickel [µg/24h]
12	Chrom [µg/24h]
Immunologische Funktionsparameter	
13	Komplementkomponente C3c [mg/dl]
14	Komplementkomponente C4 [mg/dl]
15	Immunglobulin G [mg/dl]
16	Immunglobulin M [mg/dl]
17	Immunglobulin A [mg/dl]
18	Akute-Phase-Proteine (AAG, HPT, COE) [mg/dl]
19	Zirkulierende Immunkomplexe [µg/ml]
20	Einzelstrang-DNA-Antikörper [U/ml]
21	Immunglobulin E [IU/ml]
22	Allergie / Art der Allergie
Lungenfunktion	
23	Vitalkapazität VC [l]
24	Forcierte exspiratorische Vitalkapazität FVC [l]
25	Forciertes exspiratorisches Einsekundenvolumen FEV_1 [l]
26	Anteil des in der 1. Sekunde ausgeatmeten Volumens an der forcierten exspiratorischen Vitalkapazität FEV_1/FVC
27	Maximale exspiratorische Strömung PEF [l/s]
28	Maximale exspir. Strömung bei 50 % Vitalkapazität MEF_{50} [l/s]
29	Maximale exspir. Strömung bei 25 % Vitalkapazität MEF_{25} [l/s]
30	Atemwegswiderstand RAW [kPa · s/l]
31	Spezifischer Atemwegswiderstand sRAW [kPa · s]
32	Intrathorakales Gasvolumen IGV [l]
33	Totale Lungenkapazität (TLC) [l]
34	Engegefühl / Atemnot in den letzten 3 Jahren
Blutbild	
35	Erythrozyten [10^6/µl]
36	Hämoglobin [g/dl]
37	Hämatokrit [%]
38	Erythrozytenvolumen MCV [fl]
39	Hämoglobingehalt des Erythrozyten MCH [pg]
40	Hämoglobinkonzentration im Erythrozyten MCHC [g/dl]
41	Thrombozyten [10^3/µl]
42	Leukozyten [10^3/µl]
43	Differentialblutbild [%]
Atemwegserkrankungen	
44	Häufiger Husten
45	Chronische Bronchitis nach WHO
46	Chronische Bronchitis nach Arztdiagnose
47	Bronchialasthma nach Arztdiagnose
48	Erkältungshäufigkeit in den letzten 12 Monaten
49	Nasennebenhöhlenentzündung nach Arztdiagnose
50	Heuschnupfen nach Arztdiagnose

2.4 Questionnaire 1990

Fragebogen der Querschnittstudie 55jähriger Frauen

Erwachsenenfragebogen Teil A

Diesen Teil bitte zuhause vollständig beantworten;
Zutreffendes bitte ankreuzen bzw. eintragen !

