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Association Between Long-term Exposure to Air Pollution and Biomarkers Related to Insulin Resistance, Subclinical Inflammation, and Adipokines

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Insulin resistance (IR) is present long before the onset of type 2 diabetes and results not only from inherited and lifestyle factors but also likely from environmental conditions. We investigated the association between modeled long-term exposure to air pollution at residence and biomarkers related to IR, subclinical inflammation, and adipokines. Data were based on 2,944 participants of the KORA (Cooperative Health Research in the Region Augsburg) F4 study conducted in southern Germany (2006–2008). We analyzed associations between individual air pollution concentration estimated by land use regression and HOMA-IR, glucose, insulin, HbA_{1c}, leptin, and high-sensitivity C-reactive protein levels from fasting samples using multivariable linear regression models. Effect estimates were calculated for the whole study population and subgroups of individuals who did not have diabetes, had prediabetes, or had diabetes. Among all participants, a 7.9 $\mu g/m^3$ increment in particulate matter of <10 μm was associated with higher HOMA-IR (15.6% [95% CI 4.0; 28.6]) and insulin (14.5% [3.6; 26.5]). Nitrogen dioxide was associated with HOMA-IR, glucose, insulin, and leptin. Effect estimates for individuals with prediabetes were much larger and highly statistically significant, whereas individuals who did not have diabetes or had diabetes showed rather weak associations. No association was seen for HbA_{1c} level. Our results suggested an association between long-term exposure to air pollution and IR in the general population that was attributable mainly to individuals with prediabetes.

Insulin resistance (IR) is a condition that is characterized by decreased tissue sensitivity to the action of insulin. After an initial compensatory stage when increased insulin secretion compensates for the low insulin action, the following stage indicates rapidly rising glucose levels. At this stage, IR can be diagnosed as isolated impaired fasting glucose (i-IFG), isolated impaired glucose tolerance (i-IGT), or both IFG and IGT. IR has been shown to be associated with a high risk of the development of type 2 diabetes in later life (1,2) and is considered to be an independent predictor for type 2 diabetes and therefore is

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often referred to as a prediabetic state (3–5). However, diabetes will not develop in all insulin-resistant people.

In 2013, the International Diabetes Federation estimated a diabetes prevalence of ~8.3% (382 million people) worldwide, with type 2 diabetes accounting for ~85–95% of all cases of diabetes (6). Obesity (7,8) and certain gene variants (9) were associated with diabetes and may cause the disease. Further critical factors determining the susceptibility for diabetes may be poor nutrition and sedentary lifestyle (10). In recent years, air pollution has also been discussed as a potential risk factor for the onset of type 2 diabetes (11–15). Several reviews and a meta-analysis combined the epidemiological findings and quantified the risk increases for type 2 diabetes per 10 $\mu g/m^3$ increase in exposure between 5% and 27% for particulate matter (PM) $\leq$2.5μm in diameter ($PM_{2.5}$), 1–15% for PM $\leq$10μm in diameter (PM_{10}), and 1–11% for nitrogen dioxide (NO_2) (14,16–20), depending on the studies included. Still, the underlying mechanisms are not fully understood, although a number of plausible pathways have been suggested, including systemic inflammation, oxidative stress, and neuronal mechanisms (12,14,15,21). Recent studies (10,22–27) investigating air pollution and IR as a precursor state of type 2 diabetes showed positive associations. However, these studies were experimental, investigated short-term effects, or were focused on children.

With this cross-sectional analysis, we aimed to assess the associations between long-term exposure to air pollution at residence and biomarkers related to IR, subclinical inflammation, and adipokines *1*) in the general population and *2*) in individuals without diabetes, those with prediabetes, and individuals with diabetes. For all markers investigated, we hypothesized incremented levels in association with incremented air pollutant concentrations. We evaluated HOMA-IR, fasting glucose, fasting insulin, hemoglobin A_{1c} (HbA_{1c}) levels, as well as high-sensitivity C-reactive protein (hs-CRP) levels as established markers of inflammation. In addition, leptin was examined as adipokine, which has been suggested to be associated with IR (28). In terms of environmental stressors, we evaluated modeled long-term exposures to PM (PM_{10}, PM between 2.5 and 10 μm in diameter [PM_{coarse}], $PM_{2.5}$, and $PM_{2.5}$ absorbance), and nitrogen oxides based on measurements conducted in 2008/2009 as well as two traffic indicators.

RESEARCH DESIGN AND METHODS

Study Population

The current analysis is based on data collected within the Cooperative Health Research in the Region of Augsburg (KORA) F4 study conducted in the city of Augsburg and two adjacent rural counties (southern Germany) during 2006–2008.

Altogether, 3,080 participants of the KORA F4 study were invited to the study center in Augsburg, where they answered a computer-assisted personal interview and completed a self-administered questionnaire. All individuals were physically examined, and fasting blood samples were taken. Individuals without diabetes underwent an oral glucose tolerance test (OGTT) (29).

In the KORA F4 study, data on glucose metabolism were gathered as follows: previously diagnosed diabetes was defined as a validated physician diagnosis or current use of glucose-lowering agents; and newly diagnosed diabetes, i-IGT, i-IFG, and normal glucose tolerance were defined according to World Health Organization (WHO) 1999 diagnostic criteria (30) based on fasting and post-OGTT values. For definition, diagnosis, and classification of glucose metabolism, see Supplementary Table 1.

Because of missing address information (n = 20), missing information on glucose metabolism (n = 94), the nonfasting status of some individuals (n = 10), or missing information on the main confounders (n = 12), 136 participants had to be excluded. For subgroup analysis, we stratified the remaining number of 2,944 study participants into the following subgroups: *1*) people having no diabetes (nondiabetes group n = 2,125) with normal glucose tolerance; *2*) people representing a group without diabetes with conditions that are associated with IR (prediabetes group n = 496) with i-IFG, i-IGT, or IFG and IGT; and *3*) people who already have type 2 diabetes (diabetes group n = 323). Although diabetes will not develop in all individuals in whom IR has been diagnosed, for reasons of brevity and simplicity we named all individuals with diagnosable IR as the prediabetes group. More details on study design, sampling method, and data collection are provided elsewhere (31).

Outcome Definition

Blood was collected with minimal stasis, refrigerated at 4–8°C, and shipped in refrigerant packaging within 2–4 h to the laboratory of Augsburg Central Hospital. Fasting venous blood glucose was sampled in the morning (7:00 A.M. to 11:00 A.M.). All participants without diabetes were given a 75-g dose of anhydrous glucose (Dextro OGT; Boehringer Mannheim, Ingelheim, Germany), and another blood sample was collected after 2 h. Serum glucose was measured using a hexokinase method (GLU Flex; Dade Behring Marburg, Marburg, Germany). Insulin was determined using ELISA kits from Invitrogen (Camarillo, CA). As a surrogate of IR, the homeostatic model assessment was used and defined as HOMA-IR = (fasting insulin [μU/mL]) $\times$ (fasting glucose [mmol/L])/22.5 (32).

