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FULL TITLE: Association between long-term exposure to air pollution and biomarkers related to insulin resistance, subclinical inflammation and adipokines

SHORT TITLE: Long-term air pollution and insulin resistance

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Abstract

Insulin resistance (IR) is present long before the onset of type 2 diabetes and results not only from inherited and lifestyle factors but likely also from environmental conditions. We investigated the association between modelled long-term exposure to air pollution at residence and biomarkers related to IR, subclinical inflammation and adipokines.

Data was based on 2,944 participants of the KORA (Cooperative Health Research in the Region Augsburg) F4 study conducted in southern Germany (2006-2008). We analysed associations between individual air pollution concentration estimated by land use regression and HOMA-IR, glucose, insulin, HbA_{1c}, leptin, and hs-CRP from fasting samples using multivariable linear regression models. Effect estimates were calculated for the whole study population and subgroups of non-diabetic, pre-diabetic and diabetic individuals.

Among all participants, a 7.9µg/m^3 increment in particulate matter <10µm 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 pre-diabetic individuals were much larger and highly statistically significant, while non-diabetic and diabetic individuals showed rather weak associations. No association was seen for HbA_{1c}.

Our results suggested an association between long-term exposure to air pollution and IR in the general population mainly attributable to pre-diabetic individuals.

Introduction

Insulin resistance (IR) is a condition 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) or isolated impaired glucose tolerance (i-IGT) or both IFG and IGT. IR has been shown to be associated with a high risk of developing type 2 diabetes in later life (1,2) and is considered as independent predictor for type 2 diabetes and therefore often referred to as pre-diabetic state (3-5). However, not all insulin-resistant people will develop diabetes.

In 2013, the International Diabetes Federation estimated a diabetes prevalence of around 8.3% (382 million people) worldwide, with type 2 diabetes accounting for about 85-95% of all diabetes cases (6). Obesity (7,8) and certain gene variants (9) were associated with diabetes and may cause the disease. Further critical factors determining 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 meta-analysis combined the epidemiological findings and quantified the risk increases for type 2 diabetes per 10μg/m³ increase in exposure between 5-27% for $PM_{2.5}$, 1-15% for PM_{10}, and 1-11% for 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 investigating air pollution and IR as a precursor state of type 2 diabetes showed positive associations (10,22-27). However, these studies were either experimental, investigated short-term effects or focussed 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 (i) in the general population and (ii) in non-diabetic, pre-diabetic, and diabetic individuals. For all markers investigated, we hypothesized incremented levels in association with incremented air pollutant concentrations. We evaluated homeostasis model assessment - insulin resistance (HOMA-IR), fasting glucose, fasting insulin, haemoglobin A1c (HbA_{1c}), as well as high sensitivity C-reactive protein (hs-CRP) as an established marker 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 modelled long-term exposures to particulate matter (PM_{10}: particulate matter (PM) ≤10µm in diameter, PM_{coarse}: PM between 2.5-10µm, $PM_{2.5}$: PM ≤ 2.5µm, $PM_{2.5}$ absorbance), and nitrogen oxides based on measurements conducted in 2008/09 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 to 2008.

Altogether, 3,080 participants of the KORA F4 study were invited to the study centre 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. Non-diabetic individuals underwent an oral glucose tolerance test (OGTT) (29).

In KORA F4, 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. Newly diagnosed diabetes, isolated impaired glucose tolerance (i-IGT), isolated

impaired fasting glucose (i-IFG) and normal glucose tolerance (NGT) were defined according to WHO 1999 diagnostic criteria (30) based on fasting and post OGTT values. For definition, diagnosis and classification of glucose metabolism, see Online Appendix Table 1.

Due to missing address information (n=20), missing information on glucose metabolism (n=94), a non-fasting status of some individuals (n=10) or missing information on main confounders (n=12), 136 participants had to be excluded. For subgroup analysis we stratified the remaining number of 2,944 study participants into subgroups of (i) people having no diabetes (non-diabetes group, n=2,125) with NGT, (ii) people representing a non-diabetic group with conditions that are associated with insulin resistance (pre-diabetes group, n=496) with i-IFG, i-IGT or IFG and IGT, and (iii) people who already have type 2 diabetes (diabetes group, n=323). Though not all IR diagnosed individuals will develop diabetes, for reasons of brevity and simplicity we named all individuals with diagnosable insulin resistance as group of pre-diabetes. 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 to 8°C and shipped on refrigerant packaging within 2-4 hours to the laboratory of Augsburg Central Hospital. Fasting venous blood glucose was sampled in the morning (7:00am to 11:00am). All non-diabetic participants were given a 75g dose of anhydrous glucose (Dextro OGT, Boehringer Mannheim, Germany) and another blood sample was collected after 2 hours. Serum glucose was measured using a hexokinase method (GLU Flex, Dade Behring Marburg, Germany). Insulin was determined using ELISA kits from Invitrogen (Camarillo, USA). As a surrogate of insulin resistance, the homeostatic model assessment was used and defined as HOMA-IR = (fasting insulin (μU/ml))×(fasting glucose (mmol/l))/ 22.5 (32).

HbA_{1c} was measured with a reverse-phase cation-exchange high-pressure liquid chromotography (HPLC) method (Menarini, analyzer HA 8160). Leptin concentrations were assessed using ELISA kits from Mercodia (Uppsala, Sweden). Measurement of hs-CRP was in anti-coagulated plasma samples using a high-sensitivity latex-enhanced nephelometric assay on a BN II analyzer (Dade Behring), with intra- and inter-assay 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}, $PM_{2.5}$, nitrogen dioxide (NO_2) and both, nitrogen dioxide and monoxides (NO_x) were collected at 20 (PM) and 40 (NO_x) monitoring sites for three periods of two weeks in the cold, warm and one intermediate season during 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 modelled air pollution concentration, we considered two traffic indicators i) traffic intensity on the nearest road (number of vehicles/day) and ii) traffic load on major roads within 100 m of the residence (number of vehicles/day*meter), 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, body mass index (BMI), waist-hip ratio (Spearman correlation coefficient with BMI was 0.52), and month of blood withdrawal. Second, we selected from several socio-economic variables: occupational status, years of education, per capita income, socio-economic 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, alcohol intake. The selection in steps 2 and 3 was based on minimising 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 Online Appendix 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 %-change of the geometric mean value per 5^{th}-95^{th} percentile difference of the exposure concentrations and corresponding 95% confidence intervals (CI). Effect estimates were calculated separately for all participants and the non-diabetes, pre-diabetes, and diabetes subgroups. Tests of interaction were calculated for differences between subgroups (35).

As sensitivity analysis, we applied a very basic confounder model including only sex, age and BMI to verify if 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 three degrees of freedom 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 antidiabetics or statins. We also excluded persons who reported an intake of diuretics and/or beta-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 pre-diabetes group into i-IFG (n=113), i-IGT (n=307), and IFG-IGT (n=76) groups. Moreover, we stratified the diabetes group into newly diagnosed persons (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. Mean age was 56.2 years, mean BMI was 27.6kg/m^2, and marginally more women participated. Pre-diabetic and diabetic participants were on average older, BMI was higher, and rather male than non-diabetic participants. In addition, they showed a lower prevalence of current smokers but a higher prevalence of ex-smokers. Also, socio-economic status and physical activity were in general lower for pre-diabetic and diabetic individuals. Prevalence

of hypertension, myocardial infarction, stroke, and medication intake were higher with worsened insulin sensitivity.

Plasma concentrations of the six selected biomarkers are described in Table 2 by the arithmetic mean and standard deviation 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 modelled annual average concentrations of air pollutants and traffic indicators at participants' residences can be found in Table 3. Air pollution concentrations were below EU limits (EU 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 (Online Appendix 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 while $PM_{2.5}$ 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 while 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 pre-diabetic individuals 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 while glucose was only associated with traffic load on major roads. Further associations were seen for leptin with all air pollutants (Table 5). Results in the pre-diabetic subgroup may indicate some underlying systemic inflammatory processes. Our effect estimates for hs-CRP pointed in this direction as most air pollutants were significantly associated with higher %-changes of hs-CRP in pre-diabetic individuals (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 (Online Appendix Table 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 pre-diabetes group. All air pollutants indicated no clear deviation from linearity when incorporated as a smooth function in the model (Online Appendix Figure 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 pre-diabetes group and the diabetes group which showed no clear pattern potentially due to the reduced power (Online Appendix Figure 2). The alternative quantile regression indicated no clear heterogeneity across the deciles (Online Appendix Figures 3a) – d)). When excluding participants with hs-CRP >10 mg/l (n=97), results were robust for all participants (data not shown). In the pre-diabetes 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 pre-diabetic and diabetic individuals (data not shown).

