Benefits of improved air quality on ageing lungs: impacts of genetics and obesity

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Improvement of air pollution has a beneficial effect on lung function in elderly women. In the elderly, these beneficial effects of improved air quality also depend on a person's genetic make-up, but not upon obesity. http://ow.ly/3gjU30nxHB1

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ABSTRACT

Introduction: The beneficial effect of improving air quality on lung function in the elderly remains unclear. We examined associations between decline in air pollutants and lung function, and effect modifications by genetics and body mass index (BMI), in elderly German women.

Methods: Data were analysed from the prospective SALIA (Study on the influence of Air pollution on Lung function, Inflammation and Aging) study (n=601). Spirometry was conducted at baseline (1985–1994; age 55 years), in 2007–2010 and in 2012–2013. Air pollution concentrations at home addresses were determined for each time-point using land-use regression models. Global Lung Initiative 2012 z-scores were calculated. Weighted genetic risk scores (GRSs) were determined from lung function-related risk alleles and used to investigate interactions with improved air quality. Multiple linear mixed models were fitted.

Results: Air pollution levels decreased substantially during the study period. Reduction of air pollution was associated with an increase in z-scores for forced expiratory volume in 1 s (FEV_1) and the FEV_1/forced vital capacity ratio. For a decrease of 10 $\mu g \cdot m^{-3}$ in nitrogen dioxide (NO_2), the z-score for FEV_1 increased by 0.14 (95% CI 0.01–0.26). However, with an increasing number of lung function-related risk alleles, the benefit from improved air quality decreased ($GRS \times NO_2$ interaction: p=0.029). Interactions with BMI were not significant.

Conclusions: Reduction of air pollution is associated with a relative improvement of lung function in elderly women, but also depends on their genetic make-up.

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Introduction

Air pollution is a major environmental risk factor affecting acute and chronic ageing-related conditions [1, 2]. Previous studies showed that long-term exposure to air pollution has adverse effects on chronic respiratory diseases [3–5] as well as lung function [3, 6–11].

However, beneficial effects of improved air quality on the respiratory system are less well understood. Studies from Switzerland and Germany provided evidence that improvement of air quality could have beneficial effects on respiratory symptoms [12, 13]. In addition, improved air quality in southern California in the USA was shown to be associated with improvements in lung function growth [14] and improved air quality in Switzerland was shown to be associated with an attenuated decline in lung function among adults [15]. However, most research has been conducted on data from only two time-points of investigation and little is known about the beneficial effects of improved air quality on ageing lungs of elderly people.

In addition to air pollution, studies provide evidence that the genetic make-up [16] as well as abdominal obesity [17] play a major role in impaired lung function. However, little is known about the underlying mechanisms, and about the impacts of genetics and obesity on the beneficial effects of improved air quality on ageing lungs. Thun *et al.* [18] performed a gene–environment (G×E) interaction analysis in the SAPALDIA (Swiss study on Air Pollution And Lung Disease in Adults) study to investigate the genetic make-up associated with attenuated lung function decline due to improvement of air quality. However, no interactions were found after correction for multiple testing. In the same cohort, Schikowski *et al.* [19] showed that improved air quality was associated with attenuated age-related reductions in lung function over time among low and normal body mass index (BMI) participants, but not in overweight or obese participants.

Improvements in air quality over time provide the backdrop for a "natural experiment" to examine the potential beneficial health effects. The SALIA (Study on the influence of Air pollution on Lung function, Inflammation and Aging) cohort offers a well-characterised exposure history of the study participants with an ongoing improvement of air quality over time, as well as consistently assessed health data and lung function of the study participants at up to three time-points. This cohort study was initiated in 1985 and the participating women were up to 83 years old at the last follow-up investigation.

We examined the association between improved air quality and age-related lung function decline in elderly women from the SALIA cohort at three time-points of examination (1985–1994, 2007–2010 and 2012–2013), and the effect modifications by genetics and BMI.

Methods

More details on the methods are given in the supplementary material.

Study design and study population

The SALIA study population was a sample of women from the urban Ruhr area and the adjacent rural Muensterland in Germany. Between 1985 and 1994, health examinations and lung function measurements were conducted in 2785 women [20].

The first follow-up examination was conducted between 2007 and 2010 [21] and the second between 2012 and 2013 [22]. All women with lung function measurements at baseline and at least at one follow-up investigation (2007–2010 and/or 2012–2013) were included in the analysis (n=601). Of these, we had data from 587 women at first follow-up and 333 women at second follow-up.