HbA_{1c} was measured with a reverse-phase, cation-exchange, high-performance liquid chromotography method (analyzer HA 8160; Menarini Group). Leptin concentrations were assessed using ELISA kits from Mercodia (Uppsala, Sweden). The measurement of hs-CRP was in anticoagulated plasma samples using a high-sensitivity latex-enhanced nephelometric assay on a BN II analyzer (Dade Behring), with intra-assay and interassay coefficients of variation of 2.7% and 6.3%, respectively.

Air Pollution Exposure

Residential exposure to ambient air pollution assessed as mean annual levels was estimated within the ESCAPE study (European Study of Cohorts for Air Pollution Effects [www.escapeproject.eu]). Air pollution measurements of PM_{10}, $PM_{2.5}$, NO_2, and the sum of NO_2 and nitrogen monoxides (NO_x) were collected at 20 (PM) and 40 (NO_x) monitoring sites for three periods of 2 weeks in the cold, warm, and one intermediate season during the period from October 2008 to July 2009. Land use regression (LUR) models were developed on the basis of annual average measurements and predictor variables like traffic, land use, industry, and population density derived from geographic information systems (33,34). These regression models were then applied to the residence addresses of study participants to assess individual long-term concentrations.

In addition to the modeled air pollution concentration, we considered two traffic indicators: *1*) traffic intensity on the nearest road (number of vehicles/day) and *2*) traffic load on major roads within 100 m of the residence (number of vehicles*meter/day), defined as the sum of traffic intensity on roads with >5,000 vehicles/day multiplied by the length of those roads in a 100 m buffer around the home addresses.

Covariates

As potential confounding factors might affect the different outcomes in different ways, we hierarchically optimized our confounder models for each outcome separately. First, we specified a minimum set of a priori defined covariates for all outcome variables, including age, sex, smoking status, BMI, waist-to-hip ratio (Spearman correlation coefficient with BMI was 0.52), and month of blood withdrawal. Second, we selected from several socioeconomic variables, as follows: occupational status, years of education, per capita income, and socioeconomic status (categorical variable combining education and income). In a third step, we offered further lifestyle-related variables: years and pack-years of smoking, physical activity, and alcohol intake. The selection in steps 2 and 3 was based on minimizing the Bayesian information criterion as it deals with the trade-off between the goodness-of-fit and the complexity of the model. For a detailed description of the covariates and the final confounder models, see Table 1 and Supplementary Table 2.

Statistical Analyses

We performed Pearson x^2 tests for categorical variables and Kruskal-Wallis tests for continuous variables to test for differences between the subgroups. Correlations between air pollutants and residential proximity to traffic were examined using Spearman correlation coefficients.

To assess the association between long-term residential exposure to air pollution and the biomarkers, we performed multivariable linear regression analyses. All outcomes were log transformed since residuals deviated from normality. We included the annual mean concentration of each air pollutant separately as a linear term in addition to the chosen covariates. Traffic variables were additionally adjusted for background NO_2 levels to investigate traffic effects independent of the background air pollution concentrations. To investigate potential effect modification by sex, we included an interaction term in the model. Results are presented as the percentage change of the geometric mean value per 5th − 95th percentile difference of the exposure concentrations and corresponding 95% CIs. Effect estimates were calculated separately for all participants, and for the nondiabetes, prediabetes, and diabetes subgroups. Tests of interaction were calculated for differences between subgroups (35).

As a sensitivity analysis, we applied a very basic confounder model including only sex, age, and BMI to verify whether the level of covariate adjustment was probably too high to detect an association. We used additive models incorporating separately each exposure variable as a cubic regression spline with 3 df to check the linearity of the dose-response function. In addition, we categorized the exposure variables into quartiles and alternatively ran quantile regression. Since an underlying systemic inflammation due to an acute infection might change markers of IR, we excluded study participants with an hs-CRP value >10 mg/L. To investigate the influence of glucose- and lipid-lowering medication, we excluded persons taking antidiabetic medications or statins. We also excluded persons who reported an intake of diuretics and/or β-blockers, as this type of medication may promote susceptibility for IR (36,37). To assess the sensitivity of our results to the influence of the degree of impaired glucose regulation, we stratified the prediabetes group into i-IFG (n = 113), i-IGT (n = 307), and IFG-IGT (n = 76) groups. Moreover, we stratified the diabetes group into persons with newly diagnosed diabetes (n = 113) and individuals with known type 2 diabetes (n = 210).

All statistical analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC) and R version 3.1.0 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Population

Table 1 shows the baseline characteristics of the 2,944 study participants. The mean age was 56.2 years, the mean BMI was 27.6 kg/m^2, and marginally more women participated. Participants with prediabetes and participants with diabetes, on average, were older, BMI was higher, and more usually male than participants without diabetes. In addition, they showed a lower prevalence of current smokers, but a higher prevalence of ex-smokers. Also, socioeconomic status and physical activity were in general lower for individuals with prediabetes and individuals with diabetes. The prevalence of hypertension, myocardial infarction, stroke, and medication intake were higher with worsened insulin sensitivity.

Table 1—Description of the study population: all participants and stratified by state of glucose metabolism

Variable	Missing values *N* (%)	All (*N* = 2,944) Arithmetic mean	(SD)	Nondiabetes (*N* = 2,125) Arithmetic mean	(SD)	Prediabetes (*N* = 496) Arithmetic mean	(SD)	Diabetes (*N* = 323) Arithmetic mean	(SD)	*P* value*
Age (years)		56.2	(13.1)	52.9	(12.5)	63.2	(11.0)	66.9	(9.4)	<0.001
BMI (kg/m^2)		27.6	(4.8)	26.6	(4.3)	29.7	(4.8)	31.3	(5.0)	<0.001
Waist-to-hip ratio		0.88	(0.09)	0.86	(0.08)	0.92	(0.08)	0.95	(0.07)	<0.001
Education (years)	5 (0.2)	11.8	(2.6)	12.0	(2.7)	11.3	(2.5)	11.0	(2.4)	<0.001
Per capita income (€)	109 (3.7)	1,120	(576)	1,133	(593)	1,105	(593)	1,054	(562)	0.058
Smoking (years)	8 (0.3)	13.1	(15.3)	12.6	(14.6)	13.2	(15.7)	16.9	(18.4)	0.003
Pack-years of smoking (total pack-years smoked)	81 (2.8)	11.6	(19.2)	10.2	(16.1)	12.1	(19.6)	19.9	(31.7)	0.002
Alcohol intake (g/day)		14.4	(19.6)	14.1	(18.9)	15.4	(19.8)	15.0	(23.6)	0.149
		N	(%)	*N*	(%)	*N*	(%)	*N*	(%)	*P* value*
Male sex		1,424	(48.4)	969	(45.6)	262	(52.8)	193	(59.8)	<0.001
Smoking status										
Current		522	(17.7)	437	(20.6)	46	(9.3)	39	(12.1)	<0.001
Ex		1,195	(40.6)	811	(38.2)	222	(44.8)	162	(50.2)	<0.001
Never		1,227	(41.7)	877	(41.3)	228	(46.0)	122	(37.8)	
Occupational status										
Employed/self-employed		1,483	(50.4)	1,265	(59.5)	165	(33.3)	53	(16.4)	<0.001
Unemployed		60	(2.0)	43	(2.0)	7	(1.4)	10	(3.1)	
Homemaker		304	(10.3)	242	(11.4)	42	(8.5)	20	(6.2)	
Retired		1,097	(37.3)	575	(27.1)	282	(56.9)	240	(74.3)	
Socioeconomic status†										
Low	114 (3.9)	915	(32.3)	658	(32.2)	149	(31.5)	108	(34.6)	0.002
Medium		853	(30.1)	584	(28.6)	153	(32.3)	116	(37.2)	
High		1,062	(37.5)	803	(39.3)	171	(36.2)	88	(27.2)	
Physical activity										
Low		945	(32.1)	597	(28.1)	193	(38.9)	155	(48.0)	<0.001
Medium		1,277	(43.4)	958	(45.1)	204	(41.1)	115	(35.6)	
High		722	(24.5)	570	(26.8)	99	(20.0)	53	(16.4)	
History of										
Hypertension	4 (0.1)	1,124	(38.2)	584	(27.5)	281	(56.7)	259	(80.2)	<0.001
Myocardial infarction		76	(2.6)	26	(1.2)	19	(3.8)	31	(9.6)	<0.001
Stroke		58	(2.0)	30	(1.4)	11	(2.2)	17	(5.3)	<0.001