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

The exclusion of 762 study participants taking diuretics and/or beta-blockers (with 306 who reported an intake of both) showed robust effect estimates for all participants but attenuated estimates for glucose as well as for glucose and insulin in non-diabetic individuals. In the pre-diabetic group, effect estimates for leptin and hs-CRP were not significant anymore (data not shown). The stratification of the pre-diabetes subgroup into individuals with i-IFG, i-IGT, or IFG-IGT showed in general higher %-changes for persons with i-IFG and i-IGT especially for HOMA-IR, insulin, and hs-CRP (exemplarily shown for HOMA-IR in Figure 2). For leptin, only participants with i-IGT showed an association (data not shown). The stratification of the diabetes subgroup into newly diagnosed participants 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 (Figure 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 adipokines in a

cross-sectional study conducted in the region of Augsburg, 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. 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 pre-diabetes 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 but lower estimates for glucose and HbA_{1c}. Estimates in this group were also higher for leptin and hs-CRP when excluding persons taking statins whereas results were robust for the non-diabetic and pre-diabetic group. This might indicate a mitigating or inhibiting role of this medication type with regard to inflammatory effects of air pollution in diabetic patients while healthy individuals may not be as susceptible for inflammation as individuals with metabolic disorders. Also, the stratification into newly diagnosed and known type 2 diabetes participants pointed in this direction suggesting an increased susceptibility of the first subgroup to air pollution exposure which has not been properly medicated. The exclusion of individuals with diuretic and/or beta-blocker intake mainly affected the results of the pre-diabetic group leading to non-significant estimates for all air pollutants in association with leptin and hs-CRP.

The first studies on adverse 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 have been published since, mainly referring to the same studies (14-20). However, the pooled effect estimates varied to some extent depending on 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 due to differences in outcome definition, exposure metrics, population characteristics, and covariates considered (14). As IR is a powerful predictor of 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 investigated either short-term effects or focussed on children and thus, are not directly comparable to our study. Short- and long-term effects of air pollution are hypothesized to arise from partly different biological pathways and recent epidemiological evidence showed that 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´s nature of being more vulnerable to environmental stressors. To the best of our knowledge, this is the first study investigating long-term effects of air pollution in association with biomarkers of IR in the general population.

A German study from Teichert et al. (41) used partly comparable data to ours, however applied a different approach to assess the association between long-term air pollution, sub-clinical 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 the risk differences in association with air pollution, 14 pro- 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 most consistent and highest pronounced though 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 ten-year-old children in two prospective German birth cohort studies and observed an increment of 17.0% (95% CI 5.0; 30.3) and 18.7% (95% CI 2.9; 36.9) for an increment of 10.6μg/m³ in ambient NO_2 and 6.0μg/m³ in PM_{10}. Calderon et al (27) matched 54 children living in the metropolitan area of Mexico City, thus chronically exposed to $PM_{2.5}$ and O_3 concentrations above the standards, with 26 controls and found significantly higher leptin and glucose levels in the first group but no differences for insulin and HOMA-IR. Three studies on 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 type 2 diabetes incidence, only five papers have been published so far (43-47). While two studies from the US (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 markers related to insulin resistance in our analysis. A further study from the Ruhr area (46) reported higher effect estimates for PM_{10} compared to $PM_{2.5}$ 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 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 biologic components intrinsic to PM such as lipopolysaccharide (LPS) which has a lower concentration in $PM_{2.5}$ than in PM_{10} (11). Lipopolysaccharide-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 to $PM_{2.5}$.

***Strengths and limitations*.** Major strengths of this study are the well-characterized nature of the KORA F4 cohort, the standardized and 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 three years before the air pollution measurements, it is not possible to infer causation based on our associations. However, we are investigating spatial contrasts of air pollution. Several studies could show that spatial contrasts remained stable for periods up to ten 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 2008/09 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 the measurement error to bias our effect estimates towards the null.

Furthermore, disparities in the inferences that can be drawn from insulin resistance measures in people with or without beta 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 insulin resistance, subclinical inflammation and adipokines in the general population. The effect estimates were remarkably high for individuals with i-IFG or i-IGT or both suggesting this subgroup to be particularly susceptible for adverse health effects due to air pollution exposure.

Author contributions

KW and APo performed the analyses and wrote the manuscript. AS, SB, RH, WR, CH, MR, WK and CM contributed to the design and reviewed/edited the manuscript. APe researched the data, conceived the research, provided overall supervision, and reviewed/edited the manuscript.

KW 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.

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Duality of Interest

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

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Figure legends:

Figure 1. Association between NO_2 and biomarkers presented as %-change (with 95% CI) from geometric mean per 11.9 µg/m³ increment in NO_2 for all participants (top) and diabetic individuals (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-hip ratio, month of blood withdrawal, selected socio-economic- and lifestyle variables (see Online Appendix Table 2). NO_2: nitrogen dioxide; HOMA-IR: homeostasis model assessment-insulin resistance; HbA1c: hemoglobin A1c; hs-CRP: high sensitivity C-reactive protein.

Figure 2. Association between air pollutants, traffic indicators and HOMA-IR presented as %-change (with 95% CI) from geometric mean per 5^{th}-95^{th} percentile difference in air pollutants among pre-diabetic participants 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-hip ratio, month of blood withdrawal, and pack-years smoked. HOMA-IR: homeostasis model assessment-insulin resistance; i-IFG: isolated impaired fasting glucose; i-IGT: isolated impaired glucose tolerance; PM_{10}: particulate matter (PM) with diameter < 10 µm; PM_{coarse}: PM_{10} - $PM_{2.5}$; $PM_{2.5}$: PM with diameter < 2.5 µm; $PM_{2.5}$abs: the soot content (absorbance) of $PM_{2.5}$; NO_x: sum of nitrogen monoxide and nitrogen dioxide; NO_2: nitrogen dioxide; Traffic near: Traffic intensity on the nearest road; Traffic major: Traffic load within 100m on major roads.

Figure 3. Association between air pollutants, traffic indicators and HOMA-IR presented as %-change (with 95% CI) from geometric mean per 5^{th}-95^{th} percentile difference in air pollutants among diabetic participants stratified by subgroup of newly diagnosed type 2 diabetes (squares, N=109) and known type 2 diabetes (circles, N=205). N represents the number of observation finally used for the analysis with HOMA-IR. Models were adjusted for age, sex, smoking, BMI, waist-hip ratio, month of blood withdrawal, and pack-years smoked. HOMA-IR: homeostasis model assessment-insulin resistance; i-IFG: isolated impaired fasting glucose; i-IGT: isolated impaired glucose tolerance; PM_{10}: particulate matter (PM) with diameter <10 µm; PM_{coarse}: PM_{10} - $PM_{2.5}$; $PM_{2.5}$: PM with diameter < 2.5µm; $PM_{2.5}$abs: the soot content (absorbance) of $PM_{2.5}$; NO_x: sum of nitrogen monoxide and nitrogen dioxide; NO_2: nitrogen dioxide; Traffic near: Traffic intensity on the nearest road; Traffic major: Traffic load within 100m on major roads.

Tables

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

		Missing values	All (N=2,944)		Nondiabetes (N=2,125)		Prediabetes (N=496)		Diabetes (N=323)		
Variable		**N (%)**	**Arithm. Mean**	**(SD)**	**Arithm. Mean**	**(SD)**	**Arithm. Mean**	**(SD)**	**Arithm. 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-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	(2.7)	11.3	(2.5)	11	(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	(23.6)	0.149
			N	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	
Sex	Male	-	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)	1265	(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)	
Socio-economic status†	Low	114 (3.9)	915	(32.3)	658	(31.0)	149	(30.0)	108	(33.4)	0.002
	Medium		853	(30.1)	584	(27.5)	153	(30.8)	116	(35.9)	
	High		1,062	(37.5)	803	(37.8)	171	(34.5)	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
Medication intake	Antidiabetics	2 (0.1)	155	(5.3)	-	-	-	-	155	(48.0)	-
	Insulin	2 (0.1)	41	(1.4)	-	-	-	-	41	(12.7)	-
	Oral anti-diabetics	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
	Antihyper-tensives	-	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
Betablocker	-	551	(18.7)	253	(11.9)	152	(30.6)	146	(45.2)	< 0.001
CCB	1 (0.0)	231	(7.9)	100	(4.7)	63	(12.7)	68	(21.1)	< 0.001
ACEI	1 (0.0)	388	(13.2)	162	(7.6)	99	(20.0)	127	(39.3)	< 0.001
ARB	2 (0.1)	219	(7.4)	121	(5.7)	50	(10.1)	48	(14.9)	< 0.001
Cortison	2 (0.1)	41	(1.4)	27	(1.3)	6	(1.2)	8	(2.5)	0.208

CCB: Calcium channel blocker; ACEI: angiotensin-converting-enzyme inhibitor; ARB: angiotensin receptor blocker.

*Kruskal-Wallis rank sum test (for continuous variables) or Pearson x^2 test (for categorical variables) to test for differences between the subgroups.

†Sum of "education in categories" (1: less than 10 years of education; 2: more than 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).

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

Blood markers	All (N=2,944)				Non-diabetes (N=2,125)				Pre-diabetes (N=496)				Diabetes (N=323)				
	N	Arith-metic mean	(SD)	Geo-metric mean	N	Arith-metic mean	(SD)	Geo-metric mean	N	Arith-metic mean	(SD)	Geo-metric mean	N	Arith-metic mean	(SD)	Geo-metric 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
HbA1c (%)†	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
HbA1c (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

HOMA-IR: homeostasis model assessment-insulin resistance; HbA1c: hemoglobin A1c; hs-CRP: high sensitivity C-reactive protein.