Ethical approval was obtained from the Ethical Committees of the University of Bochum (Bochum, Germany) and Heinrich Heine University (Düsseldorf, Germany). We received written informed consent from all participants.

Assessment of air pollution

Outdoor air pollution (nitrogen dioxide (NO_2), oxides of nitrogen (NO_x), and particulate matter with 50% cut-off aerodynamic diameter of 2.5 and 10 μm ($PM_{2.5}$ and PM_{10})) concentrations were assessed according to the ESCAPE (European Study of Cohorts for Air Pollution Effects) protocol [23, 24]. Air pollution was monitored over 1 year (2008–2009) in the study area. Land-use regression (LUR) models were applied to the current home addresses at each time-point of investigation.

Air pollution exposures at each time-point of investigation were estimated using extrapolation procedures. Ratios were calculated between air pollution concentrations at monitoring stations during a 2-year period around each time-point of investigation and the period of the ESCAPE monitoring campaign. The values from the LUR models were corrected for temporal trends by multiplying them with the temporal ratios

from the monitoring station in Dortmund (Germany). We used the ratio with baseline PM_{10} measurements for the extrapolation of PM_{10} as well as $PM_{2.5}$; extrapolation of NO_2 as well as NO_x was based on the ratio of NO_2 measurements (supplementary figures S1 and S2).

Assessment of genotypes

Genome-wide genotyping was performed in 462 women who participated in the follow-up investigation in 2007–2010 using the Axiom Precision Medicine Research Array (Affymetrix, Santa Clara, CA, USA). Single nucleotide polymorphisms (SNPs) were imputed on the 1000 Genomes reference panel (Phase III) using Minimac3 [25].

Assessment of pulmonary function

Spirometry was performed according to the American Thoracic Society/European Respiratory Society recommendations at all three time-points [26]. Forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were measured.

To control for age and height dependency of lung function, we calculated z-scores from the 2012 Global Lung Initiative (GLI) reference values [27]. In a previous publication, we showed that the GLI reference values can be used to assess longitudinal lung function by evaluating the fit of the individual differences in z-scores between baseline and follow-up for healthy never-smoking women from the SALIA cohort [22].

Statistical analysis

First, we analysed the cross-sectional associations between air pollution exposure and lung function at each time of investigation in linear regression models. Next, we investigated the association between long-term improvement of air quality between baseline and first follow-up and between baseline and second follow-up with the corresponding change in GLI z-scores for FEV_1, FVC and FEV_1/FVC in linear mixed models with random participant intercepts (linearity shown in supplementary figures S3–S5) [28]. *A priori* selected covariates at three time-points that could potentially act as confounders included age, BMI at baseline, change of BMI (measured), highest educational status of participant or husband, smoking status and exposure to second-hand smoke. In a sensitivity analysis, we additionally adjusted for mean income in postcode area. We fitted single- and two-pollutant models. In the two-pollutant models, we adjusted for the improvement of a second pollutant as covariate.

To investigate the impact of exposure bias due to residential mobility, we performed sensitivity analyses, in which we excluded all participants who moved during the study period.

To investigate the impact of genetics on the association between improvement of air quality and change in lung function, we conducted a G×E interaction analysis including 49 SNPs shown to be associated with impaired lung function in genome-wide association studies [16]. We summarised these genetic risk factors in weighted genetic risk scores (GRSs), which aggregate measured genetic effects and therefore increase the power to detect G×E interactions [29, 30]. External weights (β-estimates for marginal genetic effects) were acquired from the genome-wide association studies with the largest sample size available [16]. GRSs were calculated for each individual by multiplying the number of risk alleles for each of the 49 SNPs with the respective external weights and calculating the sum over all SNPs [30]. We estimated the interaction of this GRS with improved air quality in adjusted linear mixed models with a random participant intercept. Additionally, associations between genotype status at the lung function-related single SNPs (additive model) and change in lung function z-scores were estimated.

Finally, we investigated the interaction between the participants' average BMI from baseline to second follow-up and improvement of air quality on change of lung function. Associations between improvement of air quality and change in lung function were stratified by average BMI <25, 25–<30 and ⩾30 $kg \cdot m^{-2}$.

All statistical analyses were carried out with R version 3.4.3 for Windows [31].

Results

Description of study participants, air pollution and pulmonary function

The characteristics of the study participants are described in table 1.