Continued on p. 3318

Table 1—Continued

Variable	Missing values	All (*N* = 2,944)		Nondiabetes (*N* = 2,125)		Prediabetes (*N* = 496)		Diabetes (*N* = 323)		*P* value*
	N (%)	*N*	(%)	*N*	(%)	*N*	(%)	*N*	(%)	
Medication intake										
Antidiabetics	2 (0.1)	155	(5.3)					155	(48.0)	
Insulin	2 (0.1)	41	(1.4)					41	(12.7)	
Oral antidiabetic agents	2 (0.1)	139	(4.7)					139	(43.0)	
Statins	2 (0.1)	352	(12.0)	176	(8.3)	74	(14.9)	102	(31.6)	<0.001
Antihypertensive agents		899	(30.5)	430	(20.2)	232	(46.8)	237	(73.4)	<0.001
Diuretics		517	(17.6)	228	(10.7)	139	(28.0)	150	(46.4)	<0.001
β-Blocker		551	(18.7)	253	(11.9)	152	(30.6)	146	(45.2)	<0.001
Calcium channel blocker	1 (0.0)	231	(7.9)	100	(4.7)	63	(12.7)	68	(21.1)	<0.001
ACE inhibitor	1 (0.0)	388	(13.2)	162	(7.6)	99	(20.0)	127	(39.3)	<0.001
Angiotensin receptor blocker	2 (0.1)	219	(7.4)	121	(5.7)	50	(10.1)	48	(14.9)	<0.001
Cortisone	2 (0.1)	41	(1.4)	27	(1.3)	6	(1.2)	8	(2.5)	0.208

*Kruskal-Wallis rank sum test (for continuous variables) or Pearson χ^2 test (for categorical variables) to test for differences between the subgroups. †Sum of "education in categories" (1, <10 years of education; 2, ≥10 years of education but not university degree; 3, university degree) and "per capita income in tertiles" (1, lower; 2, medium; 3, upper): low (sum = 2 or 3), medium (sum = 4); high: (sum = 5 or 6).

Plasma concentrations of the six selected biomarkers are described in Table 2 by the arithmetic mean and SD as well as the geometric mean. Significant differences were found for all markers between study groups. All considered blood markers showed higher concentrations with deteriorating glucose metabolism.

Long-term Air Pollution

The distribution of modeled annual average concentrations of air pollutants and traffic indicators at participants' residences can be found in Table 3. Air pollution concentrations were below European Union limits (European Union Directive 2008/50/EC) but exceeded WHO recommendations (38). Correlations between air pollution and traffic indicators were only low to moderate. There were no significant differences in the exposure levels between the three subgroups (Supplementary Table 3).

Association Between Long-term Air Pollution and Biomarkers Related to IR

Tables 4 and 5 show the associations between long-term residential exposure to air pollutants, traffic indicators, and biomarkers related to IR. Among all study participants, exposure to NO_2 was significantly positively associated with HOMA-IR, glucose, insulin, and leptin levels. Also, PM_{10}, PM_{coarse}, $PM_{2.5}$ absorbance, and NO_x showed a positive association with HOMA-IR and insulin, whereas $PM_{2.5}$ was borderline significant for glucose. Both traffic indicators were not significantly associated with any of the blood markers.

For individuals without diabetes, exposure to NO_x was associated with HOMA-IR, glucose, and insulin, whereas NO_2 was associated with leptin. Among people with diabetes, the only significant association was seen between traffic load on major roads within 100 m from the residence and glucose levels.

The group of individuals with prediabetes yielded the strongest association with highest effect estimates. In this group, HOMA-IR was associated with all air pollutants except $PM_{2.5}$ and traffic load on major roads within 100 m. With HOMA-IR being the product of fasting glucose and insulin, regression results between air pollutants and insulin mainly replicated the associations found for HOMA-IR, whereas glucose was associated only with traffic load on major roads. Further associations were seen for leptin with all air pollutants (Table 5). Results in the prediabetes subgroup may indicate some underlying systemic inflammatory processes. Our effect estimates for hs-CRP pointed in this direction because most air pollutants were significantly associated with higher percentage changes in hs-CRP in individuals with prediabetes (Table 5).

The investigation of sex as effect modifier did not reveal any significant differences between men and women (data not shown).

Sensitivity Analyses

The reduction of covariate adjustment led to similar results (Supplementary Tables 4 and 5). We checked the

linearity of the dose-response function by including the air pollutants as cubic regression splines exemplarily for HOMA-IR in the prediabetes group. All air pollutants indicated no clear deviation from linearity when incorporated as a smooth function in the model (Supplementary Fig. 1). Also, the categorical analyses comparing the quartiles of exposure generally confirmed the linear trend except for PM_{coarse} and $PM_{2.5}$ in the prediabetes group, and the diabetes group that showed no clear pattern, potentially due to the reduced power (Supplementary Fig. 2). The alternative quantile regression indicated no clear heterogeneity across the deciles (Supplementary Fig. 3*A–D*). When excluding participants with hs-CRP >10 mg/L (n = 97), results were robust for all participants (data not shown). In the prediabetes group, effect estimates were slightly attenuated for HOMA-IR, insulin, and leptin. For the latter, the association with PM_{10}, PM_{coarse}, and $PM_{2.5}$ was not significant anymore. For HOMA-IR, the $PM_{2.5}$ estimate was slightly higher and significant for individuals with prediabetes and individuals with diabetes (data not shown).