*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): HbA1c (%) = (HbA1c/Hb) x 91.48 + 2.15.

§For mmol/mol according to International Federation of Clinical Chemistry (IFCC): HbA1c (mmol/mol) = (HbA1c/Hb) x 1,000.

Table 3. Annual average concentrations of air pollutants and traffic indicators and corresponding Spearman correlation coefficients (N = 2,944). Current European air quality standards (1 year average): 40 μg/m^3 (PM_{10}); 25 μg/m^3 ($PM_{2.5}$); 40 μg/m^3 (NO_2). WHO recommendations (1 year average): 20 μg/m³ (PM_{10}); 10 μg/m³ ($PM_{2.5}$); 40 μg/m^3 (NO_2).

	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} (μg/m^3)	20.4	(2.4)	16.5	20.5	24.4	1					
PM_{coarse} (μg/m^3)	6.2	(1.1)	4.9	6.1	8.4	0.76	1				
$PM_{2.5}$ (μg/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 (μg/m^3)	32.7	(7.2)	23.9	31.4	46.7	0.69	0.85	0.48	0.76	1	
NO_2 (μg/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 (veh/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 (veh/day*m), 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

PM_{10}: particulate matter (PM) with diameter < 10 μm; PM_{coarse}: PM_{10} - $PM_{2.5}$; $PM_{2.5}$: PM with diameter < 2.5 μm; $PM_{2.5}$abs: the soot content (absorbance) of $PM_{2.5}$; NO_x: sum of nitrogen monoxide and nitrogen dioxide; NO_2: nitrogen dioxide.

Table 4. Association between long-term air pollution, traffic indicators and biomarkers presented as %-change* (with 95% CI) from geometric mean per 5th-95th percentile difference increment in air pollutants.

Pollutant Exposure	Increment†	HOMA-IR					
		All % change (95% CI)	Non-diabetes % change (95% CI)	Pre-diabetes % change (95% CI)	p-value‡	Diabetes % change (95% CI)	p-value§
PM_{10} (μg/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} (μg/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
$PM_{2.5}$ (μg/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)**	0.001	0.1 (-28.6; 40.4)	0.345
NO_x (μg/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 (μg/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 (veh/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 100m on major roads (veh/day*m), 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} (μg/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} (μg/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
$PM_{2.5}$ (μg/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 (μg/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 (μg/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 (veh/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 100m on major roads (veh/day*m), 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 (veh/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 100m on major roads (veh/day*m), 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

PM_{10}: particulate matter (PM) with diameter < 10 µm; PM_{coarse}: PM_{10} - $PM_{2.5}$; $PM_{2.5}$: PM with diameter < 2.5 µm; $PM_{2.5}$abs: the soot content (absorbance) of $PM_{2.5}$; NO_x: sum of nitrogen monoxide and nitrogen dioxide; NO_2: nitrogen dioxide; HOMA-IR: homeostasis model assessment-insulin resistance.

*Adjusted for age, sex, smoking, BMI, waist-hip ratio, month of blood withdrawal, selected socio-economic- and lifestyle variables (see Online Appendix Table 2).

†Corresponds to the difference between the 5th-95th percentile of the corresponding exposure.

‡Test of interaction to test for differences between pre-diabetic and non-diabetic participants.

§Test of interaction to test for differences between diabetic and non-diabetic participants.

Table 5. Association of exposure to air pollution, traffic indicators on biomarkers presented as %-change* (with 95% CI) from geometric mean per 5th-95th percentile difference increment in air pollutants.

Pollutant Exposure	Increment†	HbA1c					
		All % change (95% CI)	Non-diabetes % change (95% CI)	Pre-diabetes % change (95% CI)	p-value‡	Diabetes % change (95% CI)	p-value§
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 (veh/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 100m on major roads (veh/day*m), 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 (veh/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 100m on major roads (veh/day*m), 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)	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 (veh/day), per 1,000	7.5	3.8 (-5.2; 13.7)	0.5 (-9.2; 11.3)	8.3 (-13.8; 36)	0.279	27.5 (-10.3; 81.1)	0.101
Traffic load within 100 m on major roads (veh/day*m), 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

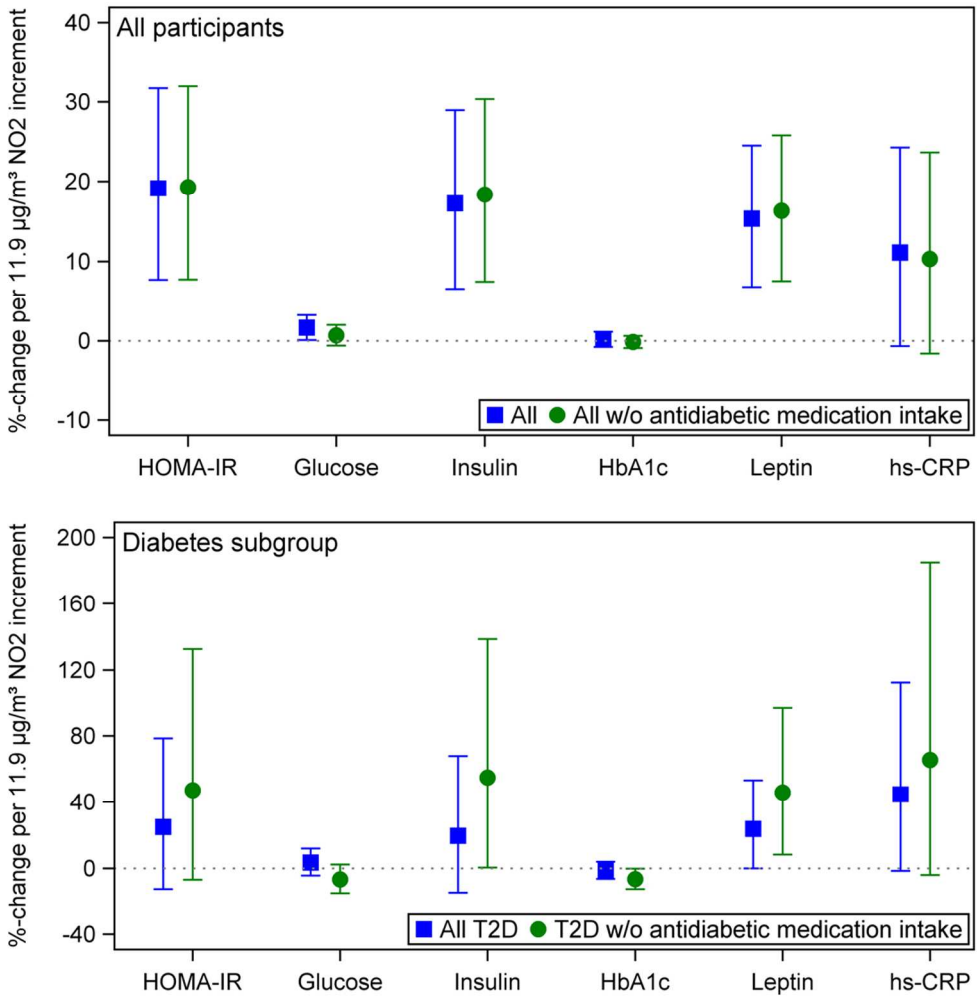
HbA1c: hemoglobin A1c; hs-CRP: high sensitivity C-reactive protein; PM_{10}: particulate matter (PM) with diameter < 10 μm; PM_{coarse}: PM_{10} - $PM_{2.5}$; $PM_{2.5}$: PM with diameter < 2.5 μm; $PM_{2.5}$abs: the soot content (absorbance) of $PM_{2.5}$; NO_x: sum of nitrogen monoxide and nitrogen dioxide; NO_2: nitrogen dioxide.

*Adjusted for age, sex, smoking, BMI, waist-hip ratio, month of blood withdrawal, selected socio-economic- and lifestyle variables (see Online Appendix Table 2).

†Corresponds to the difference between the 5th-95th percentile of the corresponding exposure.

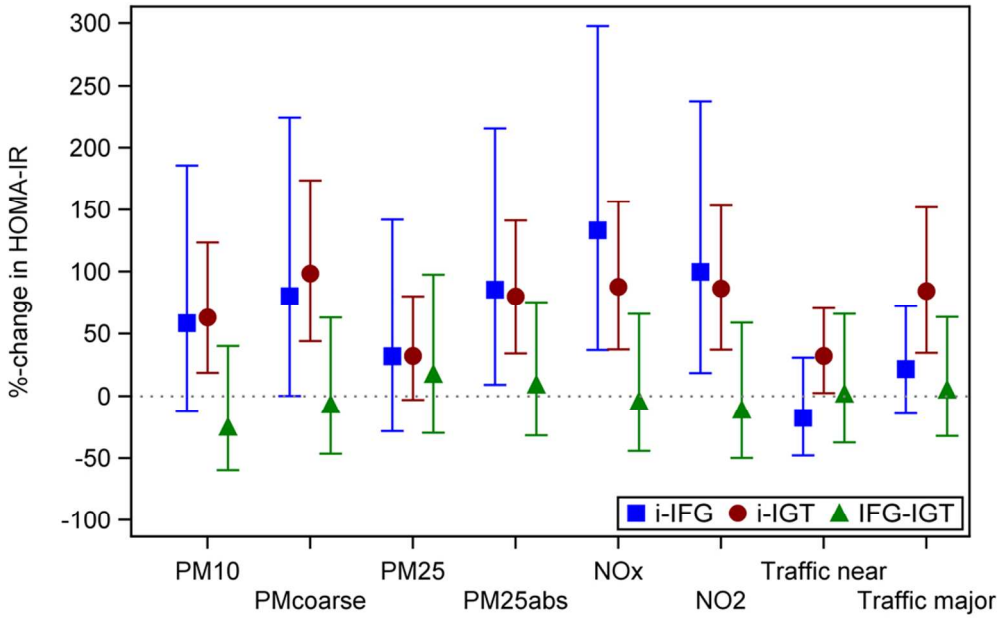
‡Test of interaction to test for differences between pre-diabetic and non-diabetic participants.