Mean GLI z-scores for FEV_1 and FVC increased from baseline to both follow-up investigations, whereas mean z-scores for FEV_1/FVC only increased from baseline to first follow-up. The same was observed in the analysis of complete cases with available lung function measurements at all three time-points of measurement (supplementary table S1) as well as in both study areas (urban *versus* rural) (supplementary table S2).

TABLE 1 Description of study population at baseline, first and second follow-up

	Baseline (1985–1994)	First follow-up (2007–2010)	Second follow-up (2012–2013)
Subjects	601	587	333
Age years	54.3±0.8	73.3±3.3	77.4±3.4
BMI kg·m^{-2}	26.7±3.9	27.3±4.5	28.5±4.5
Change from baseline BMI kg·m^{-2} #		0.7±2.7	2.0±3.0
Length of education years			
>10	203 (33.8)	200 (34.1)	117 (35.1)
10	285 (47.4)	277 (47.2)	148 (44.4)
<10	111 (18.5)	108 (18.4)	68 (20.4)
Smoking			
Smoker	62 (10.3)	19 (3.2)	13 (3.9)
Ex-smoker	61 (10.1)	99 (16.9)	48 (14.4)
Never-smoker	477 (79.4)	469 (79.9)	272 (81.7)
Passive smoking	276 (45.9)	350 (59.6)	205 (61.6)
Moved since last follow-up		74 (12.6)	53 (9.0)
GLI z-score FEV$_1$	−0.2±1.0	0.2±1.0	0.1±1.1
Change from baseline GLI z-score FEV$_1$ ¶		0.4±0.8	0.3±0.8
GLI z-score FVC	0.0±0.9	0.3±0.9	0.5±1.0
Change from baseline GLI z-score FVC ¶		0.3±0.7	0.4±0.8
GLI z-score FEV$_1$/FVC	−0.4±0.8	−0.2±0.9	−0.7±0.8
Change from baseline GLI z-score FEV$_1$/FVC ¶		0.2±0.9	−0.3±0.8

Data are presented as n, mean±SD or n (%). BMI: body mass index; GLI: Global Lung Initiative; FEV$_1$: forced expiratory volume in 1 s; FVC: forced vital capacity. All women with lung function measurements at two or more time-points of measurement were included in the analysis (n=601). #: change of BMI between baseline and first follow-up (BMI at first follow-up−BMI at baseline) and between baseline and second follow-up (BMI at second follow-up−BMI at baseline); ¶: change of lung function between baseline and first follow-up (lung function at first follow-up−lung function at baseline) and between baseline and second follow-up (lung function at second follow-up−lung function at baseline).

The distributions of air pollutants during the study period are presented in figure 1 and table 2. Air pollution levels fell during the study period. At both follow-up investigations, PM$_{2.5}$ and PM$_{10}$ levels were below the current European Union (EU) limit values for a 1-year averaging period, whereas NO_2 levels still exceeded the EU limit values in some urban areas (figure 1). Correlations between reduction of different air pollutants are presented in supplementary table S3.

Improvement of air quality and change in lung function

At baseline investigation, higher levels of air pollution exposure were associated with lower levels of lung function (FEV$_1$, FVC and FEV$_1$/FVC), whereas after reduction of air pollution, no association was found at follow-up investigations (supplementary table S4).

Reduction of air pollution during the study period was even associated with an increase in z-scores for FEV$_1$ and FEV$_1$/FVC, but not for FVC (figure 2 and supplementary table S5). A decrease of 10 μg·m^{-3} in NO_2 and 20 μg·m^{-3} in NO_x over the study period was associated with an increase in FEV$_1$ and FEV$_1$/FVC (*e.g.* for NO_2 and FEV$_1$ by 0.14 (95% CI 0.01–0.26)). For a decrease of 10 μg·m^{-3} in PM$_{10}$, the z-score for FEV$_1$/FVC increased by 0.21 (95% CI 0.07–0.35).

The significant associations between NO_2 and NO_x with FEV$_1$ as well as with FEV$_1$/FVC were robust after adjustment for PM$_{2.5}$, but slightly attenuated after adjustment for PM$_{10}$ (supplementary table S6). The significant association between PM$_{10}$ and FEV$_1$/FVC was robust after adjustment for NO_x, but not towards adjustment for NO_2 (supplementary table S7).