1 2 3 4 5 6 7 8 9: 1 2 0 9 0 | 10 11 12 13 14 15 16 17

1. Wann sind Sie geboren ?	Tag Monat Jahr _____	18 19 20 21 22 23
2. Wohnen Sie unter der jetzigen Anschrift länger als 5 Jahre ?	Ja ☐ Nein ☐	24 ☐
Wenn nein: 2.1 Lag Ihre vorige Wohnung mehr als eine halbe Stunde Fußweg von der jetzigen entfernt ?	Ja ☐ Nein ☐	25 ☐
3. Wie lange halten Sie sich durchschnittlich in Ihrer jetzigen Wohnung auf ?	___ Std. pro Tag	26 27 ☐☐
4.1 Wie oft waren Sie im Lauf der letzten 12 Monate erkältet ?	Ungefähr ___ mal Gar nicht ☐	28 ☐
4.2 Hatten Sie in den letzten 12 Monaten Heuschnupfen ?	Ja ☐ Nein ☐	29 ☐
Nasennebenhöhlenentzündung ?	Ja ☐ Nein ☐	30 ☐
5. Husten Sie gewöhnlich morgens, gleich nach dem Aufstehen, oder sonst im Lauf des Tages ?	Ja ☐ Nein ☐	31 ☐
Wenn ja: 5.1 Haben Sie bei diesem Husten Auswurf ?	Ja ☐ Nein ☐	32 ☐
5.2 Besteht der Husten während eines Jahres insgesamt länger als 3 Monate ?	Ja ☐ Nein ☐	33 ☐
5.3 Leiden Sie unter diesem Husten schon länger als 2 Jahre ?	Ja ☐ Nein ☐	34 ☐
6.1 Welche der folgenden Krankheiten besteht bei Ihnen nach ärztlichem Urteil : Bronchialasthma ?	Ja ☐ Nein ☐	35 ☐
chronische Bronchitis ?	Ja ☐ Nein ☐	36 ☐
Silikose (Quarzstaublungenerkrankung) ?	Ja ☐ Nein ☐	37 ☐
Heuschnupfen ?	Ja ☐ Nein ☐	38 ☐
Nasennebenhöhlenentzündung ?	Ja ☐ Nein ☐	39 ☐
Nierenerkrankung ?	Ja ☐ Nein ☐	40 ☐
Lebererkrankung ?	Ja ☐ Nein ☐	41 ☐
Gicht ?	Ja ☐ Nein ☐	42 ☐
rheumatische Erkrankung ?	Ja ☐ Nein ☐	43 ☐
Bluthochdruck ?	Ja ☐ Nein ☐	44 ☐
		45 ☐

6.2 Welche sonstige Erkrankungen bestehen nach ärztlichem Urteil ?

_____

_____

(ggf. bitte eintragen)

7. Nehmen Sie gegenwärtig Medikamente / bekommen Sie gegenwärtig Medikamente gespritzt ? **Wenn ja:** 7.1 Bitte nennen Sie die Namen der Medikamente ! _____ _____	Ja ☐ Nein ☐	46 ☐ 47 48 49 50 ☐☐☐☐ 51 52 53 54 ☐☐☐☐
8. Welche Ausbildung haben Sie und Ihr (Ehe-)Partner (auch falls geschieden / verwitwet) ? Volksschule / Hauptschule (1) Lehre / Berufs- / Mittelschule (2) Handels- / Fach- / höhere Schule (3) Fachhochschule / Universität (4)	Ich selbst / Mein (Ehe-) Partner ☐ 1 ☐ 1 ☐ 2 ☐ 2 ☐ 3 ☐ 3 ☐ 4 ☐ 4	55 56 ☐☐
9. Sind Sie Raucher ? **Wenn ja:** 9.1 Seit wann rauchen Sie ? 9.2 Was und durchschnittlich wie viel rauchen Sie ? Zigaretten (A) Zigarren (B) Pfeifen (C) **Wenn nein:** 9.3 Wie lange sind Sie Nichtraucher ? Schon immer (1) Mehr als ein halbes Jahr (2) Weniger als ein halbes Jahr (3)	Ja ☐ Nein ☐ Seit 19_____ A: ___Stück tägl. B: ___Stück tägl. C: ___Stück tägl. ☐ 1 ☐ 2 ☐ 3	57 58 59 ☐☐☐ 60 61 62 63 64 65 ☐☐☐☐☐☐ 66 ☐
10. Rauchen andere Personen in Ihrem Haushalt ?	Ja ☐ Nein ☐	67 ☐
11. Rauchen andere Personen an Ihrem Arbeitsplatz ?	Ja ☐ Nein ☐	68 ☐
12. Welche berufliche Tätigkeit übten Sie in den letzten 12 Monaten überwiegend aus ? _____ _____ (ggf. bitte eintragen)		69 ☐
13. Waren Sie bei dieser Tätigkeit über längere Zeit folgenden Stoffen ausgesetzt: Arsen ? Benzol ? Toluol ? Xylol ? Blei ? Cadmium ? Chlor-Kohlenwasserstoffen ? Fluor-Chlor-Kohlenwasserstoffen (FCKW) ? Methanol ? Quecksilber ?	Ja ☐ Nein ☐ Ja ☐ Nein ☐ Ja ☐ Nein ☐ Ja ☐ Nein ☐ Ja ☐ Nein ☐ Ja ☐ Nein ☐ Ja ☐ Nein ☐ Ja ☐ Nein ☐ Ja ☐ Nein ☐ Ja ☐ Nein ☐	70 ☐ 71 ☐ 72 ☐ 73 ☐ 74 ☐ 75 ☐ 76 ☐ 77 ☐ 78 ☐ 79 ☐