§Test of interaction to test for differences between diabetic and non-diabetic participants.



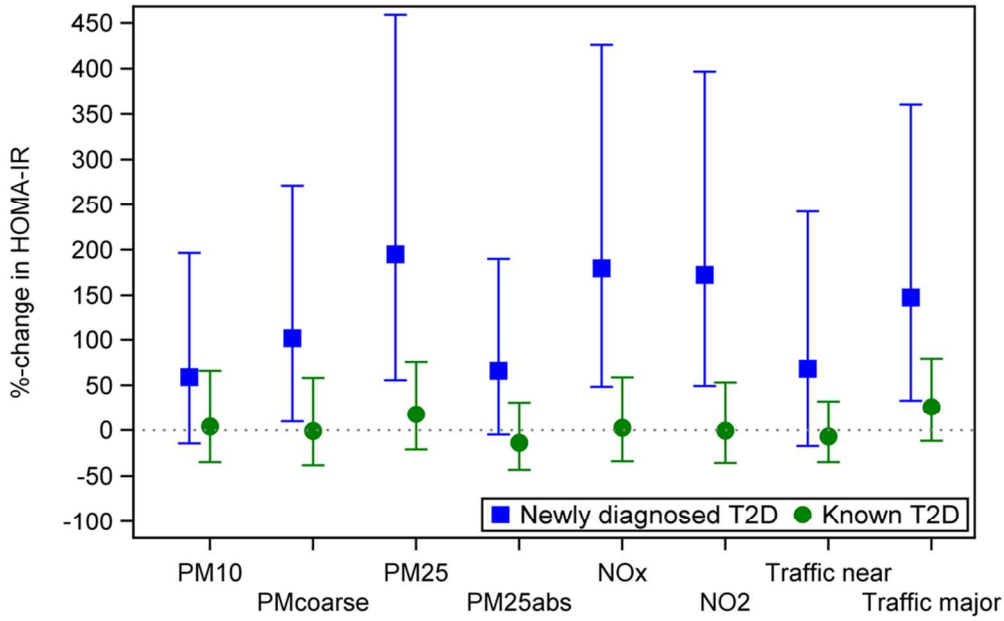
Association between NO2 and biomarkers presented as %-change (with 95% CI) from geometric mean per 11.9 µg/m³ increment in NO2 for all participants (top) and diabetic individuals (bottom). Squares: NO2 estimates for the whole group; circles: NO2 estimates for participants without antidiabetic medication intake. Models were adjusted for age, sex, smoking, BMI, waist-hip ratio, month of blood withdrawal, selected socio-economic- and lifestyle variables (see Online Supplementary Table 2). NO2: nitrogen dioxide; HOMA-IR: homeostasis model assessment-insulin resistance; HbA1c: hemoglobin A1c; hs-CRP: high sensitivity C-reactive protein.

Figure 1



Association between air pollutants, traffic indicators and HOMA-IR presented as %-change (with 95% CI) from geometric mean per 5th-95th percentile difference in air pollutants among pre-diabetic participants 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-hip ratio, month of blood withdrawal, and pack-years smoked. HOMA-IR: homeostasis model assessment-insulin resistance; i-IFG: isolated impaired fasting glucose; i-IGT: isolated impaired glucose tolerance; PM10: particulate matter (PM) with diameter < 10 µm; PMcoarse: PM10 - PM2.5; PM2.5: PM with diameter < 2.5 µm; PM2.5abs: the soot content (absorbance) of PM2.5; NOx: sum of nitrogen monoxide and nitrogen dioxide; NO2: nitrogen dioxide; Traffic near: Traffic intensity on the nearest road; Traffic major: Traffic load within 100m on major roads.

Figure 2



Association between air pollutants, traffic indicators and HOMA-IR presented as %-change (with 95% CI) from geometric mean per 5th-95th percentile difference in air pollutants among diabetic participants stratified by subgroup of newly diagnosed type 2 diabetes (squares, N=109) and known type 2 diabetes (circles, N=205). N represents the number of observation finally used for the analysis with HOMA-IR. Models were adjusted for age, sex, smoking, BMI, waist-hip ratio, month of blood withdrawal, and pack-years smoked. HOMA-IR: homeostasis model assessment-insulin resistance; i-IFG: isolated impaired fasting glucose; i-IGT: isolated impaired glucose tolerance; PM10: particulate matter (PM) with diameter < 10 µm; PMcoarse: PM10 - PM2.5; PM2.5: PM with diameter < 2.5 µm; PM2.5abs: the soot content (absorbance) of PM2.5; NOx: sum of nitrogen monoxide and nitrogen dioxide; NO2: nitrogen dioxide; Traffic near: Traffic intensity on the nearest road; Traffic major: Traffic load within 100m on major roads.
Figure 3

ONLINE APPENDIX

Supplementary Table 1. Diagnostic thresholds for IR and higher degrees of impaired glucose metabolism.

	Test	
Category	FPG	2-h PG
Normal	<110 mg/dl (<6.1 mmol/l)	<140 mg/dl (<7.8 mmol/l)
i-IFG	110-125 mg/dl (6.1-7.0 mmol/l)	-
i-IGT	-	140-199 mg/dl (7.8-11.0 mmol/l)
Diabetes	≥126 mg/dl (≥7.0 mmol/l)	≥200 mg/dl (≥11.1 mmol/l)

FPG: fasting plasma glucose; 2-h PG: plasma glucose, 2 h after OGTT; i-IFG: isolated impaired fasting glucose; i-IGT: isolated impaired glucose tolerance.

Supplementary Table 2. Final covariate selection by outcome variable.

	Personal characteristics*						**Socio-economic covariates†**		**Lifestyle covariates‡**		
Outcome	Age	Sex	Smoking	BMI	Waist-hip-ratio	Month of blood withdrawal	Edu-cation	Income	Pack-years smoked	Physical activity	Alcohol intake
HOMA-IR	●	●	●	●	●	●			●		
Glucose	●	●	●	●	●	●			●		
Insulin	●	●	●	●	●	●					
HbA1c	●	●	●	●	●	●		●	●		●
Leptin	●	●	●	●	●	●	●			●	
hs-CRP	●	●	●	●	●	●				●	

HOMA-IR: homeostasis model assessment-insulin resistance; HbA1c: hemoglobin A1c; hs-CRP: high sensitivity C-reactive protein.

*Inclusion by a-priori definition for all outcomes.

†Inclusion of socio-economic covariates if model fit increased (decrease in the Bayesian Information Criterion). Occupational status and socio-economic status (calculated as a combination of education and income) did not improve the model fit of any outcome.

‡Inclusion of lifestyle covariates (after inclusion of socio-economic covariates) if model fit increased (decrease in the Bayesian Information Criterion). Years smoked did not improve the model fit of any outcome.

Supplementary Table 3. Annual average concentrations of air pollutants and traffic indicators stratified by state of glucose metabolism (non-diabetes: N = 2,125; pre-diabetes: N = 496; diabetes: N= 323).