The exclusion of 155 participants who reported an intake of antidiabetic medication showed quite robust estimates for all participants (Fig. 1, exemplarily shown for NO_2). Estimates for the diabetes group changed considerably because the exclusion affected almost half of the participants, resulting in lower estimates for glucose and HbA_{1c} levels, but higher estimates for HOMA-IR, insulin, leptin, and hs-CRP levels. The exclusion of 352 participants taking statins slightly attenuated the estimates for HOMA-IR, glucose, and insulin levels (Supplementary Fig. 4, exemplarily shown for NO_2). Leptin and hs-CRP estimates were generally robust but were higher for the diabetes group, resulting in significant estimates for NO_2.

The exclusion of 762 study participants taking diuretics and/or β-blockers (with 306 who reported an intake of both) showed robust effect estimates for all participants, but showed attenuated estimates for glucose as well as for glucose and insulin in individuals without diabetes. In the prediabetes group, effect estimates for leptin and hs-CRP were not significant anymore (data not shown). The stratification of the prediabetes subgroup into individuals with i-IFG, i-IGT, or IFG-IGT showed in general higher percentage changes for persons with i-IFG and i-IGT, especially for HOMA-IR, insulin, and hs-CRP (Fig. 2, exemplarily shown for HOMA-IR). For leptin, only participants with i-IGT showed an association (data not shown). The stratification of the diabetes subgroup into participants with newly diagnosed diabetes and individuals with known type 2 diabetes for HOMA-IR showed significant associations for almost all exposures for the first strata but no association for the second strata (Fig. 3).

DISCUSSION

We examined the association between residential long-term exposure to air pollutants and traffic indicators on biomarkers related to IR, subclinical inflammation, and

Table 2—Plasma concentrations of blood markers for all participants and stratified by state of glucose metabolism

	All (N = 2,944)			Nondiabetes (N = 2,125)			Prediabetes (N = 496)			Diabetes (N = 323)			
Blood markers	N	Arithmetic mean (SD)	Geometric mean	N	Arithmetic mean (SD)	Geometric mean	N	Arithmetic mean (SD)	Geometric mean	N	Arithmetic mean (SD)	Geometric mean	P value*
HOMA-IR	2,928	2.3 (8.7)	1.1	2,114	1.6 (6.0)	0.9	492	3.6 (14.8)	1.8	322	5.1 (10.2)	2.8	<0.001
Glucose (mg/dL)	2,944	98.3 (19.1)	96.9	2,125	91.7 (7.6)	91.4	496	103.3 (11.1)	102.7	323	133.7 (34.4)	130.1	<0.001
Insulin (μIU/mL)	2,928	9.0 (34.6)	4.7	2,114	6.9 (26.0)	3.9	492	13.9 (59.2)	7.1	322	15.7 (31.9)	8.6	<0.001
HbA_{1c} (%)†	2,943	5.6 (0.6)	5.5	2,125	5.4 (0.3)	5.4	496	5.7 (0.3)	5.6	322	6.6 (1.1)	6.5	<0.001
HbA_{1c} (mmol/mol)‡	2,943	37.1 (6.6)	36.6	2,125	35.1 (3.3)	34.9	496	38.2 (3.7)	38.1	322	48.7 (11.8)	47.6	<0.001
Leptin (ng/mL)	2,929	18.9 (20.4)	11.1	2,116	16.4 (18.4)	9.5	493	23.3 (21.2)	15.2	320	28.8 (27.1)	18.9	<0.001
hs-CRP (mg/L)	2,929	2.5 (5.4)	1.2	2,116	2.0 (3.4)	1.0	491	3.2 (4.6)	1.8	322	4.9 (12.1)	2.3	<0.001

*Kruskal-Wallis rank sum test to test for differences between the subgroups. †Expressed as % according to National Glycohemoglobin Standardization Program/Diabetes Control and Complications Trial (NGSP/DCCT): HbA_{1c} (%) = (HbA_{1c}/Hb) × 91.48 + 2.15. §For mmol/mol according to International Federation of Clinical Chemistry and Laboratory Medicine (IFCC): HbA_{1c} (mmol/mol) = (HbA_{1c}/Hb) × 1,000.

Table 3—Annual average concentrations of air pollutants and traffic indicators and corresponding Spearman correlation coefficients (*N* = 2,944)

	Descriptives					Spearman correlation coefficients					
Exposure	Mean	SD	5%	Median	95%	PM_{10}	PM_{coarse}	$PM_{2.5}$	$PM_{2.5}$abs	NO_x	NO_2
PM_{10} ($\mu g/m^3$)	20.4	(2.4)	16.5	20.5	24.4	1					
PM_{coarse} ($\mu g/m^3$)	6.2	(1.1)	4.9	6.1	8.4	0.76	1				
$PM_{2.5}$ ($\mu g/m^3$)	13.6	(0.9)	12.5	13.4	15.3	0.43	0.32	1			
$PM_{2.5}$abs (10^{-5}/m)	1.7	(0.2)	1.5	1.7	2.0	0.67	0.84	0.48	1		
NO_x ($\mu g/m^3$)	32.7	(7.2)	23.9	31.4	46.7	0.69	0.85	0.48	0.76	1	
NO_2 ($\mu g/m^3$)	18.8	(3.8)	13.8	18.3	25.6	0.67	0.79	0.45	0.66	0.92	1
Traffic intensity on the nearest road (vehicles/day), per 1,000	1.6	(3.2)	0.5	0.5	8.1	0.13	0.19	0.22	0.20	0.26	0.26
Traffic load within 100 m on major roads (vehicles*meter/day), per 10,000	40.7	(102.3)	0.0	0.0	243.6	0.27	0.33	0.30	0.42	0.39	0.37

Current European air quality standards (1-year average): 40 $\mu g/m^3$ (PM_{10}); 25 $\mu g/m^3$ ($PM_{2.5}$); 40 $\mu g/m^3$ (NO_2). WHO recommendations (1-year average): 20 $\mu g/m^3$ (PM_{10}); 10 $\mu g/m^3$ ($PM_{2.5}$); 40 $\mu g/m^3$ (NO_2). $PM_{2.5}$abs, soot content (absorbance) of $PM_{2.5}$.

adipokines in a cross-sectional study conducted in the region of Augsburg, in southern Germany. Among all study participants, we found a positive association between PM_{10}, PM_{coarse}, $PM_{2.5}$ absorbance, NO_x, and NO_2, and HOMA-IR and insulin levels. Furthermore, NO_2 was significantly associated with glucose and leptin. When stratifying by glucose tolerance, most pollutants were statistically significant in association with HOMA-IR, insulin, leptin, and hs-CRP in the prediabetes subgroup. Individuals with or without diabetes showed, rather, no or only weak associations between air pollution and blood markers.

Sensitivity analyses suggested in general robust results for all participants and for most of the subgroup analyses. However, medication intake seemed to play a complex role, especially for the diabetes subgroup. Thus, the exclusion of participants taking glucose-lowering medication (diabetes group only) led to higher air pollution estimates for HOMA-IR, insulin, leptin, and hs-CRP levels, but lower estimates for glucose and HbA_{1c} levels. Estimates in this group were also higher for leptin and hs-CRP levels when excluding persons taking statins, whereas results were robust for the group without diabetes and the prediabetes group. This might indicate a mitigating or inhibiting role of this medication type with regard to inflammatory effects of air pollution in patients with diabetes, whereas healthy individuals may not be as susceptible to inflammation as individuals with metabolic disorders. Also, the stratification into participants with newly diagnosed diabetes and those with known type 2 diabetes pointed in this direction, suggesting an increased susceptibility of the first subgroup to air pollution exposure that has not been properly medicated. The exclusion of individuals with diuretic and/or β-blocker intake mainly affected the results of the prediabetes group, leading to nonsignificant estimates for all air pollutants in association with leptin and hs-CRP levels.

