Longitudinal associations between ambient air pollution and insulin sensitivity: results from the KORA cohort study

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Summary

Background Impaired insulin sensitivity could be an intermediate step that links exposure to air pollution to the development of type 2 diabetes. However, longitudinal associations of air pollution with insulin sensitivity remain unclear. Our study investigated the associations of long-term air pollution exposure with the degree and rate of change of insulin sensitivity.

Methods In this longitudinal study, we analysed data from the Cooperative Health Research in the Region of Augsburg (KORA) cohort from Augsburg, Germany, which recruited participants aged 25–74 years in the survey between 1999 and 2001 (KORA S4), with two follow-up examinations in 2006–08 (KORA F4) and 2013–14 (KORA FF4). Serum concentrations of fasting insulin and glucose, and homoeostasis model assessment of insulin resistance (HOMA-IR, a surrogate measure of insulin sensitivity) and β-cell function (HOMA-B, a surrogate marker for fasting insulin secretion) were assessed at up to three visits between 1999 and 2014. Annual average air pollutant concentrations at the residence were estimated by land-use regression models. We examined the associations of air pollution with repeatedly assessed biomarker levels using mixed-effects models, and we assessed the associations with the annual rate of change in biomarkers using quantile regression models.

Findings Among 9620 observations from 4261 participants in the KORA cohort, we included 6008 (62·5%) observations from 3297 (77·4%) participants in our analyses. Per IQR increment in annual average air pollutant concentrations, HOMA-IR significantly increased by 2·5% (95% CI 0·3 to 4·7) for coarse particulate matter, by 3·1% (0·9 to 5·3) for $PM_{2.5}$, by 3·6% (1·0 to 6·3) for $PM_{2.5absorbance}$, and by 3·2% (0·6 to 5·8) for nitrogen dioxide, and borderline significantly increased by 2·2% (–0·1 to 4·5) for ozone, whereas it did not significantly increase for the whole range of ultrafine particles. Similar positive associations in slightly smaller magnitude were observed for HOMA-B and fasting insulin levels. In addition, air pollutant concentrations were positively associated with the annual rate of change in HOMA-IR, HOMA-B, and fasting insulin. Neither the level nor the rate of change of fasting glucose were associated with air pollution exposure.

Interpretation Our study indicates that long-term air pollution exposure could contribute to the development of insulin resistance, which is one of the key factors in the pathogenesis of type 2 diabetes.

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Introduction

Increasing prevalence of type 2 diabetes in the past decades has contributed to a rising global burden of mortality and disability.[1] Besides traditional risk factors, such as being overweight and having sedentary lifestyles, cumulative evidence is pointing to an association between ambient air pollution and a higher risk for type 2 diabetes.[2–5] It was estimated that in 2016, around 3·2 million incident diabetes cases and more than 0·2 million deaths from diabetes worldwide were attributable to exposure to $PM_{2.5}$.[6]

Although the association is established, the underlying mechanisms through which air pollution increases the risk for type 2 diabetes remain unclear. Insulin resistance is a key factor in the pathogenesis of type 2 diabetes.[7] Recent studies have shown that long-term air pollution exposure was associated with decreased insulin sensitivity among the general population of adults and youth,[8–10] patients with diabetes,[11] and individuals prone to type 2 diabetes,[12–14] suggesting impaired insulin sensitivity could be an important intermediate step linking air pollution to the development of type 2 diabetes. Although most existing evidence is from cross-sectional studies, the longitudinal association between air pollution and insulin sensitivity has not been fully investigated.[14,15]

In addition, decreasing insulin sensitivity over time has been identified as a predictor of incident hyperglycaemia and type 2 diabetes, independent of baseline metabolic measures in prospective studies.[16,17] However, the effects of air pollution on the change of insulin sensitivity over time have rarely been reported in population-based studies to date. A cohort study[14] on Latino children who were

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Research in context

Evidence before this study

We searched PubMed and Google Scholar for studies on air pollution and insulin sensitivity published before June 1, 2020, using a combination of search terms concerning air pollution ("air pollution" OR "air pollutant*" OR "particulate matter" OR "PM" OR "ultrafine particles" OR "PNC" OR "soot" OR "black carbon" OR "nitrogen dioxide" OR "NO_2" OR "ozone" OR "O_3") and insulin sensitivity ("insulin resistance" OR "insulin sensitivity" OR "insulin" OR "glucose" OR "HOMA-IR"). Studies were selected if they were population-based cohort studies that could potentially assess longitudinal associations, if they assessed long-term air pollution exposure (exposure window ≥1 year), and if they had insulin sensitivity or resistance as the outcome. We identified seven studies, and only one examined longitudinal associations of air pollution with both the level and the rate of change of insulin sensitivity-related biomarkers among Latino children who were overweight or obese. One study analysed repeated measurements of biomarkers and assessed the association of air pollution with only the degree of insulin sensitivity. The remaining five studies did cross-sectional analyses on data collected at a single examination in cohorts, including two studies of German children and adolescents, one on German adults, one on Mexican Americans at high risk for diabetes, and one on African-American and Latino youth in Los Angeles who were overweight or obese. A meta-analysis done in 2018, which included five of the aforementioned studies, reported cross-sectional associations of insulin sensitivity with particulate matter with an aerodynamic diameter of 10 μm and nitrogen dioxide, but not with $PM_{2·5}$. Overall, little is known about the longitudinal association between ambient air pollution and insulin sensitivity, especially in the general adult population.

Added value of this study

To the best of our knowledge, this is the first epidemiological study on the longitudinal association between ambient air pollution and insulin sensitivity in the general adult population. Our study found that long-term exposure to air pollution was positively associated with the level and the rate of change of the homoeostasis model assessment of insulin resistance and fasting insulin, suggesting associations of air pollution with impaired insulin sensitivity and a more pronounced deterioration (or less pronounced improvement) of insulin sensitivity over time. In addition, our study found similar changes for the homoeostasis model assessment of β-cell function, in line with a compensatory increase in insulin secretion. Participants who were older, male, unemployed, had prediabetes or diabetes, or were physically inactive were potentially more susceptible to the adverse air pollution effects on insulin sensitivity.