Variable	Subgroup	Mean	SD	5%	Median	95%	5^{th}-95^{th} percentile	p-value*
PM_{10} ($\mu g/m^3$)	Non-diabetes	20.4	2.4	16.4	20.5	24.3	7.9	0.60
	Pre-diabetes	20.3	2.4	16.4	20.5	24.2	7.8	
	Diabetes	20.6	2.4	16.6	20.6	25.0	8.4	
PM_{coarse} ($\mu g/m^3$)	Non-diabetes	6.2	1.1	4.9	6.1	8.4	3.5	0.49
	Pre-diabetes	6.2	1.1	4.8	6.1	8.5	3.7	
	Diabetes	6.3	1.1	5.0	6.1	8.5	3.5	
$PM_{2.5}$ ($\mu g/m^3$)	Non-diabetes	13.5	0.8	12.5	13.4	15.3	2.8	0.06
	Pre-diabetes	13.6	0.9	12.5	13.4	15.5	3.0	
	Diabetes	13.6	0.9	12.4	13.5	15.4	3.0	
$PM_{2.5}$abs (10^{-5}/m)	Non-diabetes	1.7	0.2	1.5	1.7	2.0	0.5	0.95
	Pre-diabetes	1.7	0.2	1.5	1.7	2.0	0.5	
	Diabetes	1.7	0.2	1.5	1.7	2.0	0.5	
NO_2 ($\mu g/m^3$)	Non-diabetes	18.7	3.8	13.8	18.2	25.6	11.9	0.11
	Pre-diabetes	18.7	3.8	13.5	18.3	25.5	12.1	
	Diabetes	19.1	3.7	14.0	18.9	26.0	12.0	
NO_x ($\mu g/m^3$)	Non-diabetes	32.7	7.3	23.8	31.4	47.1	23.2	0.17
	Pre-diabetes	32.4	7.2	23.3	31.0	45.5	22.2	
	Diabetes	33.2	7.0	24.7	31.9	47.8	23.0	
Traffic intensity on the nearest road (veh/day) per 1,000	Non-diabetes	0.2	0.3	0.1	0.1	0.8	0.8	0.52
	Pre-diabetes	0.2	0.3	0.1	0.1	0.8	0.8	
	Diabetes	0.1	0.3	0.1	0.1	0.7	0.6	
Traffic load within 100 m on major roads (veh/day*m), per 10,000	Non-diabetes	41.8	106.6	0.0	0.0	255.7	255.7	0.87
	Pre-diabetes	39.5	92.2	0.0	0.0	228.3	228.3	
	Diabetes	35.1	87.0	0.0	0.0	202.1	202.1	

PM_{10}: particulate matter (PM) with diameter < 10 µm; PM_{coarse}: PM_{10} - $PM_{2.5}$; $PM_{2.5}$: PM with diameter < 2.5 µm; $PM_{2.5}$abs: the soot content (absorbance) of $PM_{2.5}$; NO_x: sum of nitrogen monoxide and nitrogen dioxide; NO_2: nitrogen dioxide.

*Kruskal-Wallis rank sum test (to test for differences between the subgroups).

Supplementary Table 4. Association between long-term air pollution, traffic indicators and biomarkers presented as %-change* (with 95% CI) from geometric mean per 5th-95th percentile difference increase in air pollutants (basic confounder model).

Pollutant Exposure	Increment†	HOMA-IR			
		All % change (95% CI)	Non-diabetes % change (95% CI)	Pre-diabetes % change (95% CI)	Diabetes % change (95% CI)
PM_{10} ($\mu g/m^3$)	7.9	**15.3 (3.8; 28.1)**	9.5 (-2.4; 22.9)	**40.9 (9.6; 81.2)**	3.8 (-28.2; 50.0)
PM_{coarse} ($\mu g/m^3$)	3.6	**20.0 (7.7; 33.6)**	11.4 (-1.0; 25.4)	**67.0 (30; 114.5)**	10.7 (-23.9; 61.1)
$PM_{2.5}$ ($\mu g/m^3$)	2.8	10.5 (-0.6; 22.7)	1.1 (-10.2; 13.7)	23.7 (-2.8; 57.4)	33.3 (-6.4; 89.8)
$PM_{2.5}$abs (10^{-5}/m)	0.5	**13.9 (3.5; 25.2)**	7.9 (-2.7; 19.7)	**58.4 (26.1; 98.8)**	0.0 (-28.5; 40.0)
NO_x ($\mu g/m^3$)	22.9	**21.0 (9.3; 33.9)**	**11.9 (0.1; 25)**	**70.6 (34.2; 116.9)**	19.5 (-16.7; 71.6)
NO_2 ($\mu g/m^3$)	11.9	**18.6 (7.3; 31.1)**	8.3 (-2.9; 20.9)	**63.2 (28.8; 106.7)**	23.5 (-13.2; 75.9)
Traffic intensity on the nearest road (veh/day), per 1,000	7.5	-4.5 (-12.0; 3.7)	-5.4 (-13.4; 3.3)	16.8 (-4.9; 43.5)	-10.9 (-35.6; 23.3)
Traffic load within 100m on major roads (veh/day*m), per 10,000	243.6	5.9 (-2.1; 14.5)	00. (-8; 8.6)	**49.8 (21.8; 84.3)**	27.6 (-7.0; 75.1)
		Glucose			
PM_{10} ($\mu g/m^3$)	7.9	1.0 (-0.7; 2.6)	0.5 (-0.5; 1.5)	-0.4 (-3.4; 2.7)	-0.3 (-8.0; 8.1)
PM_{coarse} ($\mu g/m^3$)	3.6	1.4 (-0.3; 3.1)	0.6 (-0.4; 1.7)	1.2 (-1.8; 4.4)	3.3 (-4.9; 12.2)
$PM_{2.5}$ ($\mu g/m^3$)	2.8	**1.7 (0.1; 3.4)**	0.7 (-0.3; 1.8)	1.5 (-1.4; 4.5)	0.3 (-7.3; 8.4)
$PM_{2.5}$abs (10^{-5}/m)	0.5	0.6 (-0.9; 2.1)	0.6 (-0.3; 1.5)	0.7 (-2.1; 3.6)	-0.5 (-7.5; 7.2)
NO_x ($\mu g/m^3$)	22.9	1.3 (-0.3; 2.9)	0.8 (-0.2; 1.8)	1.8 (-1.1; 4.9)	1.2 (-6.6; 9.6)
NO_2 ($\mu g/m^3$)	11.9	**1.7 (0.1; 3.3)**	0.7 (-0.2; 1.7)	1.8 (-1.1; 4.8)	2.9 (-4.8; 11.2)
Traffic intensity on the nearest road (veh/day), per 1,000	7.5	-0.1 (-1.4; 1.2)	0.7 (-0.1; 1.5)	1.1 (-1.4; 3.7)	-1.9 (-8.7; 5.4)
Traffic load within 100m on major roads (veh/day*m), per 10,000	243.6	0.2 (-1; 1.4)	-0.4 (-1.2; 0.3)	**3.2 (0.6; 5.8)**	**8.0 (0.7; 15.8)**
		Insulin			
PM_{10} ($\mu g/m^3$)	7.9	**14.0 (3.0; 26.1)**	8.9 (-2.8; 21.9)	**40.9 (10.4; 80.0)**	4.2 (-27.1; 48.9)
PM_{coarse} ($\mu g/m^3$)	3.6	**18.1 (6.5; 30.9)**	10.6 (-1.5; 24.2)	**64.5 (29; 109.8)**	7.3 (-25.4; 54.4)
$PM_{2.5}$ ($\mu g/m^3$)	2.8	8.6 (-1.9; 20.1)	0.4 (-10.6; 12.6)	21.8 (-3.7; 53.9)	32.8 (-5.7; 87.1)
$PM_{2.5}$abs (10^{-5}/m)	0.5	**13.0 (3.2; 23.8)**	7.2 (-3.2; 18.6)	**56.9 (25.8; 95.8)**	0.6 (-27.4; 39.3)
NO_x ($\mu g/m^3$)	22.9	**19.3 (8.2; 31.5)**	11.0 (-0.5; 23.7)	**67.1 (32.3; 111.1)**	18.2 (-16.7; 67.9)
NO_2 ($\mu g/m^3$)	11.9	**16.5 (5.9; 28.3)**	7.5 (-3.4; 19.8)	**59.9 (27.0; 101.3)**	20.2 (-14.7; 69.2)
Traffic intensity on the nearest road (veh/day), per 1,000	7.5	-4.4 (-11.6; 3.5)	-6.0 (-13.8; 2.4)	15.6 (-5.4; 41.2)	-9.3 (-33.8; 24.3)
Traffic load within 100m on major roads (veh/day*m), per 10,000	243.6	5.6 (-2.0; 13.9)	0.4 (-7.5; 8.9)	**45.0 (18.4; 77.4)**	18.0 (-13.2; 60.5)

PM_{10}: particulate matter (PM) with diameter < 10 µm; PM_{coarse}: PM_{10} - $PM_{2.5}$; $PM_{2.5}$: PM with diameter < 2.5 µm; $PM_{2.5}$abs: the soot content (absorbance) of $PM_{2.5}$; NO_x: sum of nitrogen monoxide and nitrogen dioxide; NO_2: nitrogen dioxide; HOMA-IR: homeostasis model assessment-insulin resistance.

*Adjusted for age, sex, and BMI.

† Corresponds to the difference between the 5th-95th percentile of the corresponding exposure.

Supplementary Table 5. Association of exposure to air pollution, traffic indicators on biomarkers presented as %-change* (with 95% CI) from geometric mean per 5th-95th percentile difference increase in air pollutants (basic confounder model).