Our findings were not affected by exposure bias due to residential mobility (supplementary table S8) and neither confounded by neighbourhood effects (additional adjustment for income in postcode area) (supplementary table S9) nor by selection bias (analysis of complete cases) (supplementary table S10).

Supplementary table S11 presents an overview of the lung function-related SNPs that were included in the calculation of the GRSs (45 out of 49 SNPs available after quality control). Four SNPs were associated with change in lung function at a nominal significance level ($p<0.05$), but none of the associations were robust after correction for multiple testing, possibly due to our small sample size and the limited power of single SNPs approaches.

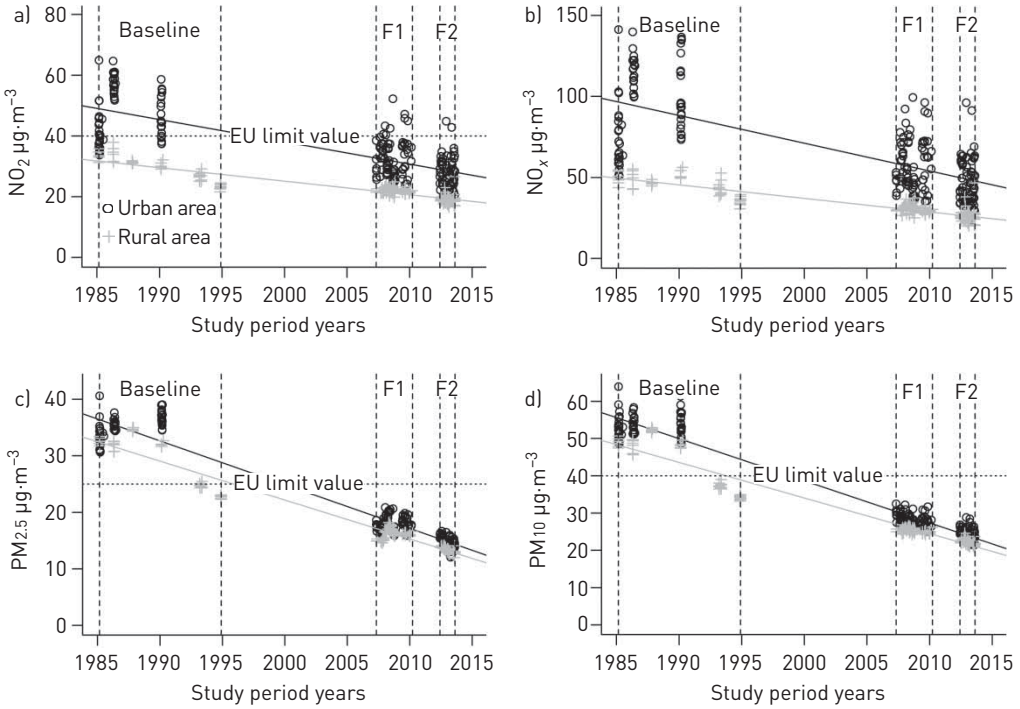

FIGURE 1 Improvement of air quality during the study period (1985–2013): a) nitrogen dioxide (NO_2), b) oxides of nitrogen (NO_x), c) particulate matter with 50% cut-off aerodynamic diameter of 2.5 µm ($PM_{2.5}$) and d) particulate matter with 50% cut-off aerodynamic diameter of 10 µm (PM_{10}). EU: European Union; F1: first follow-up investigation; F2: second follow-up investigation. Air quality standards (http://ec.europa.eu/environment/air/quality/standards.htm): EU limit values for a 1-year averaging period (no EU limit values available for NO_x). All women with lung function measurements at two or more time-points of measurement were included in the analysis (n=601).

Combining all SNPs to a GRS, we found a negative interaction between reduced levels of NO_2 and NO_x with the GRS on change in FEV_1 z-scores (interaction with NO_2: p=0.029; interaction with NO_x: p=0.021) (figure 3 and supplementary table S5). These interactions reveal that with an increasing number of lung function-related risk alleles, the benefit from improved air quality decreased.

The participants' average BMI during the study period was not associated with change in lung function in the elderly (supplementary table S12), and there was no interaction between BMI and improved air quality (table 3).