Implications of all the available evidence

Together with the evidence from previous studies, our study helps understand the mechanisms through which air pollution might be associated with the development of type 2 diabetes. Such findings imply an urgent need for air quality improvement to mitigate the adverse health effects of air pollution. In addition, reducing air pollution exposure could be considered as a prevention strategy for type 2 diabetes at the population level.

overweight or obese showed that long-term exposure to elevated $PM_{2·5}$ and nitrogen dioxide (NO_2) was associated with a faster decrease in insulin sensitivity during a mean follow-up of 3·4 years (SD 3·1). Such associations are yet to be assessed in the general adult population.

In this study, we examined longitudinal associations of air pollution with the repeatedly assessed homoeostasis model assessment of insulin resistance (HOMA-IR), as a surrogate marker of insulin sensitivity, and the homoeostasis model assessment of β-cell function (HOMA-B), as a surrogate marker of fasting insulin secretion, as well as fasting insulin and glucose. We also investigated whether air pollution was associated with a change in those biomarkers over time, and we explored individual characteristics potentially related to the susceptibility to air pollution effects. We hypothesised that air pollution would be positively associated with the level and the rate of change of all investigated biomarkers, especially among more susceptible subgroups, such as older adults.

See Online for appendix

Methods

Study design and participants

In this longitudinal study, we analysed data from the Cooperative Health Research in the Region of Augsburg (KORA) cohort, which was done in the city of Augsburg, Germany, and two adjacent counties.[18] Between 1999 and 2001, 4261 participants aged 25–74 years with German citizenship were recruited in the fourth cross-sectional health survey of the KORA cohort (KORA S4), with examinations between Oct 25, 1999, and April 28, 2001. Two follow-up examinations were carried out: the first follow-up, KORA F4, consisted of 3080 participants with examinations between Oct 9, 2006, and May 31, 2008; and the second follow-up, KORA FF4, consisted of 2279 participants with examinations between June 3, 2013, and Sept 27, 2014. Participants were invited to the KORA study centre, Augsburg, Germany, and completed a computer-assisted personal interview, a self-administered questionnaire, and physical examinations at each visit. Individual characteristics relevant in the current study are defined in the appendix (p 2).

The KORA study was approved by the ethics committee of the Bavarian Chamber of Physicians (Munich, Germany); all participants gave written informed consent.

Procedures and outcomes

Blood samples were drawn between 0700 h and 1100 h after fasting for at least 8 h for the measurements of

fasting insulin and glucose concentrations. Blood samples were kept on ice after withdrawal and transported at 4°C to the laboratories for analysis (to the German Diabetes Center laboratory, Düsseldorf, in KORA S4, and to the central laboratory in Augsburg in KORA F4 and KORA FF4). Detailed information about the standard operating procedure, assays of serum concentrations of fasting insulin and glucose, and the comparability and calibration of different assays is in the appendix (p 3). Fasting insulin and glucose in KORA S4 were only measured in participants older than 54 years (n=1357). HOMA-IR was calculated as fasting insulin (μIU/mL)×fasting glucose (mmol/L)/22·5. HOMA-B was calculated as 20×fasting insulin (μIU/mL)/(fasting glucose [mmol/L]−3·5). A higher HOMA-IR indicates reduced insulin sensitivity, and a lower HOMA-B indicates decreased fasting insulin secretion. For the validity of the assessment, we excluded observations by the timepoint of which glucose-lowering medication (Anatomical Therapeutic Chemical code A10) had been used.

Annual average concentrations of ultrafine particles (particles ≤100 nm in aerodynamic diameter, represented by particle number concentration [PNC]), particulate matter with an aerodynamic diameter of 2·5–10 μm (PM_{coarse}), $PM_{2·5}$, $PM_{2·5}$ absorbance ($PM_{2·5abs}$, a proxy of elemental carbon related to traffic exhaust), NO_2, and ozone (O_3) were estimated using land-use regression (LUR) models. In brief, we carried out three 2-week measurements at 20 locations within the KORA study area between March 6, 2014, and April 7, 2015, covering the warm, cold, and intermediate seasons, and we calculated annual average air pollutant concentrations at those sites. We built LUR models by regressing the measured annual average concentrations in 2014–15 against geographic information system-based spatial predictors, and we applied the fitted models to participants' home addresses to determine residential exposure levels. The adjusted model-explained variance (R^2) ranged from 0·68 (PM_{coarse}) to 0·94 (NO_2), and the adjusted leave-one-out cross-validation R^2s were between 0·55 (PM_{coarse}) and 0·89 (NO_2), indicating good model fit. Further information about this approach is given elsewhere.[19] For participants who moved house during the study period, the updated residential addresses were used for exposure assignment; otherwise, the same exposure levels were assigned across different visits.

To control for potential confounding effects of road traffic noise and greenspace, we assigned annual average day–night sound level and normalised difference vegetation index (NDVI) in a 300 m buffer (as a surrogate for surrounding greenness) to participants' residential addresses. Assessments of noise and NDVI are in the appendix (p 4).

The outcome variables were HOMA-IR, HOMA-B, fasting insulin, and fasting glucose. Participant observations were excluded from analysis if the residential address was unavailable, there was no data on fasting insulin and glucose, they were taking glucose-lowering medication, the blood sample was drawn after 1100 h, or there were missing values in the covariates of the main model.

Statistical analysis

We applied linear mixed-effects models with random intercepts for participants to examine associations of air pollution with repeatedly assessed HOMA-IR, HOMA-B, fasting insulin, and fasting glucose levels. All outcome values were natural log-transformed to increase the conformity to normal distributions of residuals. Covariates in models were selected a priori on the basis of the disjunctive cause criterion,[20] the covariate being the cause of either the exposure or the outcome, or both, but not in the potential causal pathway linking exposure to the outcome. Minimum models were adjusted for age, sex, body-mass index (BMI), visits (KORA S4, KORA F4, or KORA FF4), and the yearly season of blood withdrawal. Main models additionally included educational attainment, occupational status, smoking status and pack-years, alcohol consumption, and physical activity. Extended models were further controlled for waist–hip ratio, high-density lipoprotein, and total cholesterol. To assess the potential confounding effect of residential road traffic noise and greenspace, we built a second extended model by adding noise and NDVI to the main model. Annual average air pollutant concentrations were included separately in each model as a linear term. Effect estimates are presented as percent changes with 95% CIs in the geometric mean of the repeatedly assessed biomarker per IQR increase in air pollutant concentrations. We examined the linearity of the exposure–response relationship using a penalised spline of the air pollutant with degrees of freedom chosen by generalised cross validation.