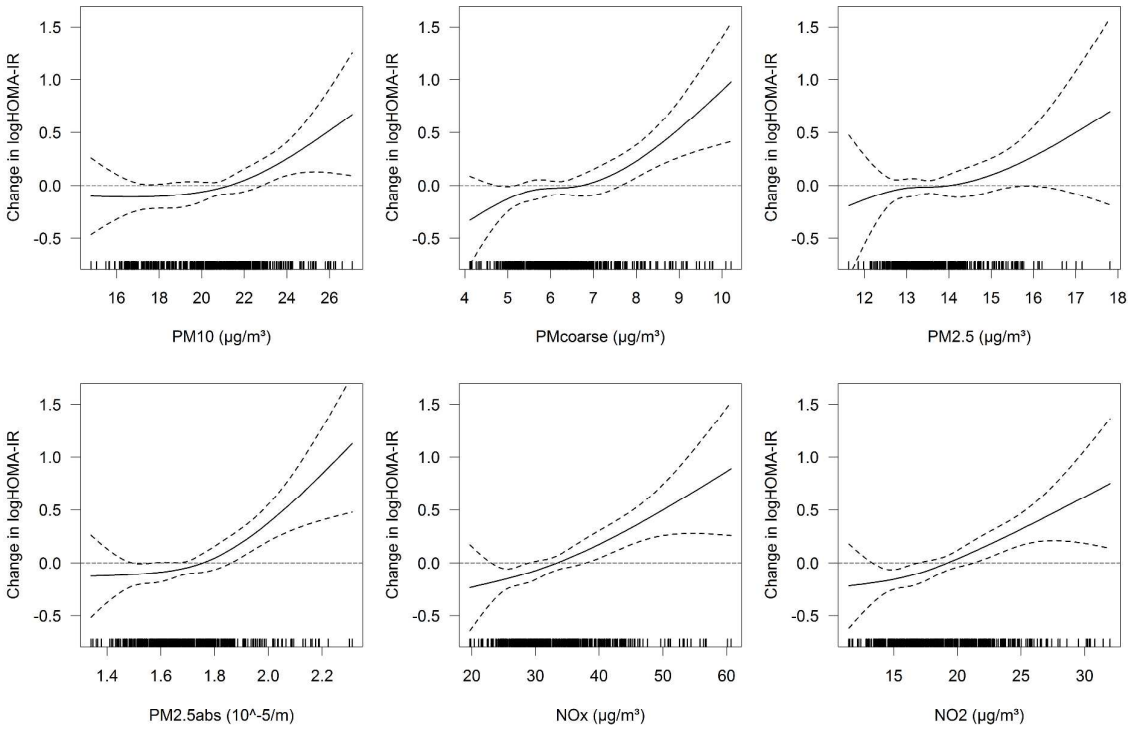
Pollutant Exposure	Increment†	HbA1c			
		All % change (95% CI)	Non-diabetes % change (95% CI)	Pre-diabetes % change (95% CI)	Diabetes % change (95% CI)
PM_{10} ($\mu g/m^3$)	7.9	0.8 (-0.2; 1.9)	0.3 (-0.4; 1.1)	-0.8 (-2.5; 0.8)	2.7 (-2.6; 8.3)
PM_{coarse} ($\mu g/m^3$)	3.6	0.6 (-0.4; 1.6)	0.3 (-0.5; 1.0)	-0.3 (-2.0; 1.4)	1.9 (-3.5; 7.5)
$PM_{2.5}$ ($\mu g/m^3$)	2.8	**1.1 (0.1; 2.1)**	0.5 (-0.2; 1.3)	0.6 (-1.0; 2.2)	1.2 (-3.8; 6.5)
$PM_{2.5}$abs (10^{-5}/m)	0.5	0.2 (-0.7; 1.2)	0.3 (-0.4; 0.9)	-0.5 (-2.0; 1.0)	0.3 (-4.4; 5.2)
NO_x ($\mu g/m^3$)	22.9	0.7 (-0.3; 1.6)	0.5 (-0.2; 1.2)	0.3 (-1.3; 1.9)	0.2 (-4.9; 5.5)
NO_2 ($\mu g/m^3$)	11.9	**0.9 (0.0; 1.9)**	0.7 (0.0; 1.4)	0.6 (-1.0; 2.2)	-0.3 (-5.2; 4.9)
Traffic intensity on the nearest road (veh/day), per 1,000	7.5	0.1 (-0.7; 0.9)	0.2 (-0.4; 0.7)	1.0 (-0.4; 2.3)	1.8 (-2.8; 6.6)
Traffic load within 100m on major roads (veh/day*m), per 10,000	243.6	-0.1 (-0.9; 0.6)	-0.3 (-0.8; 0.3)	0.7 (-0.7; 2.1)	2.3 (-2.3; 7.0)
		Leptin			
PM_{10} ($\mu g/m^3$)	7.9	7.2 (-1.2; 16.3)	5.6 (-4.1; 16.4)	15.9 (-3.1; 38.7)	-0.6 (-20.7; 24.6)
PM_{coarse} ($\mu g/m^3$)	3.6	7.1 (-1.5; 16.5)	3.8 (-6.0; 14.6)	17.9 (-1.5; 41.2)	7.2 (-14.8; 35.0)
$PM_{2.5}$ ($\mu g/m^3$)	2.8	6.9 (-1.5; 16.0)	3.5 (-6.2; 14.2)	16.8 (-1.6; 38.6)	8.2 (-13.0; 34.4)
$PM_{2.5}$abs (10^{-5}/m)	0.5	2.0 (-5.3; 9.8)	-0.8 (-9.1; 8.2)	**22.5 (4.0; 44.2)**	-4.6 (-22.4; 17.2)
NO_x ($\mu g/m^3$)	22.9	**13.1 (4.6; 22.4)**	9.0 (-0.7; 19.6)	**31.5 (10.7; 56.2)**	16.6 (-6.5; 45.5)
NO_2 ($\mu g/m^3$)	11.9	**15.8 (7.2; 25.2)**	**11.8 (2.0; 22.5)**	**26.0 (6.3; 49.4)**	22.3 (-1.5; 51.8)
Traffic intensity on the nearest road (veh/day), per 1,000	7.5	-2.5 (-8.5; 3.9)	-2.7 (-9.5; 4.7)	5.1 (-9.2; 21.6)	0.4 (-17.7; 22.6)
Traffic load within 100m on major roads (veh/day*m), per 10,000	243.6	-2.0 (-8.0; 4.3)	-2.0 (-8.7; 5.3)	4.2 (-10.3; 20.9)	9.5 (-9.9; 33.0)
		hs-CRP			
PM_{10} ($\mu g/m^3$)	7.9	10.4 (-2.0; 24.3)	4.2 (-9.1; 19.3)	**38.6 (4.7; 83.6)**	8.0 (-27.7; 61.3)
PM_{coarse} ($\mu g/m^3$)	3.6	5.0 (-7.0; 18.5)	-1.7 (-14.5; 13.0)	**34.2 (1.2; 78.0)**	7.3 (-28.7; 61.5)
$PM_{2.5}$ ($\mu g/m^3$)	2.8	10.6 (-1.8; 24.5)	8.1 (-5.9; 24.1)	11.1 (-15.1; 45.4)	21.2 (-17.6; 78.2)
$PM_{2.5}$abs (10^{-5}/m)	0.5	7.1 (-3.7; 19.2)	1.8 (-9.9; 14.9)	22.9 (-4.9; 59.0)	23.5 (-14.2; 77.9)
NO_x ($\mu g/m^3$)	22.9	**14.6 (2.2; 28.5)**	8.3 (-4.9; 23.5)	**38.6 (5.7; 81.8)**	30.1 (-12.2; 92.8)
NO_2 ($\mu g/m^3$)	11.9	**14.7 (2.4; 28.3)**	5.3 (-7.4; 19.8)	**36.3 (4.4; 78.0)**	**52.4 (3.9; 123.4)**
Traffic intensity on the nearest road (veh/day), per 1,000	7.5	5.6 (-3.7; 15.8)	3.1 (-7.0; 14.3)	8.8 (-13.7; 37.1)	31.0 (-7.9; 86.4)
Traffic load within 100 m on major roads (veh/day*m), per 10,000	243.6	0.2 (-8.3; 9.5)	0.7 (-8.7; 11.1)	4.1 (-17.7; 31.6)	-0.9 (-29.8; 40.0)

HbA1c: hemoglobin A1c; hs-CRP: high sensitivity C-reactive protein; PM_{10}: particulate matter (PM) with diameter < 10 µm; PM_{coarse}: PM_{10} - $PM_{2.5}$; $PM_{2.5}$: PM with diameter < 2.5 µm; $PM_{2.5}$abs: the soot content (absorbance) of $PM_{2.5}$; NO_x: sum of nitrogen monoxide and nitrogen dioxide; NO_2: nitrogen dioxide.

*Adjusted for age, sex, and BMI.