14. Waren Sie bei dieser Tätigkeit über längere Zeit folgenden Einflüssen ausgesetzt: Stäuben / Gasen / Dämpfen ? Hitze / Kälte / Nässe ?	Ja ☐ Nein ☐ Ja ☐ Nein ☐	80 ☐ 81 ☐
15. Sind Sie mehr als eine Stunde täglich im Freien Kraftfahrzeugabgasen ausgesetzt ?	Ja ☐ Nein ☐	82 ☐
16. Wie weit liegt ihre Wohnung (Luftlinie) von einer verkehrsreichen Straße (Berufs-, Durchgangsverkehr, ...) entfernt ? 0 - 50 m (1) 50 - 500 m (2) mehr als 500 m (3)	☐ 1 ☐ 2 ☐ 3	83 ☐
17. Welchen Freizeitbeschäftigungen gehen Sie mit gewisser Regelmäßigkeit nach ? handwerklich: _____ sportlich: _____		84 85 ☐☐
18. Wie wird Ihre jetzige Wohnung überwiegend beheizt ? Durch Fernheizung (1) Zentralheizung (2) Etagen- / Einzelraumheizung (3) offenen Kamin / Kaminofen (4) **Bei Etagen- bzw. Einzelraumheizung:** 18.1 Womit heizen Sie ? Mit Koks / Kohle / Briketts (1) Holz (2) Gas (3) Öl (4) Strom (5)	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5	86 ☐ 87 ☐
19. Benutzen Sie in Ihrer Wohnung Gas zum a) Kochen ? b) Warmwasserbereiten (mittels Boiler / Durchlauferhitzer) ? Wenn ja: 19.1 Gibt es einen gesonderten Abzug a) für den Kochherd ? b) für den Warmwasserbereiter ?	 Ja ☐ Nein ☐ Ja ☐ Nein ☐ Ja ☐ Nein ☐ Ja ☐ Nein ☐	 88 ☐ 89 ☐ 90 ☐ 91 ☐
20. Essen Sie regelmäßig Gemüse aus Ihrem / aus einem anderen privaten Garten ? Wenn ja: 20.1 Liegt dieser Garten mehr als eine halbe Stunde Fußweg von Ihrer Wohnung entfernt ? 20.2 Werden in diesem Garten chemische Pflanzenschutzmittel benutzt ?	Ja ☐ Nein ☐ Ja ☐ Nein ☐ Ja ☐ Nein ☐	92 ☐ 93 ☐ 94 ☐
21. Essen Sie regelmäßig Fisch ?	Ja ☐ Nein ☐	95 ☐

Erwachsenenfragebogen Teil B

Diesen Teil bitte nicht zuhause beantworten;
er wird im Gesundheitsamt ausgefüllt !