The first studies on adverse the health effects of ambient air pollution mainly looked at respiratory outcomes and somewhat later on cardiovascular outcomes (39,40). Recent research also suggested a link between air pollution and type 2 diabetes involving multiple pathophysiological pathways (11,12,15). Several reviews and meta-analyses (14–20) have been published since, mainly referring to the same studies. However, the pooled effect estimates varied to some extent, depending on the inclusion and exclusion criteria. As the number of eligible studies is quite sparse, the meta-analyses usually combined prevalent and incident diabetes and could not distinguish between type 1 and type 2 diabetes. Thus, clear evidence is still limited because of differences in outcome definition, exposure metrics, population characteristics, and the covariates that were considered (14). As IR is a powerful predictor of the future development of type 2 diabetes, it came into focus in several recent epidemiological studies on air pollution (10,24–27,41). However, these studies either investigated short-term effects or focused on children, and, thus, are not directly comparable to our study. Short- and long-term effects of air pollution are hypothesized to arise partly from different biological pathways, and recent epidemiological evidence showed that the adverse health effects of long-term exposure are generally larger than those observed for short-term exposure (42). In addition, studies among children might be more pronounced due to the children being more vulnerable to environmental stressors. To the best of our knowledge, this is the first study investigating the long-term effects of air pollution in association with biomarkers of IR in the general population.

A German study by Teichert et al. (41) used data that were partly comparable to ours; however, they applied a different approach to assess the association between long-term exposure to air pollution, subclinical inflammation, and impaired glucose metabolism in 363 women. The authors stratified the women by impaired (defined as i-IFG or previous diagnosis of type 2 diabetes by a physician) versus normal glucose metabolism and compared

Table 4—Association between long-term air pollutants, traffic indicators, and biomarkers

		All	Nondiabetes	Prediabetes		Diabetes	
Pollutant Exposure	Increment†	% Change (95% CI)	% Change (95% CI)	% Change (95% CI)	*P* value‡	% Change (95% CI)	*P* value§
HOMA-IR							
PM_{10} ($\mu g/m^3$)	7.9	**15.6 (4.0; 28.6)**	10.4 (−1.8; 24.1)	**45.9 (12.8; 88.8)**	0.027	3.5 (−29.2; 51.1)	0.374
PM_{coarse} ($\mu g/m^3$)	3.6	**18.8 (6.6; 32.4)**	11.1 (−1.5; 25.3)	**68.7 (30.8; 117.7)**	0.002	13.5 (−22.2; 65.5)	0.458
$PM_{2.5}$ ($\mu g/m^3$)	2.8	9.7 (−1.3; 21.9)	0.6 (−10.7; 13.2)	26.8 (−0.8; 62.1)	0.048	38.6 (−2.1; 96.4)	0.044
$PM_{2.5}$abs (10^{-5}/m)	0.5	**13.2 (2.9; 24.6)**	7.6 (−3.1; 19.5)	**61.3 (28.1; 103.0)**	0.001	0.1 (−28.6; 40.4)	0.345
NO_x ($\mu g/m^3$)	22.9	**21.2 (9.4; 34.3)**	**12.4 (0.4; 25.8)**	**78.1 (39.6; 127.3)**	0.000	23.2 (−14.5; 77.5)	0.319
NO_2 ($\mu g/m^3$)	11.9	**19.2 (7.7; 31.8)**	9.2 (−2.3; 22.1)	**73.1 (36.1; 120.1)**	0.000	24.9 (−12.6; 78.5)	0.241
Traffic intensity on the nearest road (vehicles/day), per 1,000	7.5	−5.6 (−13.0; 2.4)	−6.8 (−14.7; 1.7)	16.3 (−5.4; 43.0)	0.026	−9.1 (−34; 25.3)	0.443
Traffic load within 100 m on major roads (vehicles*meter/day), per 10,000	243.6	6.9 (−1.2; 15.6)	0.6 (−7.4; 9.4)	**50.6 (22.4; 85.5)**	0.000	28.0 (−6.4; 75)	0.072
Glucose							
PM_{10} ($\mu g/m^3$)	7.9	1.0 (−0.7; 2.6)	0.6 (−0.4; 1.7)	0.2 (−2.9; 3.4)	0.389	0.3 (−7.7; 9.0)	0.468
PM_{coarse} ($\mu g/m^3$)	3.6	1.4 (−0.3; 3.1)	0.9 (−0.2; 1.9)	1.3 (−1.9; 4.5)	0.405	4.4 (−3.9; 13.5)	0.207
$PM_{2.5}$ ($\mu g/m^3$)	2.8	**1.6 (0.0; 3.3)**	0.8 (−0.3; 1.8)	1.9 (−1.1; 5.0)	0.248	0.4 (−7.0; 8.5)	0.468
$PM_{2.5}$abs (10^{-5}/m)	0.5	0.6 (−0.9; 2.1)	0.8 (−0.2; 1.7)	0.8 (−2.1; 3.7)	0.497	0.9 (−6.4; 8.6)	0.489
NO_x ($\mu g/m^3$)	22.9	1.3 (−0.3; 2.9)	**1.0 (0.0; 2.0)**	2.2 (−0.8; 5.3)	0.239	2.6 (−5.3; 11.2)	0.353
NO_2 ($\mu g/m^3$)	11.9	**1.7 (0.1; 3.3)**	0.9 (−0.1; 1.9)	2.4 (−0.6; 5.5)	0.184	3.5 (−4.3; 11.9)	0.267
Traffic intensity on the nearest road (vehicles/day), per 1,000	7.5	−0.2 (−1.5; 1.0)	0.7 (−0.1; 1.4)	1.0 (−1.5; 3.6)	0.408	−0.7 (−7.5; 6.6)	0.357
Traffic load within 100 m on major roads (vehicles*meter/day), per 10,000	243.6	0.3 (−0.9; 1.5)	−0.4 (−1.1; 0.3)	**3.3 (0.7; 6.0)**	0.004	**8.9 (1.6; 16.6)**	0.006
Insulin							
PM_{10} ($\mu g/m^3$)	7.9	**14.5 (3.6; 26.5)**	10.3 (−1.4; 23.4)	**44.5 (13.0; 84.7)**	0.025	0.0 (−29.8; 42.4)	0.302
PM_{coarse} ($\mu g/m^3$)	3.6	**17.8 (6.4; 30.5)**	11.0 (−1.0; 24.6)	**65.8 (30.1; 111.4)**	0.002	6.7 (−25.3; 52.4)	0.417
$PM_{2.5}$ ($\mu g/m^3$)	2.8	8.3 (−2.0; 19.6)	0.4 (−10.4; 12.6)	24.2 (−1.9; 57.1)	0.056	35.6 (−2.9; 89.4)	0.047
$PM_{2.5}$abs (10^{-5}/m)	0.5	**13.2 (3.4; 23.8)**	7.9 (−2.4; 19.4)	**59.1 (27.6; 98.4)**	0.001	−2.5 (−29.3; 34.5)	0.278
NO_x ($\mu g/m^3$)	22.9	**20.0 (8.9; 32.2)**	**11.9 (0.4; 24.7)**	**72.0 (36.4; 117.1)**	0.001	17.8 (−16.7; 66.5)	0.392
NO_2 ($\mu g/m^3$)	11.9	**17.2 (6.6; 29.0)**	8.5 (−2.5; 20.8)	**67.2 (32.8; 110.4)**	0.000	19.6 (−14.7; 67.8)	0.295
Traffic intensity on the nearest road (vehicles/day), per 1,000	7.5	−5.6 (−12.6; 2.1)	−7.7 (−15.2; 0.5)	14.7 (−5.9; 39.8)	0.024	−8.4 (−32.7; 24.7)	0.481
Traffic load within 100 m on major roads (vehicles*meter/day), per 10,000	243.6	6.4 (−1.3; 14.6)	1.0 (−6.8; 9.5)	**44.9 (18.5; 77.2)**	0.001	16.6 (−13.7; 57.5)	0.183