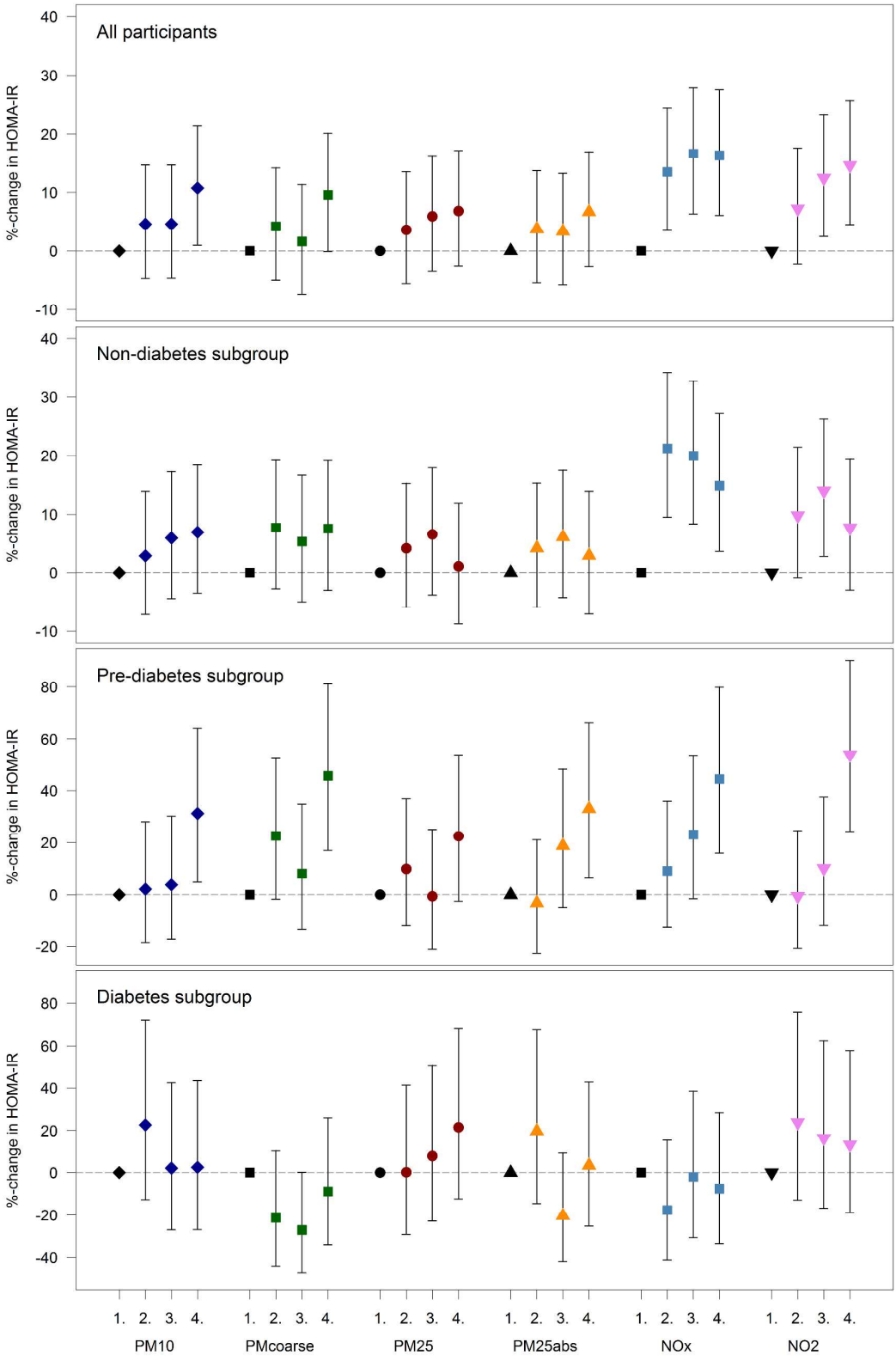
† Corresponds to the difference between the 5th-95th percentile of the corresponding exposure.

Supplementary Figure 1. Dose-response function for air pollutants (restricted cubic spline with 3 degrees of freedom) and HOMA-IR, adjusted for age, sex, BMI, waist-hip ratio, smoking status, month of blood withdrawal, and pack-years smoked (pre-diabetes group, n=496).



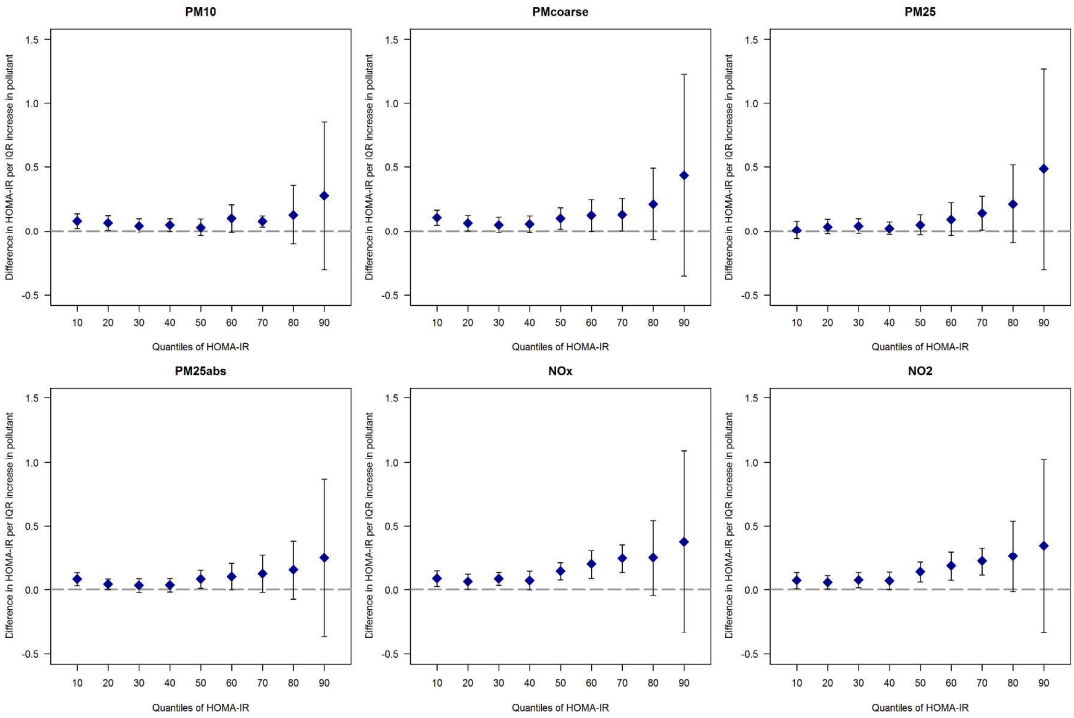
HOMA-IR: homeostasis model assessment-insulin resistance; PM_{10}: particulate matter (PM) with diameter < 10 µm; PM_{coarse}: PM_{10} - $PM_{2.5}$; $PM_{2.5}$: PM with diameter < 2.5 µm; $PM_{2.5}$abs: the soot content (absorbance) of $PM_{2.5}$; NO_x: sum of nitrogen monoxide and nitrogen dioxide; NO_2: nitrogen dioxide.

Supplementary Figure 2. Association between HOMA-IR and quartiles of air pollutant exposure (1. quartile is reference) adjusted for age, sex, BMI, waist-hip ratio, smoking status, month of blood withdrawal, and pack-years smoked.

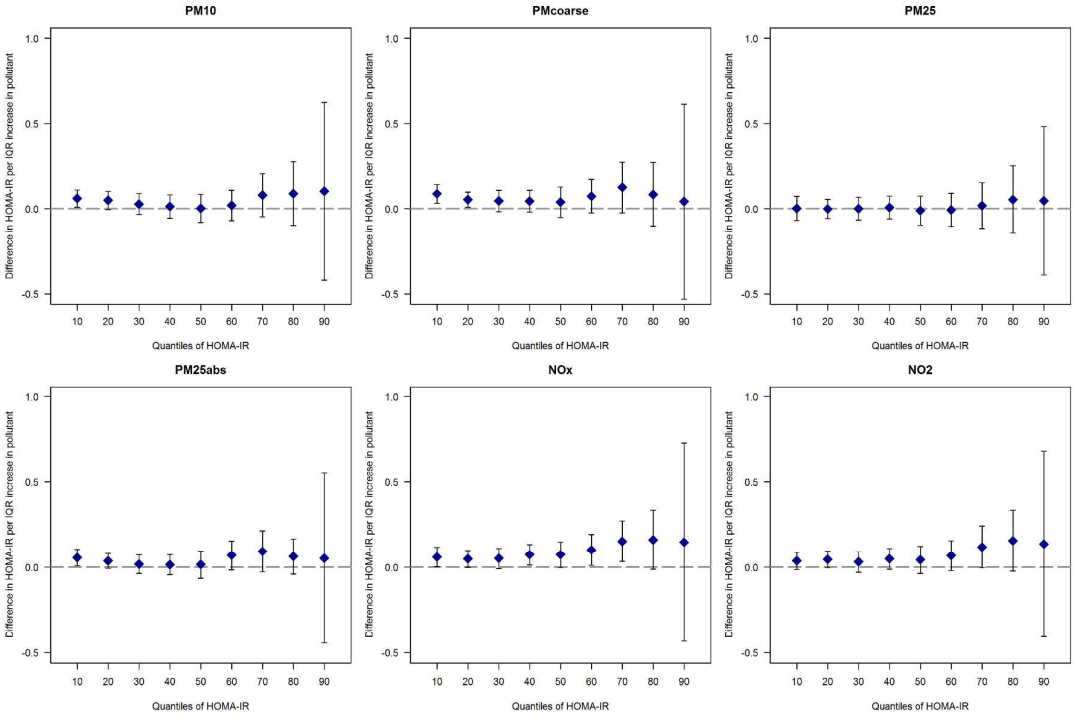


Supplementary Figures 3a) – d). Absolute difference in HOMA IR with 95% CI associated with an interquartile range increase in air pollutant exposure according to the deciles of HOMA IR adjusted for age, sex, BMI, waist-hip ratio, smoking status, and pack-years smoked*.