For participants with biomarkers measured at more than one visit, we calculated the annual rate of change in HOMA-IR, HOMA-B, fasting insulin, and fasting glucose as the slope coefficient of a linear regression of biomarker levels regressed against years since baseline (KORA S4 or KORA F4, whichever the first measurement occurred in). Because the rate values were not normally distributed and the log-transformation was not applicable to negative values, we assessed associations between air pollution and the annual rate of change in biomarkers (original scale) using quantile regression models, which do not make assumptions about the residual distribution and are more robust to outliers in the outcome. To reduce the selection bias introduced by the selection of individuals with more than one measurement, we first estimated the weight for the included participants using the inverse probability weighting approach.[21] Specifically, we modelled the probability of being included in the rate of change analysis among all participants in KORA S4 via logistic regression, using individual characteristics in the

	KORA S4 examination (n=1312)*†	KORA F4 examination (n=2704)†	KORA FF4 examination (n=1992)†
HOMA-IR	3·7 (5·1); median 2·5	2·6 (2·1); median 2·0	2·7 (2·1); median 2·1
HOMA-B	137·8 (202·9); median 99·0	120·0 (66·4); median 104·9	109·6 (62·1); median 95·1
Fasting insulin, µIU/mL	14·1 (19·5); median 10·1	10·6 (7·2); median 8·7	10·6 (6·9); median 8·9
Fasting glucose, mg/dL	102·4 (17·2); median 99·0	95·8 (14·3); median 93·0	98·9 (14·0); median 97·0
Age, years	63·9 (5·5)	55·2 (12·9)	59·6 (12·3)
Sex			
Female	635 (48%)	1407 (52%)	1041 (52%)
Male	677 (52%)	1297 (48%)	951 (48%)
Body-mass index (kg/m²)	28·4 (4·2)	27·4 (4·6)	27·5 (4·9)
Occupation (employed)	313 (24%)	1581 (58%)	1165 (58%)
Education (high)	1049 (80%)	2492 (92%)	1867 (94%)
Smoking pack-years	14·2 (23·1)	11·9 (18·8)	11·4 (18·0)
Smoking status			
Current smoker	183 (14%)	505 (19%)	320 (16%)
Former smoker	493 (38%)	1037 (38%)	803 (40%)
Never	636 (48%)	1162 (43%)	869 (44%)
Alcohol consumption			
No	338 (26%)	790 (29%)	526 (26%)
Moderate	702 (54%)	1430 (53%)	1093 (55%)
High	272 (21%)	484 (18%)	373 (19%)
Physical activity			
Low	534 (41%)	830 (31%)	529 (27%)
Medium	540 (41%)	1191 (44%)	931 (47%)
High	238 (18%)	683 (25%)	532 (27%)
Diabetes status‡			
Normal glucose tolerance	596 (46%)	1690 (64%)	1045 (54%)
Prediabetes	588 (45%)	812 (31%)	751 (39%)
Diabetes	124 (9%)	156 (6%)	137 (7%)
Waist–hip ratio‡	0·90 (0·08)	0·88 (0·09)	0·90 (0·09)
Cholesterol, mg/dL‡	243·3 (41·8)	217·1 (39·4)	217·9 (39·2)
HDL, mg/dL‡	58·3 (16·4)	56·2 (14·4)	66·3 (18·8)

Data are mean (SD) or n (%), unless otherwise indicated. KORA=Cooperative Health Research in the Region of Augsburg. S4=fourth cross-sectional health survey of the KORA cohort. F4=first follow-up examination of KORA S4. FF4=second follow-up examination of KORA S4. HOMA-IR=homeostasis model assessment of insulin resistance. HOMA-B=homeostasis model assessment of β-cell function. HDL=high-density lipoproteins. *Participants in KORA S4 were restricted to individuals older than 54 years. †Medians of some outcomes were reported due to their skewed distributions. ‡Diabetes status was missing for four (<0·5%) participants in in KORA S4, 46 (2%) in KORA F4, and 59 (3%) in KORA FF4; waist–hip ratio was missing for one (<0·5%) participant in KORA FF4; cholesterol was missing for one (<0·5%) participant in KORA S4; and HDL was missing for two (<0·5%) participants in KORA S4.

Table 1: **Descriptive statistics of participant characteristics at each examination**

main mixed-effects model as predictors. The inverse of the predicted probability derived from the regression model was used as the weight in the quantile regression model, aiming to up-weight participants who were under-represented in the rate of change analysis. The quantile regression model was adjusted for baseline covariates including age, sex, BMI, educational attainment, occupational status, smoking status and pack-years, alcohol consumption, physical activity, and baseline levels of the investigated biomarker, as well as annual rates of change in BMI and smoking pack-years, and an indicator for the visits used in the calculation of the rate of change. Results are presented as absolute changes (with 95% CIs) in the annual rate of change at deciles of the distribution of rate values per IQR increase in air pollutant concentrations.

Effect modification was investigated by including an interaction term between the air pollutant and the potential effect modifier, which was assessed at each visit for the mixed-effects models and at the first visit for the quantile regression models. The examined modifiers included age (<60 years *vs* ≥60 years), sex (male *vs* female), educational attainment (high *vs* low), occupational status (employed *vs* not employed), smoking status (current *vs* former smoker or never), physical activity (low *vs* medium or high), obesity (BMI <30 kg/m² *vs* ≥30 kg/m²), and diabetes status (normal glucose tolerance *vs* prediabetes or diabetes).

In sensitivity analyses, we first built two-pollutant models by simultaneously including two pollutants that were not strongly correlated (r <0·7). Second, we excluded observations with fasting insulin higher than the 90th percentile in KORA S4, to generate a similar distribution across the three visits. Third, we excluded participants who moved during the study period to reduce exposure misclassification. Fourth, we excluded observations without a documented time of blood withdrawal. Moreover, we did the following sensitivity analyses for only the repeated measurements (mixed-effects model). We excluded outliers in outcomes defined as natural log-transformed values less than Q1−1·5×IQR or more than Q3+1·5×IQR (appendix p 11). Additionally, we adjusted for fasting insulin or fasting glucose in models of HOMA-IR and HOMA-B, and we used back-extrapolated annual average air pollutant concentrations in the year of each visit instead of the LUR-estimated annual average in 2014–15, which further took into account the temporal variation in exposure. A detailed description of the back-extrapolation approach is in the appendix (pp 4–5). For the annual rate of change analysis, we fitted models without control for the annual rate of change in BMI and smoking pack-years to examine the effect of time-varying adjustment, and models with control for road traffic noise and NDVI.