Data presented as the percentage change (95% CI) from geometric mean per 5th–95th percentile difference increment in air pollutants adjusted for age, sex, smoking, BMI, waist-to-hip ratio, month of blood withdrawal, and selected socioeconomic and lifestyle variables (see Supplementary Table 2). $PM_{2.5}$abs, soot content (absorbance) of $PM_{2.5}$. Boldface type indicates effect estimates were statistically significant, $P < 0.05$. †Corresponds to the difference between the 5th and 95th percentile of the corresponding exposure. ‡Test of interaction to test for differences between participants with prediabetes and participants without diabetes. §Test of interaction to test for differences between participants with and without diabetes.

Table 5—Association between long-term air pollutants, traffic indicators, and biomarkers

		All	Nondiabetes	Prediabetes		Diabetes	
Pollutant exposure	Increment†	% Change (95% CI)	% Change (95% CI)	% Change (95% CI)	*P* value‡	% Change (95% CI)	*P* value§
HbA_{1c}							
PM_{10} ($\mu g/m^3$)	7.9	0.5 (−0.5; 1.5)	0.3 (−0.4; 1.0)	−0.4 (−2.0; 1.2)	0.200	2.7 (−2.6; 8.4)	0.193
PM_{coarse} ($\mu g/m^3$)	3.6	0.1 (−0.9; 1.1)	0.1 (−0.6; 0.8)	−0.2 (−1.8; 1.4)	0.368	1.1 (−4.3; 6.7)	0.365
$PM_{2.5}$ ($\mu g/m^3$)	2.8	0.9 (−0.1; 1.9)	0.4 (−0.2; 1.1)	0.7 (−0.8; 2.3)	0.360	0.7 (−4.2; 5.8)	0.465
$PM_{2.5}$abs (10^{-5}/m)	0.5	−0.1 (−0.9; 0.8)	0.1 (−0.5; 0.7)	−0.4 (−1.9; 1.0)	0.248	0.1 (−4.6; 5.0)	0.494
NO_x ($\mu g/m^3$)	22.9	0.0 (−0.9; 1.0)	0.1 (−0.5; 0.8)	0.1 (−1.4; 1.7)	0.498	−0.5 (−5.6; 4.9)	0.413
NO_2 ($\mu g/m^3$)	11.9	0.2 (−0.8; 1.1)	0.2 (−0.4; 0.9)	0.3 (−1.3; 1.8)	0.483	−1.3 (−6.3; 3.9)	0.274
Traffic intensity on the nearest road (vehicles/day), per 1,000	7.5	−0.3 (−1.1; 0.5)	0.0 (−0.5; 0.5)	0.7 (−0.6; 2.0)	0.161	1.1 (−3.5; 5.9)	0.332
Traffic load within 100 m on major roads (vehicles*meter/day), per 10,000	243.6	−0.2 (−0.9; 0.5)	−0.3 (−0.7; 0.2)	0.7 (−0.6; 2.0)	0.090	2.6 (−1.9; 7.3)	0.107
Leptin							
PM_{10} ($\mu g/m^3$)	7.9	7.9 (−0.4; 17.0)	6.6 (−3.1; 17.3)	**20.2 (0.7; 43.5)**	0.122	−1.8 (−21.7; 23.0)	0.254
PM_{coarse} ($\mu g/m^3$)	3.6	6.5 (−1.9; 15.7)	3.6 (−6.1; 14.3)	**19.9 (0.4; 43.1)**	0.079	5.4 (−16.0; 32.2)	0.446
$PM_{2.5}$ ($\mu g/m^3$)	2.8	5.8 (−2.4; 14.6)	2.3 (−7.2; 12.7)	**18.8 (0.3; 40.7)**	0.066	9.5 (−11.5; 35.5)	0.282
$PM_{2.5}$abs (10^{-5}/m)	0.5	1.4 (−5.7; 9.1)	−1.2 (−9.3; 7.7)	**25.7 (7.1; 47.6)**	0.005	−8.4 (−25.4; 12.4)	0.251
NO_x ($\mu g/m^3$)	22.9	**12.6 (4.2; 21.7)**	8.1 (−1.4; 18.5)	**34.5 (13.6; 59.3)**	0.013	17.9 (−5.3; 46.7)	0.238
NO_2 ($\mu g/m^3$)	11.9	**15.3 (6.8; 24.5)**	**10.9 (1.3; 21.5)**	**29.3 (9.3; 52.9)**	0.058	23.7 (−0.1; 53.2)	0.180
Traffic intensity on the nearest road (vehicles/day), per 1,000	7.5	−3.8 (−9.6; 2.4)	−4.4 (−11.1; 2.7)	4.3 (−9.5; 20.3)	0.141	0.4 (−17.3; 22.0)	0.321
Traffic load within 100 m on major roads (vehicles*meter/day), per 10,000	243.6	−2.8 (−8.6; 3.3)	−3.0 (−9.6; 4.1)	3.3 (−10.8; 19.6)	0.225	5.0 (−13.2; 27.1)	0.222
hs-CRP							
PM_{10} ($\mu g/m^3$)	7.9	8.5 (−3.5; 22.0)	3.1 (−9.8; 17.9)	**35.7 (2.6; 79.5)**	0.041	3.3 (−31.3; 55.3)	0.497
PM_{coarse} ($\mu g/m^3$)	3.6	2.0 (−9.5; 15.0)	−3.9 (−16.3; 10.3)	**32.9 (0.5; 75.8)**	0.021	−0.5 (−33.9; 49.7)	0.437
$PM_{2.5}$ ($\mu g/m^3$)	2.8	8.4 (−3.6; 21.8)	5.4 (−8.0; 20.8)	9.7 (−16.1; 43.4)	0.396	21.3 (−17.4; 78.0)	0.250
$PM_{2.5}$abs (10^{-5}/m)	0.5	4.6 (−5.9; 16.3)	−0.3 (−11.6; 12.5)	21.7 (−5.6; 57.0)	0.083	15.7 (−19.9; 67.1)	0.226
NO_x ($\mu g/m^3$)	22.9	10.8 (−1.1; 24.1)	4.0 (−8.6; 18.4)	**35.2 (3.4; 76.8)**	0.042	24.2 (−16.4; 84.5)	0.202
NO_2 ($\mu g/m^3$)	11.9	11.1 (−0.6; 24.3)	1.1 (−11.1; 14.9)	**33.9 (2.7; 74.6)**	0.031	44.6 (−1.6; 112.6)	0.042
Traffic intensity on the nearest road (vehicles/day), per 1,000	7.5	3.8 (−5.2; 13.7)	0.5 (−9.2; 11.3)	8.3 (−13.8; 36.0)	0.279	27.5 (−10.3; 81.1)	0.101
Traffic load within 100 m on major roads (vehicles*meter/day), per 10,000	243.6	−1.2 (−9.4; 7.9)	−1.9 (−10.9; 8.1)	6.7 (−15.5; 34.7)	0.257	−4.0 (−32.1; 35.6)	0.452