TABLE 2 Description of air pollution exposures during the study period (1985–2013)

	Baseline (1985–1994)		First follow-up (2007–2010)		Second follow-up (2012–2013)	
	Median (IQR)	Range[#]	Median (IQR)	Range[#]	Median (IQR)	Range[#]
NO_2 µg·m^{-3}	33.4 (13.8)	20.3–84.1	23.4 (7.5)	18.4–68.2	19.7 (6.3)	16.1–46.1
NO_x µg·m^{-3}	52.8 (39.0)	26.8–184.1	34.1 (19.7)	21.7–116.1	27.7 (16.1)	18.7–98.9
$PM_{2.5}$ µg·m^{-3}	33.0 (4.8)	22.0–41.3	16.6 (1.7)	14.2–21.4	13.9 (1.5)	12.0–17.9
PM_{10} µg·m^{-3}	49.9 (8.0)	32.2–65.1	26.0 (2.2)	23.2–33.2	22.9 (1.8)	20.3–28.9
Improvement of NO_2 from baseline[¶] µg·m^{-3}			9.4 (7.5)	−29.2–41.3	12.6 (7.0)	−7.3–44.2
Improvement of NO_x from baseline[¶] µg·m^{-3}			20.0 (18.3)	−39.6–107.2	24.7 (21.8)	−19.6–113.1
Improvement of $PM_{2.5}$ from baseline[¶] µg·m^{-3}			16.4 (5.6)	5.6–23.6	19.2 (3.5)	8.6–28.6
Improvement of PM_{10} from baseline[¶] µg·m^{-3}			23.6 (8.8)	6.9–36.4	26.6 (5.0)	9.8–42.8

IQR: interquartile range; NO_2: nitrogen dioxide; NO_x: oxides of nitrogen; $PM_{2.5}$: particulate matter with 50% cut-off aerodynamic diameter of 2.5 µm; PM_{10}: particulate matter with 50% cut-off aerodynamic diameter of 10 µm. All women with lung function measurements at two or more time-points of measurement were included in the analysis (n=601). [#]: minimum–maximum; [¶]; improvement of air quality between baseline and first follow-up (air pollution at baseline−air pollution at first follow-up) and between baseline and second follow-up (air pollution at baseline−air pollution at second follow-up).

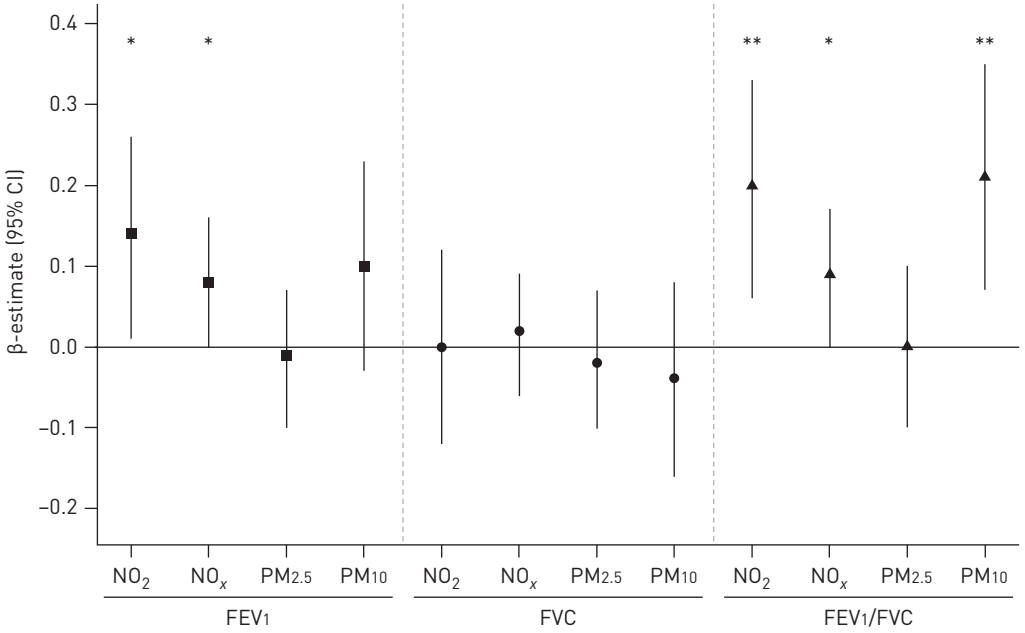

FIGURE 2 Association between improvement of air quality and change in lung function z-scores over the study period (n=601). NO_2: nitrogen dioxide; NO_x: oxides of nitrogen; $PM_{2.5}$: particulate matter with 50% cut-off aerodynamic diameter of 2.5 µm; PM_{10}: particulate matter with 50% cut-off aerodynamic diameter of 10 µm; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; BMI: body mass index. Data are presented as β-estimates (95% CI) per an improvement of 10 $\mu g \cdot m^{-3}$ in NO_2, 20 $\mu g \cdot m^{-3}$ in NO_x, 5 $\mu g \cdot m^{-3}$ in $PM_{2.5}$ and 10 $\mu g \cdot m^{-3}$ in PM_{10}. Adjusted for age, BMI at baseline, change of BMI during the study period, level of education, smoking (categorised as current, ex- or never-smoker) and exposure to second-hand smoke. *: p<0.05; **: p<0.01.