All statistical analyses were done with R (version 3.6.2), and the significance level was set at two-sided p value of less than 0·05.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, or data interpretation, the writing of the report, or the decision to submit the paper for publication. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication.

Results

Among 9620 observations from 4261 participants in the KORA cohort, we included 6008 (62·5%) observations from 3297 (77·4%) participants in our analyses. The exclusion process is detailed in the appendix (p 12). Altogether, 466 (14·1%) of 3297 participants completed all three examinations, 1776 (53·9%) completed two, and the remaining 1055 (32·0%) completed one examination, giving a total of 1312 participants in KORA S4, 2704 in KORA F4, and 1992 in KORA FF4. In general, the distributions of fasting insulin and glucose concentrations were similar across KORA S4, KORA F4, and KORA FF4 among participants of the same age range, except that the 90th percentile of fasting insulin in KORA S4 was higher than that in KORA F4 and KORA FF4. In addition, these concentration distributions did not show substantial diurnal variations between 0700 h and 1100 h (appendix p 10).

Due to the age restriction in KORA S4 (fasting insulin and glucose were only measured in participants aged >54 years), only 1366 (32·1%) of 4261 participants contributed data on HOMA-IR, HOMA-B, fasting insulin, and fasting glucose, and thus, KORA S4 participants were on average older and had higher mean concentrations of these biomarkers than KORA F4 and KORA FF4 participants (table 1). We observed moderate to strong positive correlations between these biomarkers, except for a weak negative correlation between HOMA-B and fasting glucose (appendix p 13). Compared with all KORA participants, participants included in the analysis of repeated measurements had generally similar characteristics, whereas participants in the rate of change analysis had lower BMI and smoke exposure, and higher educational attainment, alcohol consumption, and physical activity at recruitment (appendix p 6).

The annual rate of change in HOMA-IR ranged from –6·20 to 3·96 units per year, with a median of 0·03 (IQR –0·05 to 0·12) units per year (appendix p 7). Participants with increasing HOMA-IR (n=1336) were more likely to have normal glucose tolerance and lower HOMA-IR, HOMA-B, fasting insulin, and fasting glucose at the first visit than were participants with unchanged (n=12) or decreasing (n=894) HOMA-IR over time; this pattern was reversed for the last visit (appendix p 8). Although BMI was similar between the two subgroups with increasing or unchanged and decreasing HOMA-IR at the first visit, it tended to be higher among participants with increasing HOMA-IR at the last visit.

Annual average concentrations of $PM_{2·5}$ and NO_2 at participants' residences were well below the EU air quality standards values of 25 μg/m³ for $PM_{2·5}$ and 40 μg/m³ for NO_2, although the $PM_{2·5}$ level exceeded the WHO guideline value of 10 μg/m³ (table 2). Correlations between air pollutants were moderate to strong, except for weak correlations with O_3 (appendix p 13).

Concerning repeated measurements of biomarkers, elevated PM_{coarse}, $PM_{2·5}$, $PM_{2·5abs}$, NO_2, and, to a lesser extent, O_3, were linearly associated with increases in HOMA-IR, HOMA-B, and fasting insulin (table 3). We did not find associations between air pollution and fasting glucose. The results were robust to the adjustment for additional covariates in the extended models; only $PM_{2·5abs}$ and NO_2 effects on HOMA-IR and fasting insulin slightly increased with further control for noise and NDVI (appendix p 14). Exposure–response relationships did not substantially deviate from linearity except for PNC with HOMA-IR, HOMA-B, and fasting insulin (appendix p 15). When restricting our analyses to the linear section of the relationship (PNC <12·7×10³/cm³), we observed positive associations of PNC with HOMA-IR, HOMA-B, and fasting insulin.

	Mean (SD)	Range	Median (IQR)
PNC, ×10³/cm³	7·3 (1·8)	3·2–15·7	7·3 (6·2–8·2)
PM_{coarse}, μg/m³	5·0 (1·0)	2·5–9·2	5·0 (4·3–5·7)
$PM_{2·5}$, μg/m³	11·8 (1·0)	8·3–14·8	11·9 (11·1–12·5)
$PM_{2·5abs}$, 10^{-5}/m	1·2 (0·2)	0·8–1·9	1·2 (1·1–1·4)
NO_2, μg/m³	14·4 (4·5)	6·9–28·2	14·0 (10·8–17·9)
O_3, μg/m³	39·0 (2·4)	31·3–46·2	39·0 (37·2–40·7)
Road traffic noise, dB	54·8 (6·6)	22·3–75·4	53·9 (50·6–58·6)
NDVI	0·1 (0·1)	0·0–0·3	0·1 (0·0–0·1)

Exposure levels were estimated at participants' residences in KORA S4 in this descriptive analysis. For 19 participants whose residential information was missing in the KORA S4 survey, residential addresses in KORA F4 were used. NDVI=normalised difference vegetation index. NO_2=nitrogen dioxide. O_3=ozone. PM_{coarse}=particulate matter with an aerodynamic diameter of 2·5–10 μm. $PM_{2·5abs}$=$PM_{2·5}$ absorbance. PNC=particle number concentration. KORA=Cooperative Health Research in the Region of Augsburg. S4=fourth cross-sectional health survey of the KORA cohort. F4=first follow-up examination of KORA S4.

Table 2: **Distribution of annual average air pollutant concentrations, road traffic noise, and NDVI at residences (n=3297)**

	HOMA-IR	HOMA-B	Fasting insulin	Fasting glucose
PNC	0·7 (–1·0 to 2·4)	0·8 (–0·8 to 2·4)	0·7 (–0·8 to 2·3)	–0·1 (–0·4 to 0·3)
PNC (linear)*	2·1 (0·2 to 4·0)	2·3 (0·5 to 4·1)	2·1 (0·4 to 3·9)	0·0 (–0·5 to 0·4)
PM_{coarse}	2·5 (0·3 to 4·7)	2·0 (–0·1 to 4·0)	2·4 (0·4 to 4·4)	0·1 (–0·4 to 0·6)
$PM_{2·5}$	3·1 (0·9 to 5·3)	2·7 (0·6 to 4·7)	3·0 (1·0 to 5·0)	0·1 (–0·4 to 0·6)
$PM_{2·5abs}$	3·6 (1·0 to 6·3)	2·7 (0·2 to 5·2)	3·4 (1·0 to 5·9)	0·2 (–0·4 to 0·8)
NO_2	3·2 (0·6 to 5·8)	2·5 (0·1 to 4·9)	3·1 (0·7 to 5·4)	0·2 (–0·4 to 0·7)
O_3	2·2 (–0·1 to 4·5)	1·0 (–1·1 to 3·2)	1·9 (–0·2 to 4·0)	0·3 (–0·3 to 0·8)