Data are reported as the presented as percentage change (95% CI) from geometric mean per 5th–95th percentile difference increment in air pollutants adjusted for age, sex, smoking, BMI, waist-to-hip ratio, month of blood withdrawal, and selected socioeconomic and lifestyle variables (see Supplementary Table 2). $PM_{2.5}$abs, soot content (absorbance) of $PM_{2.5}$. Boldface type indicates effect estimates were statistically significant, $P < 0.05$. †Corresponds to the difference between the 5th and 95th percentiles of the corresponding exposure. ‡Test of interaction to test for differences between participants with prediabetes and those without diabetes. §Test of interaction to test for differences between participant with and without diabetes.

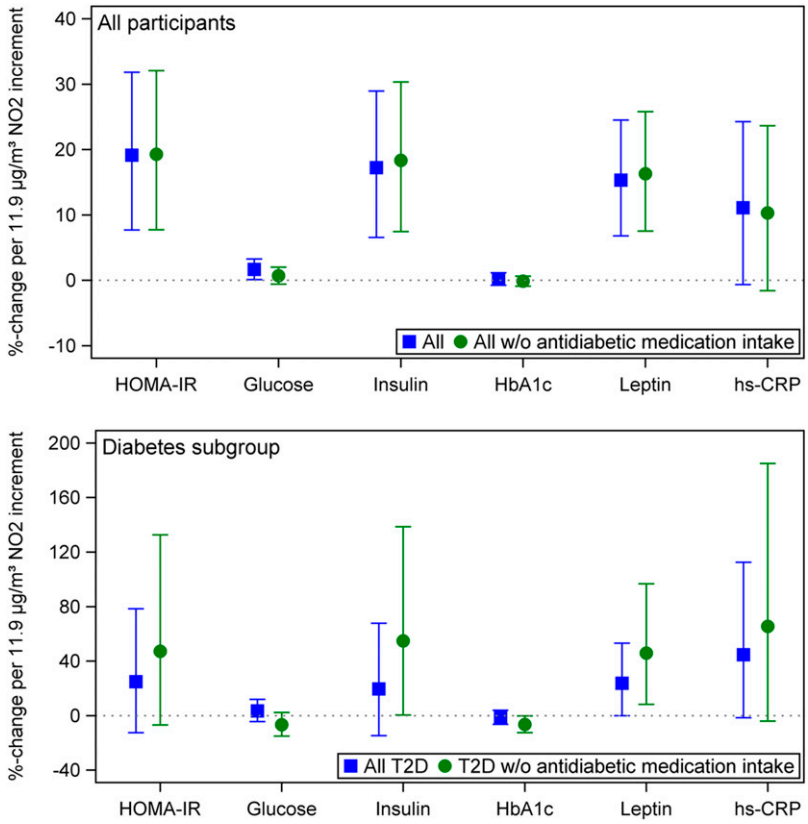

Figure 1—Association between NO_2 and biomarkers presented as the percentage change (%-change) (95% CI) from geometric mean per 11.9 $\mu g/m^3$ increment in NO_2 for all participants (top) and individuals with diabetes (bottom). Squares, NO_2 estimates for the whole group; circles, NO_2 estimates for participants without antidiabetic medication intake. Models were adjusted for age, sex, smoking, BMI, waist-to-hip ratio, month of blood withdrawal, and selected socioeconomic and lifestyle variables (see Supplementary Table 2). T2D, type 2 diabetes.

the risk differences in association with air pollution, 14 proinflammatory and anti-inflammatory immune mediators, and fasting glucose and insulin levels. The authors reported higher odds ratios for NO_2 and NO_x, but not for the PM fractions. Among all exposures investigated in our study, NO_2 and NO_x effect estimates were the most consistent and most pronounced, although we also observed an association for the coarse PM fraction. Similar to our analysis, the study by Thiering et al. (26) was based on long-term exposure estimates from the ESCAPE project. The authors looked at HOMA-IR in 397 10-year-old children in two prospective German birth cohort studies and observed increments of 17.0% (95% CI 5.0; 30.3) and 18.7% (95% CI 2.9; 36.9) for increments of 10.6 $\mu g/m^3$ in ambient NO_2 and 6.0 $\mu g/m^3$ in PM_{10}. Calderón-Garcidueñas et al. (27) matched 54 children living in the metropolitan area of Mexico City, who were thus chronically exposed to $PM_{2.5}$ and O_3 concentrations above the standards, with 26 control children and found significantly higher leptin and glucose levels in the first group, but no differences for insulin and HOMA-IR. Three studies on the short-term effects of air pollution conducted in highly selected populations reported higher levels of HOMA-IR in association with NO_2, PM_{10}, and $PM_{2.5}$ (10,24,25).

Regarding long-term air pollution and the incidence of type 2 diabetes, only five articles have been published so far (43–47). Although two studies from the U.S. (43,44) did not observe an association between diabetes incidence and long-term air pollution, Coogan et al. (47) reported a significant risk increase in association with NO_x, but not with $PM_{2.5}$, in a cohort of black women living in Los Angeles. A similar pattern was seen in our study, with rather significant estimates for NO_x, but rarely for $PM_{2.5}$. Also, a prospective study among women from the highly industrialized Ruhr district (western Germany) observed stronger associations with NO_2 than with PM_{10} (45). In addition, significant associations were seen for $PM_{2.5}$ absorbance and proximity to major roads, which were also associated with elevated levels of markers related to IR in our analysis. A further study from the Ruhr area (46) reported higher effect estimates for PM_{10} compared with $PM_{2.5}$, which was similar to our results.