Discussion

In the present analysis, we used air pollution estimates and spirometric measurements from three time-points over a study period of 28 years to show the beneficial effect of improved air quality on lung function in elderly women. In addition, this analysis revealed that the beneficial effects of improved air quality also depended on a person's genetics. Carriers of more lung function-related risk alleles benefited less from improved air quality.

By using data from women up to the age of 83 years, our study extends previous epidemiological studies that showed associations of improved air quality with improvements in childhood lung function growth [14], as well as with an attenuated decline in lung function among adults [15]. Furthermore, our analysis used data from three measurement time-points over a period of 28 years, whereas the maximum duration of previous studies was 11 years with only two measurement time-points in adults [15, 18, 19].

In our study, improved air quality was associated with increased z-scores of FEV_1 and FEV_1/FVC, but not with FVC, which is in line with the results of adults from the SAPALDIA cohort [15]. We found the strongest associations for a decrease in NO_2 and NO_x. Nitrogen oxides are known to be the best proxy measures of urban-scale variability in chronic exposures to complex urban air pollution mixtures [32]. They are highly correlated with ultrafine particles as well as with black carbon, which are both mainly linked to traffic emissions [32].

Previous studies from the SAPALDIA cohort only included a decrease of PM_{10} as a marker of air pollution [12, 15, 18, 19]. Gauderman *et al.* [14] also included NO_2, ozone and $PM_{2.5}$ in their study of childhood lung function growth. However, due to high correlations among reductions of $PM_{2.5}$, PM_{10} and NO_2, these authors could not assess the independent associations between lung function and each of these pollutants. In contrast, in our study, the correlation between reduction of particulate matter and nitrogen oxides was only moderate, which enabled us to analyse associations with lung function in two-pollutant models. In these analyses, associations with nitrogen oxides were slightly attenuated after adjustment for PM_{10} and *vice versa*. This indicated that effect estimates from single-pollutant models were likely to overestimate the true effects.

In the last three decades, air quality has improved substantially in the German Ruhr area. Since the 1970s a series of legislations, *e.g.* the "Lead Law" and the Federal Emission Control Act, or administrative