Mixed-effects models for repeated measurements of biomarkers were adjusted for age, sex, BMI, visits, season, educational attainment, occupational status, smoking status and pack-years, alcohol consumption, and physical activity. Outcome variables were natural log-transformed in analyses, and the effect estimates are presented as the percentage changes in the geometric mean of repeatedly assessed biomarkers. The geometric mean was 2·2 for HOMA-IR, 102·3 for HOMA-B, 9·4 μIU/mL for fasting insulin, and 97·3 mg/dL for fasting glucose. An IQR increase was 2·0×10³/cm³ for PNC, 1·4 μg/m³ for PM_{coarse}, 1·4 μg/m³ for $PM_{2·5}$, 0·3×10^{-5}/m for $PM_{2·5abs}$, 7·1 μg/m³ for NO_2, and 3·5 μg/m³ for O_3. HOMA-IR=homeostasis model assessment of insulin resistance. HOMA-B=homeostasis model assessment of β-cell function. PNC=particle number concentration. PM_{coarse}=particulate matter with an aerodynamic diameter of 2·5–10 μm. $PM_{2·5abs}$=$PM_{2·5}$ absorbance. NO_2=nitrogen dioxide. O_3=ozone. *Exposure–response relationships between the whole range of PNC and repeated measurements of HOMA-IR, HOMA-B, and fasting insulin were not linear. We restricted the analyses to PNC <12·7×10³/cm³ (cutoff values suggested by the exposure–response curve; n=5927) to assess the linear relationship. The association between PNC and fasting glucose was also investigated in the reduced PNC range.

Table 3: **Percentage changes (95% CIs) in the repeated measurements (n=6008) of biomarkers per IQR increase in air pollutant concentrations**