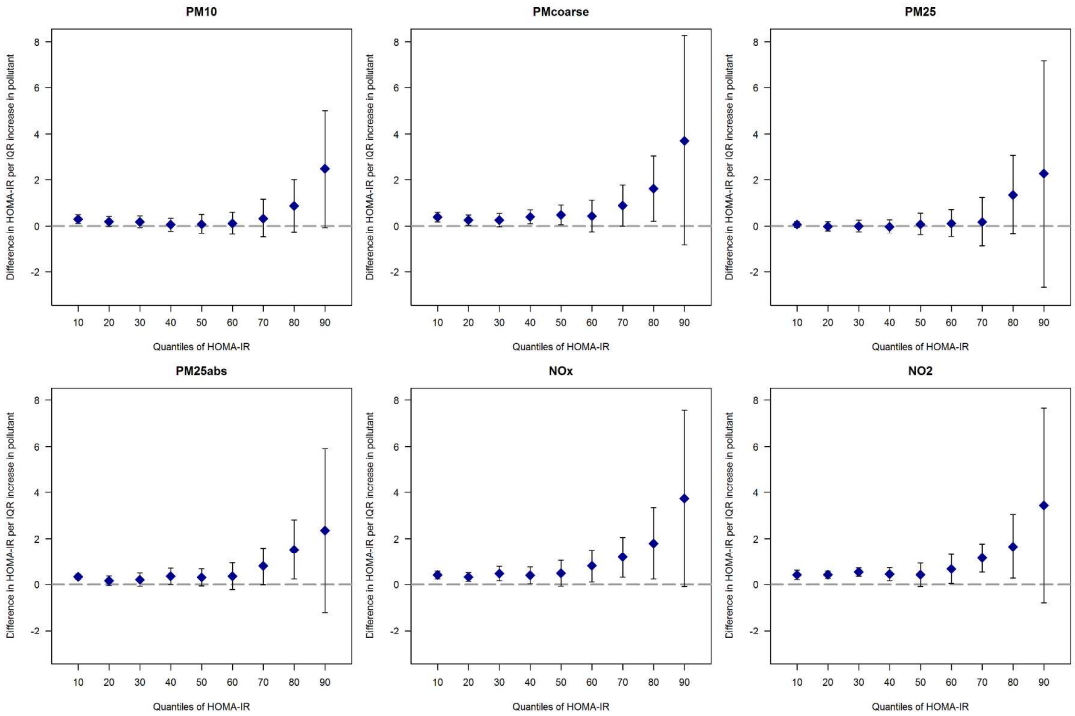
a) All participants



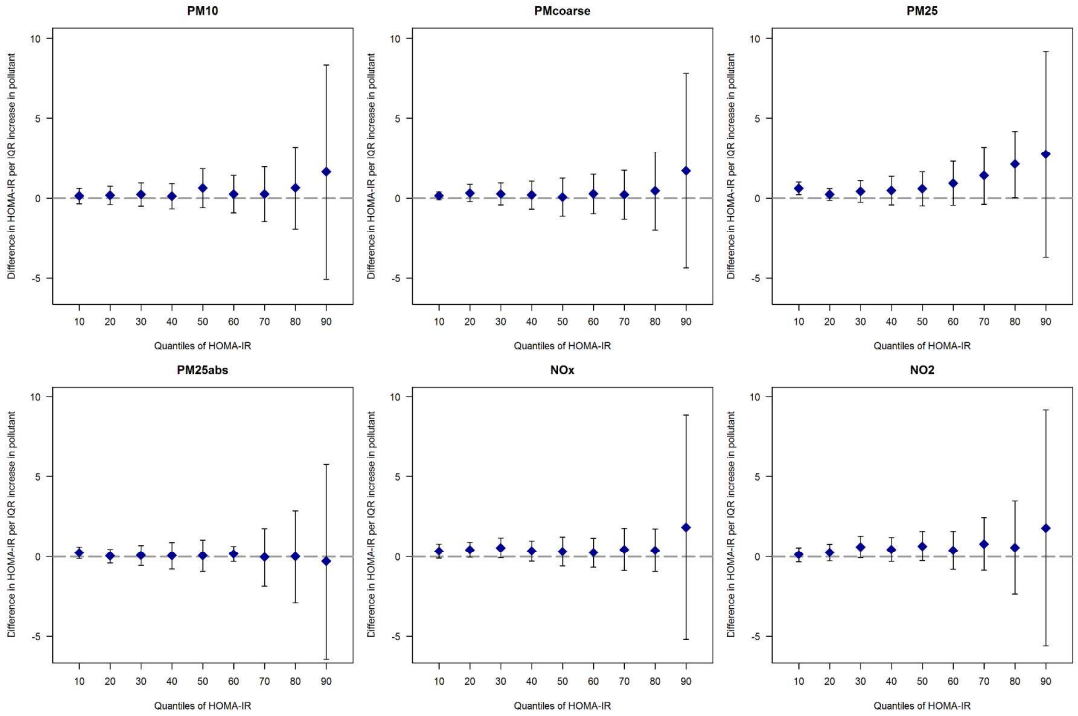
b) Non-diabetic participants



c) Pre-diabetic participants

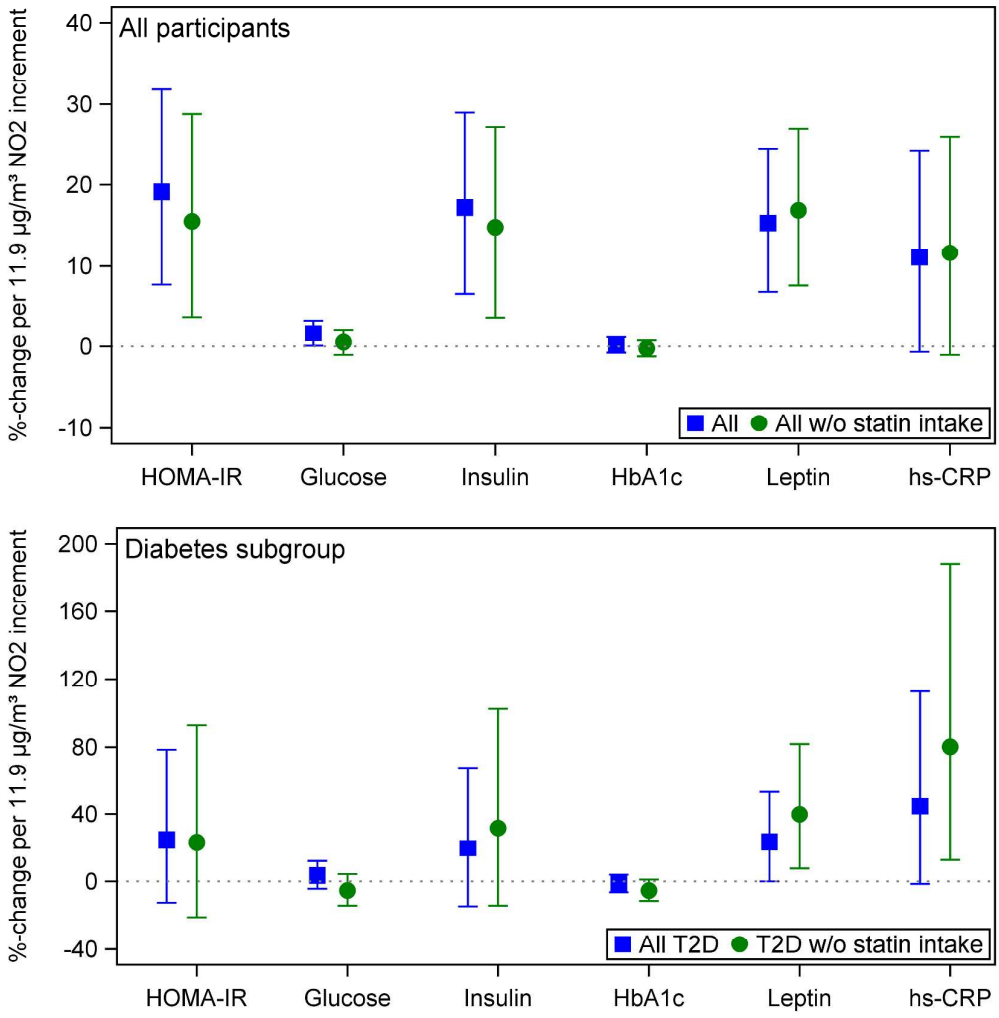


d) Diabetic participants



*We did not adjust for month of blood withdrawal as models partly did not converge. However, the air pollutant estimates of the default used mean regression models were almost similar when adjusted or not adjusted for month.

Supplementary Figure 4. Association between NO_2 and biomarkers presented as %-change* (with 95% CI) from geometric mean per 11.9 µg/m³ increment in NO_2 for all participants (top) and diabetic individuals (bottom).



NO_2: nitrogen dioxide; HOMA-IR: homeostasis model assessment-insulin resistance; HbA1c: hemoglobin A1c; hs-CRP: high sensitivity C-reactive protein.
*Adjusted for age, sex, smoking, BMI, waist-hip ratio, month of blood withdrawal, selected socio-economic- and lifestyle variables (see Online Supplementary Table 2).