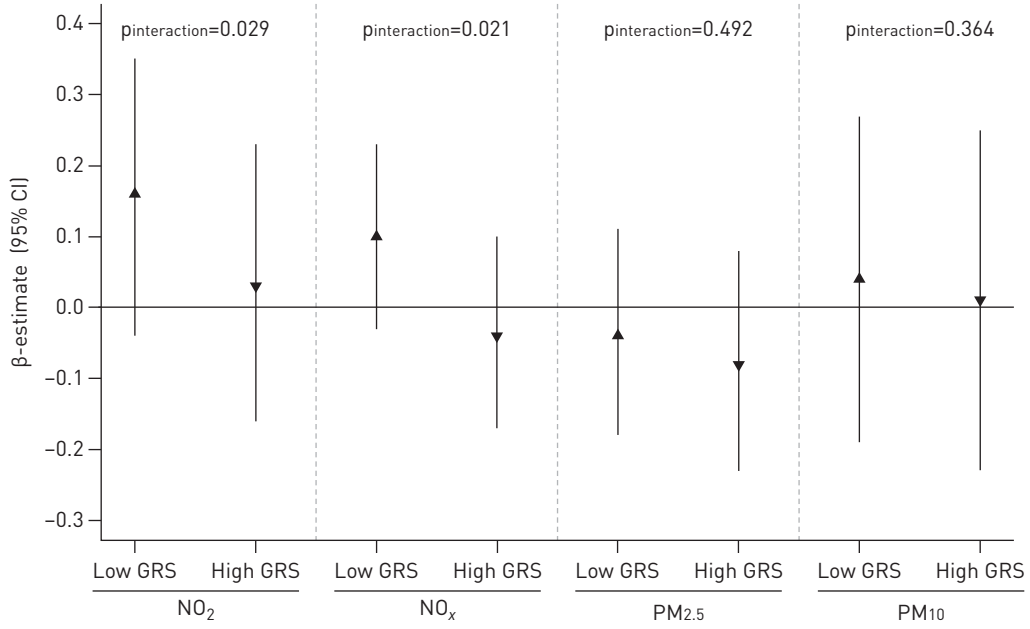

FIGURE 3 Interaction between genetic risk scores (GRSs) of lung function-related single nucleotide polymorphisms and reduction of air pollution on change in forced expiratory volume in 1 s z-scores over the study period (n=401 with available genotype data). NO_2: nitrogen dioxide; NO_x: oxides of nitrogen; $PM_{2.5}$: particulate matter with 50% cut-off aerodynamic diameter of 2.5 µm; PM_{10}: particulate matter with 50% cut-off aerodynamic diameter of 10 µm; BMI: body mass index. Data are presented as β-estimates (95% CI) for the association between improvement of air quality and change in lung function z-scores per an improvement of 10 µg·m^{-3} in NO_2, 20 µg·m^{-3} in NO_x, 5 µg·m^{-3} in $PM_{2.5}$ and 10 µg·m^{-3} in PM_{10} stratified by a low *versus* high GRS (cut-point median of GRS). $p_{interaction}$-values are given for the interaction terms between the continuous GRS and air pollution. Adjusted for age, BMI at baseline, change of BMI during the study period, level of education, smoking (categorised as current, ex- or never-smoker) and exposure to second-hand smoke.

TABLE 3 Association between improvement of air quality and change in lung function z-scores stratified by average body mass index (BMI) within the study period[#]

	Improvement in exposure	Underweight to normal (BMI <25 kg·m^{-2})	Overweight (BMI 25– <30 kg·m^{-2})	Obese (BMI ⩾30 kg·m^{-2})	$p_{interaction}$-value
Subjects n		182	279	140	
Change in lung function					
FEV_1	NO_2 (per 10 µg·m^{-3})	0.09 (−0.09–0.28)	0.15 (−0.01–0.31)	0.14 (−0.04–0.31)	0.585
	NO_x (per 20 µg·m^{-3})	0.04 (−0.10–0.18)	0.10 (−0.01–0.21)	0.06 (−0.08–0.19)	0.741
	$PM_{2.5}$ (per 5 µg·m^{-3})	−0.08 (−0.20–0.05)	−0.01 (−0.11–0.10)	0.00 (−0.15–0.15)	0.337
	PM_{10} (per 10 µg·m^{-3})	0.03 (−0.15–0.21)	0.13 (−0.03–0.28)	0.13 (−0.08–0.34)	0.369
FVC	NO_2 (per 10 µg·m^{-3})	−0.07 (−0.25–0.11)	0.04 (−0.11–0.19)	−0.01 (−0.17–0.16)	0.563
	NO_x (per 20 µg·m^{-3})	−0.02 (−0.15–0.11)	0.05 (−0.05–0.15)	−0.02 (−0.15–0.10)	0.745
	$PM_{2.5}$ (per 5 µg·m^{-3})	−0.06 (−0.18–0.06)	0.00 (−0.11–0.10)	−0.04 (−0.18–0.10)	0.840
	PM_{10} (per 10 µg·m^{-3})	−0.09 (−0.27–0.08)	−0.01 (−0.16–0.14)	−0.06 (−0.26–0.14)	0.882
FEV_1/FVC	NO_2 (per 10 µg·m^{-3})	0.24 (0.04–0.45)[¶]	0.14 (−0.04–0.31)	0.23 (0.04–0.43)[¶]	0.846
	NO_x (per 20 µg·m^{-3})	0.09 (−0.06–0.24)	0.05 (−0.07–0.17)	0.13 (−0.02–0.28)	0.857
	$PM_{2.5}$ (per 5 µg·m^{-3})	0.01 (−0.13–0.15)	−0.04 (−0.16–0.08)	0.06 (−0.10–0.23)	0.450
	PM_{10} (per 10 µg·m^{-3})	0.23 (0.03–0.43)	0.16 (−0.02–0.33)	0.32 (0.08–0.55)[¶]	0.378