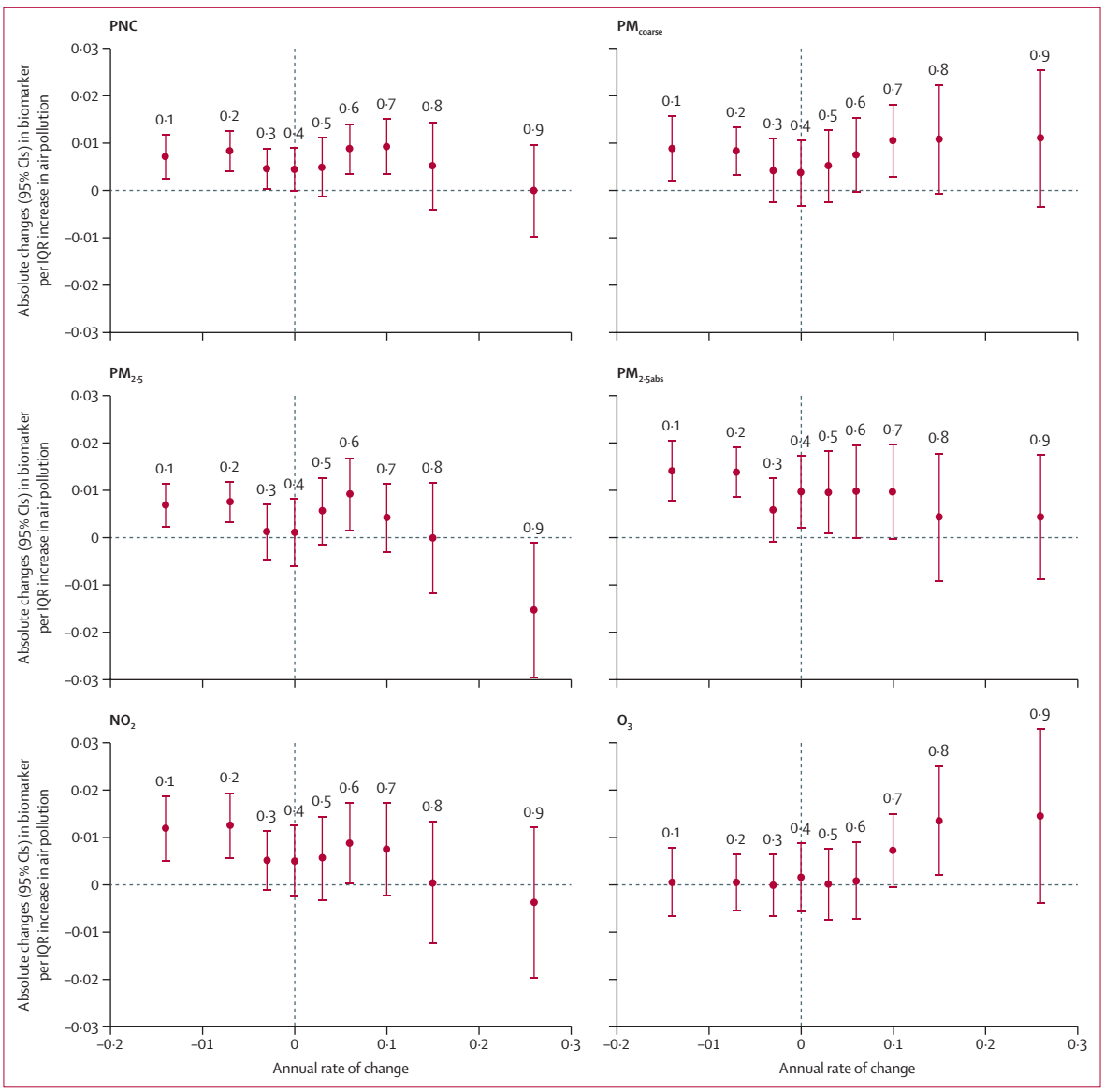

Figure 1: **Absolute changes (95% CIs) in the annual rate of change in HOMA-IR at deciles of the distribution per IQR increase in air pollutant concentrations**
Quantile regression models for the annual rate of change were adjusted for baseline levels of the investigated biomarker, age (baseline), sex, BMI (baseline), annual rate of change in BMI, educational attainment (baseline), occupational status (baseline), smoking status and pack-years (baseline), annual rate of change in smoking pack-years, physical activity (baseline), and an indicator for the visits used in the calculation of the rate of change. Area on the left side of the dashed line indicates increasing insulin sensitivity over years (annual rate of change below zero); area on the right side of the dashed line indicates decreasing insulin sensitivity over years (annual rate of change above zero). Values (ie, 0·1–0·9) above the error bars indicate deciles of the distribution of the annual rate of change. An IQR increase was $2·0 \times 10^3$/cm^3 for PNC, 1·4 μg/m^3 for PM$_{coarse}$, 1·4 μg/m^3 for PM$_{2·5}$, $0·3 \times 10^{-5}$/m for PM$_{2·5abs}$, 7·1 μg/m^3 for NO$_2$, and 3·5 μg/m^3 for O$_3$. HOMA-IR=homeostasis model assessment of insulin resistance. PNC=particle number concentration. PM$_{coarse}$=particulate matter with an aerodynamic diameter of 2·5–10 μm. PM$_{2·5abs}$=PM$_{2·5}$ absorbance. NO$_2$=nitrogen dioxide. O$_3$=ozone.

The annual rate of change in HOMA-IR was positively associated with PNC, PM$_{2·5abs}$, and NO$_2$ at the 10th to 70th percentiles of the rate value distribution (ie, rate of change ≤0·10 units per year), with PM$_{coarse}$ at all deciles, with PM$_{2·5}$ at lower percentiles, and with O$_3$ at higher percentiles (figure 1; appendix p 9). Positive associations at rate values above zero (ie, the 40th to 90th percentiles) indicate air pollution-related greater decline in insulin sensitivity over time, whereas positive associations at rate values below zero indicate that air pollution attenuated improvement in insulin sensitivity. Particles and NO$_2$ were positively associated with the annual rate of change in HOMA-B and fasting insulin, with exceptions at the lowest or highest end, or both, for PM$_{2·5}$, PM$_{2·5abs}$, and NO$_2$ (figure 2; appendix pp 9, 16). Associations of O$_3$ with HOMA-B and fasting insulin were similar to those with HOMA-IR. No consistent associations were observed for the annual rate of change in fasting glucose (appendix pp 9, 17).