Arzt-Code Nr. _____

1 2 3 | 2 2 0 | 9 0 | | | | 10 11

22. Untersuchungsdatum	Tag Monat Jahr 90	12 13 14 15 16 17
23. Körpergröße / Körpergewicht	___ cm / ___ kg	18 19 20 21 22 23
24. Fischverzehr in den letzten 48 Stunden vor Abgabe der Urinprobe	Ja ☐ Nein ☐	24
25. Erkältung mit Husten am Untersuchungstag	Ja ☐ Nein ☐	25
26. Fieber in der letzten Woche	Ja ☐ Nein ☐	26
27. Zustände von Engegefühl / Atemnot / pfeifender Atmung in den letzten 3 Jahren	Ja ☐ Nein ☐	27
28. Vorliegen einer Allergie	Ja ☐ Nein ☐	28
28.1 Ggf. Art der Allergie (Organ / Symptom) _____		29 30 31
28.2 Ggf. allergisch gegen (Stoffe) _____		32 33 34
29. Allergie bei Vater / Mutter	Ja ☐ Nein ☐	35
Geschwister(n)	Ja ☐ Nein ☐	36
Kind(ern)	Ja ☐ Nein ☐	37
30. Wohnen Sie neben / über / gegenüber einer a) Tankstelle ?	Ja ☐ Nein ☐	38
b) chemischen Reinigung ?	Ja ☐ Nein ☐	39
31. Sind in Ihrer Wohnung in den letzten 3 Monaten Anstreich-/Lackierarbeiten durchgeführt worden ?	Ja ☐ Nein ☐	40
32. Uhrzeit der Blutentnahme	___:___ h	41 42 43 44 45
33. Zeitbedarf für den Weg hierher	___ Min.	46 47
34. Zuletzt geraucht vor	___ Std., ___ Min.	48 49 50 51
Nichtraucher	☐	

Danksagung

Ganz besonderen Dank schulde ich meiner Chefin und Doktormutter, Frau PD Dr. Ursula Krämer, die meine Arbeit betreut hat und immer ein offenes Ohr für meine Probleme und Unsicherheiten hatte. Mit ihren inhaltlichen Anregungen und ihren konstruktiven Rückmeldungen hat sie mir oft weitergeholfen.
Ich bedanke mich bei Herrn Prof. Johannes Siegrist für seine Bereitschaft, meine Dissertation zu betreuen, und für seine Unterstützung, die er mir dabei zukommen ließ.

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Ich möchte mich herzlich auch bei meinen Kolleginnen am Institut für Umweltmedizinische Forschung an der Heinrich-Heine-Universität Düsseldorf bedanken, die immer ein offenes Ohr für mich hatten und mich tatkräftig unterstützt haben. Mein Dank gilt ganz besonders Frau Andrea Schofer, die mich als Kollegin und Freundin immer wieder motiviert hat und meine Arbeit intensiv Korrektur gelesen hat.

Ich möchte mich auch bei meinem Bruder und meiner Schwägerin für die tatkräftige Unterstützung bedanken.

Vielen Dank auch den Probandinnen, die ihre Daten für diese Studie zur Verfügung gestellt haben.

Diese Arbeit ist meinem Mann Angelo und meinen Kindern Isabel und Valentin gewidmet, die mit mir von Australien nach Deutschland umgezogen sind. Sie haben von Anfang die Belastung durch meine berufsbegleitende Dissertation mitgetragen und mich immer wieder vorbehaltlos unterstützt.

Eidesstattliche Erklärung

Hiermit versichere ich an Eides statt, dass ich die zur Promotionsprüfung eingereichte Arbeit mit dem Titel
„Long-term air pollution exposure from industry and traffic and respiratory health in elderly women from the Ruhr Basin”
Im Institut für Umweltmedizinische Forschung an der Heinrich-Heine-Universität Düsseldorf unter Betreuung von

PD Dr. Ursula Krämer

selbständig angefertigt und bei der Abfassung der Arbeit keine anderen als die angegebenen Quellen und Hilfsmittel verwendet habe.
Ich habe bisher an keiner in-oder ausländischen Universität ein Gesuch um Zulassung zur Promotion eingereicht.

Curriculum vitae

PERSONAL

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EDUCATION

Since 2004	Doctoral Student Heinrich-Heine University of Düsseldorf, Germany Thesis title „ Long-term air pollution exposure from industry and traffic and respiratory health in elderly women from the Ruhr Basin”
2003-2004	Master of Public Health Monash University, Melbourne
1999-2002	Bachelor of Health Sciences (Environmental Health Management) Swinburne University, Melbourne
1991-1996	Medicine (State Examination) University of Cologne, Germany (not completed)
1988	German University Entry Examination (Abitur) Erftgymnasium, Bergheim, Germany