Data are presented as β-estimates (95% CI) per indicated improvement in nitrogen dioxide (NO_2), oxides of nitrogen (NO_x), particulate matter with 50% cut-off aerodynamic diameter of 2.5 µm ($PM_{2.5}$) and particulate matter with 50% cut-off aerodynamic diameter of 10 µm (PM_{10}). $p_{interaction}$-value are given for the interaction terms between the continuous BMI measurements (average BMI within the study period) and air pollution. Adjusted for age, level of education, smoking (categorised as current, ex- or never-smoker) and exposure to second-hand smoke. [#]: n=601; [¶]: significant association (p<0.05).

regulations such as the Technical Instructions on Air Quality Control and the Large Combustion Installations Ordinance have reduced environmental pollution through technological means. Flue gas desulfurisation in power plants and less use of coal-fired heating in households have all helped to significantly improve air quality in Germany [33].

However, due to the growth in road traffic, in particular vehicles fuelled by diesel, NO_2 levels still exceed the EU limit values in some urban areas. Our observation of improvements in air quality and associated improvements in longitudinal respiratory health provides evidence that reduction of traffic-related air pollution can lead to further improved public health.

The beneficial effects of a reduction of air pollution also depend on a person's genetic make-up. The first G×E interaction analysis on this topic was conducted in the Swiss SAPALDIA cohort by Thun *et al.* [18], indicating that lung function-associated SNPs slightly modified the association between improvement of air quality and attenuated lung function decline. However, their interaction findings were not robust after adjustment for multiple testing. Their study differed in two points from our approach. First, Thun *et al.* [18] only considered 10 of the 34 SNPs that had been found to be associated with reduced lung function at the time-point of their analysis. In the meantime, the number of significantly associated SNPs has been extended to 49 [16], of which we included 45 in our analysis. Second, Thun *et al.* [18] conducted a common single SNP analysis with Bonferroni correction for multiple testing, whereas we used weighted GRSs to increase the statistical power to detect interaction effects [29, 34].

In our study of elderly women, there was neither an association between BMI and change in lung function nor an interaction between improvement of air quality and BMI. This is in contrast to Schikowski *et al.* [19], who indicated that obese adults might not benefit from improved air quality. The main difference between the two studies is the age range of the participants. In SAPALDIA, the participants had a mean age of 52 years at second follow-up, which is still younger than the baseline age in SALIA (55 years). This suggests a different impact of BMI on the beneficial effects of air pollution on lung function during adulthood than at an older age.

Strengths and limitations

The strengths of our study were the long follow-up period of 28 years and the availability of three repeated lung function measures as well as a range of potential confounders prospectively collected over the study period. In addition, to the best our knowledge, this is the first longitudinal analysis of air pollution and lung function applying the most recent spirometric reference values (GLI z-scores [27]) allowing to control for age and height dependencies. Furthermore, we used weighted GRSs in our G×E interaction analyses, which is currently considered the most powerful approach to detect interactions even in small study populations [29, 34]. However, more studies are needed to replicate our interaction findings.

One limitation of our study is the loss to follow-up, resulting in a reduced study sample at the first and second follow-up investigations. Women lost to follow-up were less well educated, smoked more heavily, were exposed to higher levels of air pollution and their respiratory health was worse than those who participated in the follow-up [35]. These factors have already been shown to be predictors for cardiovascular mortality in the SALIA cohort [20].

Due to the limited sample size at the second follow-up investigation, and the small exposure contrasts between first and second follow-up, we were not able to fully investigate the impact of small changes of air pollution on ageing lungs (supplementary table S13).

Although exposure estimates were individually assigned to each participant and at each time-point of investigation, exposure misclassification is a potential limitation. However, it is unlikely that any unsystematic exposure misclassification had a modifying impact on our results. Another limitation of our study is that the study population is clustered into two study areas (the urban Ruhr area and the adjacent rural Muensterland), which correlate with the levels of air pollution, that might lead to additional sources of unmeasured confounding. Furthermore, we were not able to compare the effects of improvement of air quality with the effects of other positive lifestyle changes, *e.g.* quitting smoking. Future studies are needed to investigate these effects in more detail and compare them with our findings to make our conclusions more meaningful.

Conclusions

The results of the present analysis suggest a beneficial effect of improved air quality on lung function in elderly women. The elderly are considered a high-risk group for health effects of air pollution. Thus, these findings support current efforts to further improve air quality. In addition, this study reveals that beneficial effects of improved air quality depend also on a person's genetics, which might be helpful for the identification of susceptible subgroups as well as for future treatment strategies.

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