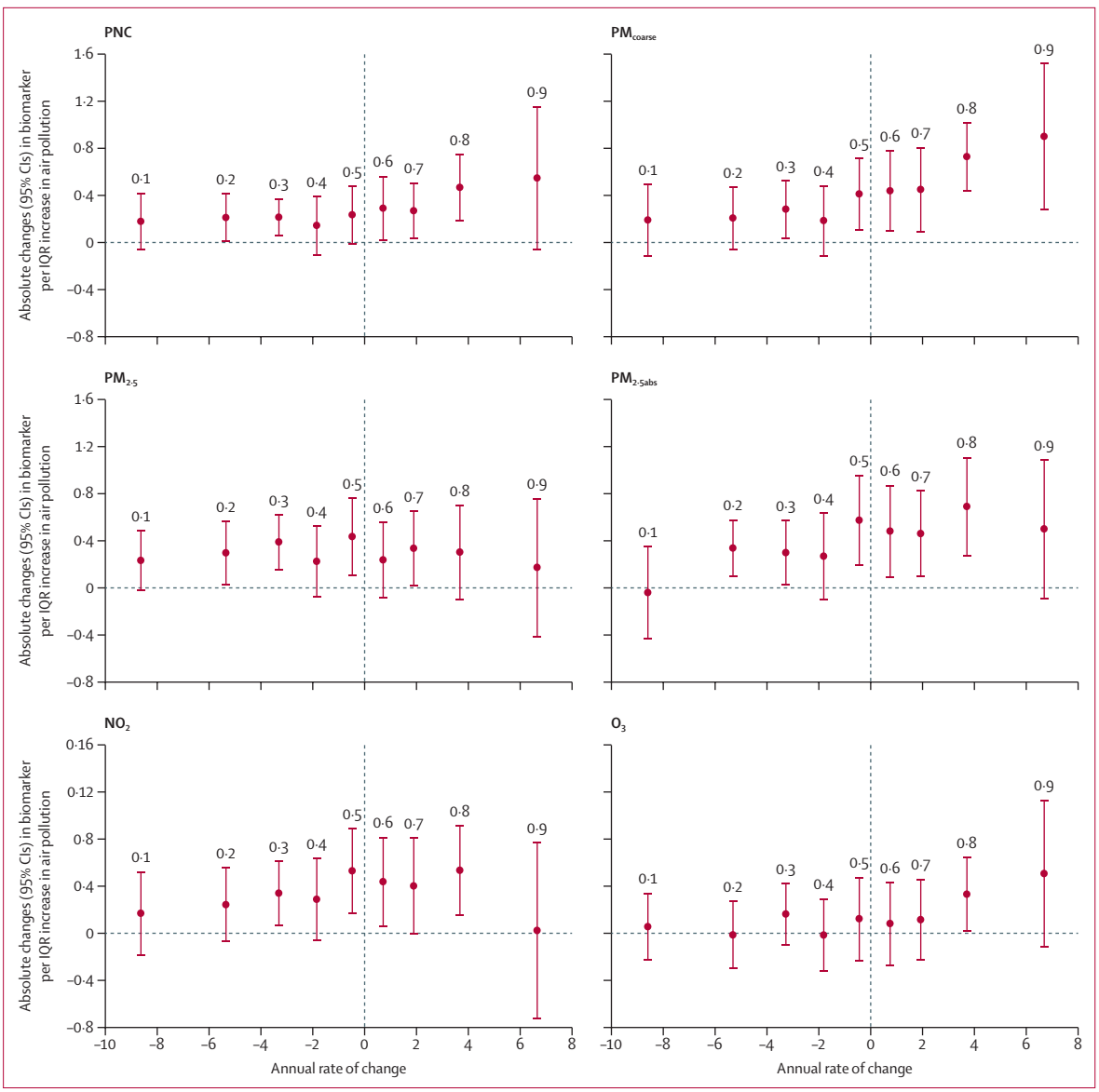

Figure 2: **Absolute changes (95% CIs) in the annual rate of change in HOMA-B at deciles of the distribution per IQR increase in air pollutant concentrations**
Quantile regression models for the annual rate of change were adjusted for baseline levels of the investigated biomarker, age (baseline), sex, BMI (baseline), annual rate of change in BMI, educational attainment (baseline), occupational status (baseline), smoking status and pack-years (baseline), annual rate of change in smoking pack-years, physical activity (baseline), and an indicator for the visits used in the calculation of the rate of change. Area on the left side of the dashed line indicates decreasing insulin secretion over years (annual rate of change below zero); area on the right side of the dashed line indicates increasing insulin secretion over years (annual rate of change above zero). Values (ie, 0·1–0·9) above the error bars indicate deciles of the distribution of the annual rate of change. An IQR increase was $2·0 \times 10^3$/cm^3 for PNC, 1·4 μg/m^3 for PM$_{coarse}$, 1·4 μg/m^3 for PM$_{2·5}$, $0·3 \times 10^{-5}$/m for PM$_{2·5abs}$, 7·1 μg/m^3 for NO$_2$, and 3·5 μg/m^3 for O$_3$. HOMA-B=homeostasis model assessment of β-cell function. PNC=particle number concentration. PM$_{coarse}$=particulate matter with an aerodynamic diameter of 2·5–10 μm. PM$_{2·5abs}$=PM$_{2·5}$ absorbance. NO$_2$=nitrogen dioxide. O$_3$=ozone.

The associations of particles and NO$_2$ with repeated measurements of HOMA-IR, HOMA-B, and fasting insulin were significantly stronger among participants who were older than 60 years, male, or not employed, and suggestively stronger among physically inactive individuals (appendix pp 18–19). Males also showed higher susceptibility to air pollution effects on fasting glucose. For the annual rate of change, we observed stronger associations of particles and NO$_2$ with HOMA-IR, fasting insulin, and fasting glucose (rate values above zero) among older adults, and with HOMA-IR, HOMA-B, and fasting insulin among males and participants with prediabetes or diabetes (examples in the appendix pp 20–21). No effect modification was found for other potential modifiers (data not shown).

In terms of sensitivity analysis, the associations of particles and NO$_2$ with repeated measurements of biomarkers were robust to additional adjustment for O$_3$,

and vice versa (appendix p 22). Adjustment for $PM_{2·5}$ attenuated the effect estimates of other particles, and the effect estimates of $PM_{2·5}$ slightly decreased after including PM_{coarse} and $PM_{2·5abs}$. For the annual rate of change, the effect estimates of $PM_{2·5}$ were attenuated by adjustment for PNC, PM_{coarse}, and $PM_{2·5abs}$. The other associations remained stable in two-pollutant models (appendix pp 23–26).

Associations between air pollution and biomarkers were generally robust in sensitivity analyses (appendix pp 27, 29–32). However, air pollution effects on repeated measurements of HOMA-IR and HOMA-B substantially decreased when controlled for fasting insulin (appendix p 28). Additionally, further adjustment for road traffic noise and NDVI increased the effects of air pollution on the annual rate of change in HOMA-IR, fasting insulin, and fasting glucose. Excluding observations with fasting insulin in KORA S4 that were higher than the 90th percentile attenuated effects on the annual rate of change in fasting insulin at specific percentiles.

Discussion

In this longitudinal study with biomarkers measured up to three times, participants exposed to elevated particulate matter, NO_2, and O_3 had higher levels of HOMA-IR, HOMA-B, and fasting insulin. Moreover, we observed positive associations between air pollution and the annual rate of change in HOMA-IR, HOMA-B, and fasting insulin over time. No significant associations were found between air pollution and fasting glucose in the whole study population. Participants who were older than 60 years, male, not employed, physically inactive, or who had prediabetes or diabetes were potentially more susceptible to the effects of air pollution on the investigated biomarkers.

Insulin resistance is characterised by a lower response of tissues to insulin stimulation and is usually measured as impaired insulin-stimulated skeletal muscle glucose uptake and glycogen synthase activity.[22] It has an important role in the development of type 2 diabetes and is also associated with higher incident cardiovascular disease.[23] Our finding of positive associations between air pollution and HOMA-IR and fasting insulin levels suggest an air pollution-related decrease in insulin sensitivity. Consistent findings were reported in our previous cross-sectional analyses[10] on data from KORA F4, as well as among children and adolescents in two German birth cohorts[8,9] and a US childhood obesity study,[12] and among Mexican-American adults with higher risks of type 2 diabetes.[13] However, other long-term exposure studies did not find significant associations between air pollution and insulin sensitivity, including the Framingham Heart Study[15] and the Meta-AIR study.[24] The mixed results could be partly due to different population susceptibility. Studies have shown that children are more susceptible to adverse health effects of air pollution because of their higher minute ventilation, higher levels of physical activity, and dynamic developmental physiology.[25] Individuals with higher genetic risk of type 2 diabetes were also shown to be more susceptible to the effects of particulate matter on diabetes.[26] Moreover, effects on insulin sensitivity could vary across different air pollutants; for example, stronger effects have been observed for traffic-related exposure metrics than for $PM_{2·5}$.[15]

In addition, we observed positive associations of air pollution with the annual rate of change in HOMA-IR and fasting insulin, suggesting a faster deterioration of insulin sensitivity related to air pollution exposure. In the subgroup with increasing insulin sensitivity over time (annual rate of change below zero), which might be attributable to beneficial lifestyle changes, weight loss, or both, such positive associations indicate that elevated air pollution exposure could slow down the process of improvement. So far, air pollution effects on the change in insulin sensitivity were assessed only among 314 Latino children (8–15 years) in Los Angeles who were overweight or obese, showing that long-term exposure to $PM_{2·5}$ and NO_2 was associated with an increased decline in insulin sensitivity.[14] Our study replicated these findings among the general adult population, and further provided evidence for the heterogeneity of air pollutant effects across different degrees of change in insulin sensitivity.

Our study did not find associations between air pollution and fasting glucose, and the air pollution effects on HOMA-IR were attenuated only by further adjustment for fasting insulin. These findings indicate that the positive associations between air pollution and HOMA-IR are mainly driven by the air pollution-related increase in fasting insulin rather than fasting glucose. This conclusion is supported by the theory that impaired insulin sensitivity might first lead to an increase in insulin secretion to compensate for reduced insulin signalling and maintain normal glucose tolerance.[27] Therefore, our positive associations between air pollution and HOMA-B indicate increased fasting β-cell insulin secretion in response to impaired insulin sensitivity, rather than improved β-cell function.