Biological Mechanism

Potential pathways between air pollution and adverse cardiometabolic changes may occur through a multitude of mechanisms. Liu et al. (11) compiled a comprehensive evaluation of potentially underlying biological mechanisms

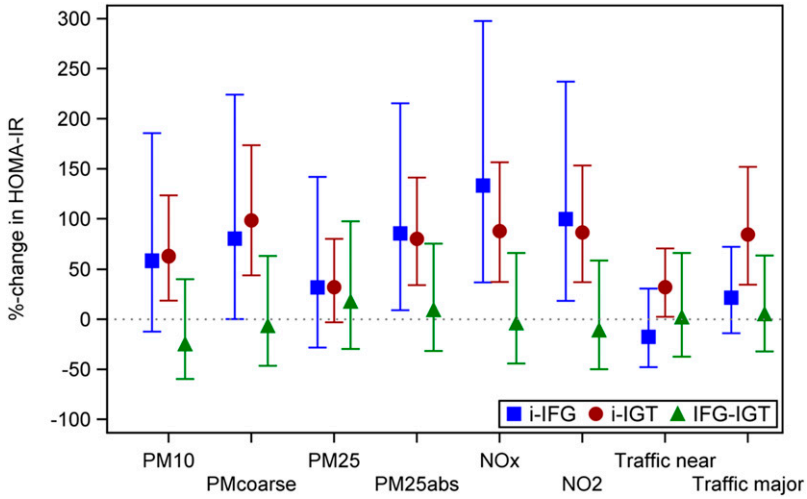

Figure 2—Associations between air pollutants, traffic indicators, and HOMA-IR presented as the percentage change (%-change) (95% CI) from geometric mean per 5th–95th percentile difference in air pollutants among participants with prediabetes stratified by subgroup of i-IFG (squares, *N* = 110), i-IGT (circles, *N* = 298), and IFG-IGT (triangles, *N* = 73). *N* represents the number of observation finally used for the analysis with HOMA-IR. Models were adjusted for age, sex, smoking, BMI, waist-to-hip ratio, month of blood withdrawal, and pack-years smoked. $PM_{2.5}$abs, soot content (absorbance) of $PM_{2.5}$; traffic major, traffic load within 100 m on major roads; traffic near, traffic intensity on the nearest road.

linking air pollution and IR/type 2 diabetes, including pulmonary and systemic inflammation, endoplasmic reticulum stress, alterations in glucose and lipid metabolism, and activation of the central nervous system, among others. Alveolar macrophages and bronchial epithelial cells are initial cellular sensors of PM. These sensors do not react on PM per se but more on biological components intrinsic to PM, such as lipopolysaccharide (LPS), which has a lower concentration in $PM_{2.5}$ than in PM_{10} (11). LPS-binding protein, a soluble acute-phase protein that binds to bacterial LPS, has been found to be associated with obesity, metabolic syndrome, and type 2 diabetes (48). This might be a possible explanation for the higher effect estimates we and others observed for PM_{10} and PM_{coarse} compared with $PM_{2.5}$.

Strengths and Limitations

The major strengths of this study are the well-characterized nature of the KORA F4 cohort, the standardized and

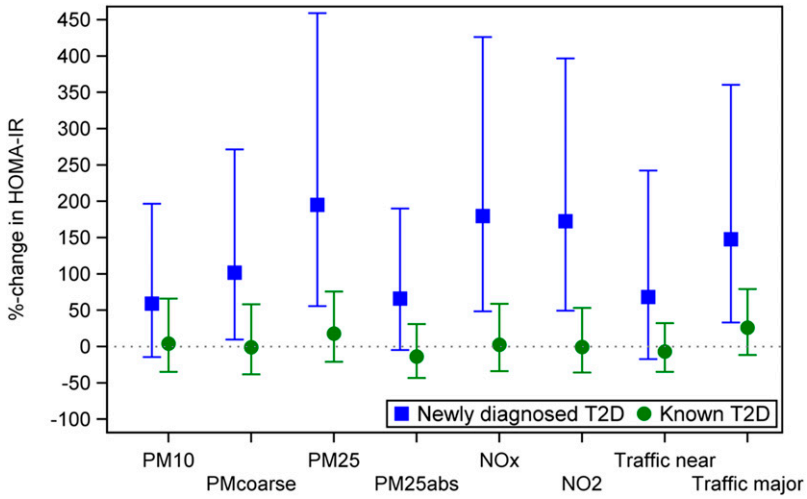

Figure 3—Association between air pollutants, traffic indicators, and HOMA-IR presented as the percentage change (%-change) (95% CI) from geometric mean per 5th–95th percentile difference in air pollutants among participants with diabetes stratified by subgroup of participants with newly diagnosed type 2 diabetes (squares, *N* = 109) and known type 2 diabetes (circles, *N* = 205). *N* represents the number of observations finally used for the analysis with HOMA-IR. Models were adjusted for age, sex, smoking, BMI, waist-to-hip ratio, month of blood withdrawal, and pack-years smoked. $PM_{2.5}$abs, soot content (absorbance) of $PM_{2.5}$; T2D, type 2 diabetes; traffic major, traffic load within 100 m on major roads; traffic near, traffic intensity on the nearest road.

comprehensive estimation of residential air pollution exposure, and the availability of OGTT measurements to allow for stratification by impaired glucose regulation. Thus, the study delivered a high degree of representativeness in terms of a large number of study participants to conduct subgroup analyses and a large scale of information on patient characteristics for the examination of potential confounding.

The cross-sectional study design limits our study findings in a way that we have one-time measurements giving no indication of the sequence of events. The observed elevation of IR-related biomarkers at one time point may have occurred before the onset of adverse health effects due to air pollution. Since biomarkers were determined up to 3 years before the air pollution measurements, it is not possible to infer causation based on our associations. However, we are investigating the spatial contrasts of air pollution. Several studies could show that spatial contrasts remained stable for periods of up to 10 years and longer, even with decreases in concentrations over time (49,50). Thus, we believe that our LUR models based on measurements from the years 2008/2009 are not necessarily restricted to this period but may be also valid predictors of the historic spatial contrasts. With the application of LUR models to estimate the residential long-term concentrations, we cannot rule out the possibility of exposure misclassification. However, we assume that the measurement error biases our effect estimates toward the null.

Furthermore, disparities in the inferences that can be drawn from IR measures in people with or without β-cell failure might have limited the comparability of the results.

Conclusion

In conclusion, our results point to an association between traffic-related air pollution and biomarkers related to IR, subclinical inflammation, and adipokines in the general population. The effect estimates were remarkably high for individuals with i-IFG, i-IGT, or both, suggesting that this subgroup is particularly susceptible to adverse health effects due to air pollution exposure.

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Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. K.W. and A.Po. performed the analyses and wrote the manuscript. A.S., S.B., R.H., W.R., C.H., M.R., W.K., and C.M. contributed to the design of the study and reviewed and edited the manuscript. A.Pe. researched the data, conceived the research, provided overall supervision, and reviewed and edited the manuscript. K.W. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix

Members of the KORA Study Group. A. Peters (speaker), J. Heinrich, R. Holle, R. Leidl, C. Meisinger, K. Strauch, and their coworkers, who are responsible for the design and conduct of the KORA studies.

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