AWARDS

TGO Jordan Memorial Prize, Student with the highest academic results in. the final year of the Bachelor of Health Science of 2002 by the Australian Institute of Environmental Health, Victorian Division

Langzeitexposition mit Luftschadstoffen aus Industrie und Straßenverkehr und Atemwegsbeeinträchtigungen bei älteren Frauen aus dem Ruhrgebiet

(engl: Long-term air pollution exposure from industry and traffic and respiratory health in elderly women from the Ruhr Basin)

Tamara Schikowski

Der Langzeiteffekt von Luftschadstoffen aus der Umwelt auf die Gesundheit ist ein wichtiges Forschungsgebiet im Rahmen von Public Health. Zwischen 1985 und 1994 wurden vom damaligen Medizinischen Institut für Umwelthygiene solche Effekte bei etwa 4800 Frauen in Querschnittsuntersuchungen in ausgewählten Arealen des Ruhrgebietes und des südlichen Münsterlandes im Rahmen von so genannten Wirkungskatasteruntersuchungen bestimmt. Im Jahr 2004 wurde die ursachenspezifische Mortalität dieser Frauen durch das Institut für Epidemiologie der GSF in München erfasst. Die Daten dieser Untersuchungen bilden die Basis der Dissertation.

Das Ziel dieser Dissertation war es, den Zusammenhang zwischen der Luftschadstoffbelastung und Atemwegserkrankungen insbesondere Chronisch Obstruktive Lungenerkrankungen (COPD) bei Frauen zu quantifizieren. Zusätzlich wurde untersucht, ob das durch Luftschadstoffe erhöhte Risiko für Atemwegserkrankungen auch die luftschadstoffbedingte Mortalität erklärt. Des Weiteren wurde untersucht, ob der Sozialstatus einen Einfluss auf Atemwegserkrankungen und auf die Lungenfunktion hat und ob dieser Einfluss durch unterschiedliche Lebensweise und Lebensbedingungen, wie etwa Rauchen oder erhöhte Luftschadstoffbelastung, erklärbar ist.

Die Dissertation setzt sich aus drei Publikationen zusammen, die in peer reviewed Zeitschriften veröffentlicht wurden und jeweils eine der vorgenannten Zielstellungen behandeln.

Die erste Publikation zeigt, dass eine Langzeitbelastung mit den Luftschadstoffen PM_{10} und NO_2, sowie die Nähe der Wohnung zu einer verkehrsreichen Straße das Risiko einer Entstehung von COPD erhöht und zu einer Reduzierung der Lungenfunktion führen kann.

Die zweite Publikation weist auf, dass Frauen mit einer reduzierten Lungenfunktion oder einer schon bestehenden Atemwegserkrankung ein höheres Risiko hatten an einer kardio-vaskuläre Todesursache zu sterben, und dass der Zusammenhang zwischen einer Exposition gegenüber Luftschadstoffen und der kardio-vaskuläre Mortalität statistisch signifikant war. Der Zusammenhang zwischen kardio-vaskulärer Mortalität und PM_{10} war jedoch weitgehend unabhängig von einer vorangegangen Atemwegsbeeinträchtigung.

Die dritte Publikation schließlich zeigt, dass eine erhöhte Langzeitexposition mit PM_{10} signifikant mit einem niedrigen Sozialstatus assoziiert war. Frauen mit niedrigem Sozialstatus zeigten überaus mehr Atemwegssymptome und hatten eine reduzierte Lungenfunktion. Dieser Zusammenhang war teilweise durch vermehrtes Rauchen, belastende Berufe und höhere Belastung mit Außenluftschadstoffen zu erklären.

Im Hinblick auf die demographischen Änderungen sowohl in Deutschland als auch weltweit, wird sich Public Health und Umweltmedizin in Zukunft immer mehr mit den Bedürfnissen der älteren Bevölkerung befassen müssen. Insbesondere wird es darum gehen, Bedingungen für gesundes Altern für alle Gruppen der Bevölkerung zu sichern.

Düsseldorf, 13.05.2008 PD Dr. Ursula Krämer