Several mechanisms have been proposed whereby air pollution could potentially affect insulin sensitivity. For example, air pollution exposure has been shown to increase systemic levels of pro-inflammatory cytokines, such as tumour necrosis factor-α and interleukin-1. These cytokines could contribute to the development of insulin resistance by activating c-Jun N-terminal kinase, which inhibits insulin signalling through serine phosphorylation of insulin receptor substrate proteins.[28] In addition, $PM_{2·5}$ exposure was shown to induce pulmonary oxidative stress, thereby decreasing AKT and endothelial nitric oxide synthase phosphorylation, and impairing insulin signalling via the PI3-kinase–AKT pathway.[29,30] Moreover, air pollution-mediated over-activity of the sympathetic nervous system could further exacerbate insulin resistance.[31]

Our study identified subgroups with stronger responses to the effect of air pollution on insulin sensitivity. Such predisposition is determined by both intrinsic and external factors. The greater susceptibility of older adults has been frequently reported, which could be explained by declines in physiological processes (eg, reduced clearance of particulate matter) and a higher prevalence of pre-existing diseases that might confer increased risks for adverse health effects.[32] The sex-related difference in the effects of air pollution is potentially associated with sex-specific biological, social, or behavioural traits that could affect the deposition rate of pollutants and exposure patterns. Given the currently mixed evidence regarding effect modification by sex,[33] further investigation is needed to elucidate possible mechanisms. Stronger associations in participants with prediabetes or diabetes could be related to their chronic inflammatory state,[34] which might enhance the inflammatory response to air pollution.[26,35] Additionally, these participants might have a higher genetic risk of type 2 diabetes and thus be more susceptible to air pollution effects than individuals without diabetes.[26] The interpretation of effect modification should also consider the potential non-differential exposure misclassification, which has been proved to underestimate the effects of air pollution assessed at a residence. In our study, employed participants who commuted to their workplaces had a greater risk of exposure misclassification than participants who were not employed and were likely to spend more time around their residences, and thus smaller effect estimates were expected in employed individuals.

Our study used HOMA-IR rather than direct measures of insulin sensitivity, such as the glucose clamp technique and the minimal model assessment, in consideration of convenience and cost savings. Of note, HOMA-IR reflects fasting-state insulin sensitivity, whereas the dynamic tests reflect post-prandial insulin stimulated conditions. The limitations of HOMA-IR have been previously documented. For instance, Bergman and colleagues[36] reported that HOMA-IR did not measure the same genetic contribution to insulin resistance as is reflected in minimal model-based insulin sensitivity, but that it captured more in terms of environmental factors. Furthermore, differences related to ethnicity and sex have been found in the ability of HOMA-IR to predict insulin sensitivity.[37] However, several studies have shown a strong correlation between HOMA-IR and insulin sensitivity as determined by the glucose clamp in various populations ($r=-0{\cdot}82$; $p<0{\cdot}0001$ in one study;[38] $r=-0{\cdot}71$; $p<0{\cdot}01$ in another;[39] and $R_s=0{\cdot}88$; $p<0{\cdot}0001$ in a third study[40]). HOMA-IR has also been recently validated against the hyperinsulinaemic clamp in a German cohort and both tests identified groups of diabetes clusters.[41] In sum, HOMA-IR has developed as a reliable and practical measure of insulin sensitivity in comparable cohorts. In addition, it should be noted that HOMA-B only assesses fasting insulin secretion, and data for dynamic measures of insulin secretion, such as the insulinogenic index, were not available in our study.

The KORA cohort is a well characterised study with a standardised and comprehensive collection of individual information, which enhanced the reliability of our results. The longitudinal study design with repeated measurements of biomarkers strengthened statistical power and reduced potential residual confounding from unmeasured factors. In addition, the design enabled examination of the change of insulin sensitivity over time, which provided a better understanding of the longitudinal air pollution effects on the development of type 2 diabetes. Furthermore, the residential air pollutant concentrations, which were estimated using well defined LUR models, captured the spatial variation in exposure and enabled us to draw conclusions from consistent patterns across various air pollutants, reducing the risk of chance findings. The finding of associations between PNC and insulin sensitivity provide evidence for the adverse long-term health effect of ultrafine particles, which has been understudied so far.

One limitation of our study is that the air pollutant concentrations were estimated using spatial models for 2014–15. Although we believe that these exposure estimates are valid for the historical spatial contrasts, because previous studies have shown that the spatial variation in exposure remained stable over time,[42] we did not take into account the temporal variation in exposure. By applying back-extrapolated air pollution concentrations, we assessed the potential effect of temporal variation, and the robust results validated our exposure assessment approach. Second, we assigned air pollution concentrations to residential addresses and did not allow for the mobility of participants. This non-differential exposure misclassification might have biased the effect estimates towards the null. Third, we did not adjust for time-varying covariates other than BMI and smoking pack-years in the rate of change analysis, which might have resulted in residual confounding. Additionally, there could also be residual confounding by unmeasured factors.

In conclusion, our study suggests that long-term exposure to elevated air pollution was associated with decreased insulin sensitivity and a more pronounced deterioration (or less pronounced improvement) of insulin sensitivity over time, with compensatory increased insulin secretion. These findings support one underlying mechanism of the effects of air pollution on the development of type 2 diabetes in the general adult population. From a public health perspective, our study indicates that it would be beneficial to reduce air pollution exposure, in addition to making lifestyle interventions, to mitigate the health burden of type 2 diabetes.

Contributors

SZ and SM did the data analyses and wrote the manuscript. SZ, CHu, WR, CHe, AP, KW, and AS, have verified the underlying data. RP, SB, AP, KW, and AS were involved in the study design, results

interpretation, and review of the manuscript. AP provided oversight on the KORA study design. CHu, WK, WR, CHe, and MR were involved in the acquisition of the KORA data and reviewed the manuscript. JC and KW were involved in the measurement and modelling of the air pollution data. All authors read and approved the final manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

Data collected for the study, including de-identified individual participant data and a data dictionary defining each field in the set, are available on reasonable request. Study protocol and statistical analysis plan will be available on reasonable request. These data will be available with publication from the corresponding author (siqi.zhang@helmholtz-muenchen.de). Data will be shared by the following access criteria: with investigator support; after approval of a scientific research proposal; and with a signed data access agreement.

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