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Air pollution and diabetes association: Modification by type 2 diabetes genetic risk score

Ikenna C. Eze [a,b], Medea Imboden [a,b], Ashish Kumar [a,b,c], Arnold von Eckardstein [d], Daiana Stolz [e], Margaret W. Gerbase [f], Nino Künzli [a,b], Marco Pons [g], Florian Kronenberg [h], Christian Schindler [a,b], Nicole Probst-Hensch [a,b,*]

[a] Swiss Tropical and Public Health Institute, Basel, Switzerland
[b] University of Basel, Basel, Switzerland
[c] Karolinska Institutet, Stockholm, Sweden
[d] Institute of Clinical Chemistry, University Hospital Zurich, Zurich, Switzerland
[e] Clinic of Respiratory Medicine and Pulmonary Cell Research, University Hospital Basel, Basel, Switzerland
[f] Faculty of Medicine, University of Geneva, Geneva, Switzerland
[g] Department of Internal Medicine, Regional Hospital of Lugano, Lugano, Switzerland
[h] Division of Genetic Epidemiology, Department of Medical Genetics, Molecular and Clinical Pharmacology, Medical University of Innsbruck, Innsbruck, Austria

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ABSTRACT

Exposure to ambient air pollution (AP) exposure has been linked to type 2 diabetes (T2D) risk. Evidence on the impact of T2D genetic variants on AP susceptibility is lacking. Compared to single variants, joint genetic variants contribute substantially to disease risk. We investigated the modification of AP and diabetes association by a genetic risk score (GRS) covering 63 T2D genes in 1524 first follow-up participants of the Swiss cohort study on air pollution and lung and heart diseases in adults. Genome-wide data and covariates were available from a nested asthma case-control study design. AP was estimated as 10-year mean residential particulate matter <10 μm (PM_{10}). We computed count-GRS and weighted-GRS, and applied PM_{10} interaction terms in mixed logistic regressions, on odds of diabetes. Analyses were stratified by pathways of diabetes pathology and by asthma status. Diabetes prevalence was 4.6% and mean exposure to PM_{10} was 22 μg/m^3. Odds of diabetes increased by 8% (95% confidence interval: 2, 14%) per T2D risk allele and by 35% (−8, 97%) per 10 μg/m^3 exposure to PM_{10}. We observed a positive interaction between PM_{10} and count-GRS on diabetes [$OR_{interaction}$ = 1.10 (1.01, 1.20)], associations being strongest among participants at the highest quartile of count-GRS [OR: 1.97 (1.00, 3.87)]. Stronger interactions were observed with variants of the GRS involved in insulin resistance [($OR_{interaction}$ = 1.22 (1.00, 1.50)] than with variants related to beta-cell function. Interactions with count-GRS were stronger among asthma cases. We observed similar results with weighted-GRS. Five single variants near *GRB14*, *UBE2E2*, *PTPRD*, *VPS26A* and *KCNQ1* showed nominally significant interactions with PM_{10} ($P < 0.05$). Our results suggest that genetic risk for T2D may modify susceptibility to air pollution through alterations in insulin sensitivity. These results need confirmation in diabetes cohort consortia.

1. Introduction

Epidemiologic evidence shows a positive association between air pollution and type 2 diabetes (T2D) risk (Eze et al., 2014a, 2015a; Park et al., 2015). The underlying mechanisms and susceptibilities are still subject to active research. Effects of inhaled pollutants that are supported by experimental and epidemiological evidence include the contribution to systemic inflammation, autonomic imbalance, weight gain, and to insulin resistance, thought to be in part the result of inhalants stimulating an innate immune response, influencing endoplasmic reticulum, glucose and lipid metabolism, and activating the central nervous system (Rao et al., 2015).

Abbreviations: BCF, beta cell function; BMI, body mass index; CI, confidence interval; CNG, Centre National de Génotypage; DNA, deoxyribonucleic acid; EDTA, ethylenediaminetetraacetic acid; GEI, gene-environment interaction; GWAS, genome-wide association studies; GRS, genetic risk score; GRS_{IR}, genetic risk score of variants in the insulin resistance pathway; GRS_{BCF}, genetic risk score of variants in the beta-cell function pathway; HbA1c, glycosylated haemoglobin; HWE, Hardy-Weinberg equilibrium; IPW, inverse probability weighting; IR, insulin resistance; MAF, minor allele frequency; OR, odds ratio; $PM_{2.5}$, particulate matter with diameter < 2.5 μm; PM_{10}, particulate matter with diameter < 10 μm; RAF, risk allele frequency; SAPALDIA, Swiss cohort study on air pollution and lung and heart diseases in adults; SNP, single nucleotide polymorphism; T1D, type 1 diabetes; T2D, type 2 diabetes.

* Corresponding author at: Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Socinstrasse 57, CH-4002 Basel, Switzerland.
E-mail address: Nicole.Probst@unibas.ch (N. Probst-Hensch).

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Gene-environment interaction (GEI) can inform on biological pathways by which air pollution affects diabetes, an aspect of relevance to air quality regulation. So far, GEI studies in areas of air pollution have focused on candidate genes in the domains of oxidative stress and inflammation on cardio-respiratory and metabolic outcomes (Curjuric et al., 2012; Eze et al., 2016; Minelli et al., 2011; Zanobetti et al., 2011). The degree of reduction in markers of heart rate variability, in relation to air pollutants, was associated with deletions in *GSTM1* (Chahine et al., 2007), long GT repeats of *HMOX-1* (Schwartz et al., 2005), wild-type *HFE* (Park et al., 2006), and *IL6*-572GC (Adam et al., 2014). A stronger effect of ozone on lung function was reported among carriers of combined *NQOI* wild-type/*GSTM1* null genotype, *GSTP1* and long GT repeats on *HMOX-1* (Alexeeff et al., 2008; Chen et al., 2007). A variant in *CDH13* showed the strongest signal in a genome-wide interaction study between PM_{10} and lung function decline (Imboden et al., 2015). Particle number significantly increased fibrinogen concentrations in individuals with high genetic risk score (GRS) of genes in the oxidative stress pathway, and increased C-reactive proteins and intracellular adhesion molecule-1 concentrations in individuals with higher genetic scores of metal-processing gene variants (Bind et al., 2014).

Over the years, T2D susceptibility loci have been increasingly identified through meta-analyses of agnostic genome-wide analyses. So far, >60 T2D genetic risk variants have been identified (Morris et al., 2012). By selecting diabetes gene risk variants identified in genome-wide association studies (GWAS) for interaction with air pollution, a novel mechanistic understanding may evolve. This approach has been applied to factors other than air pollution, and to single diabetes gene risk variants (Cornelis and Hu, 2012).

Physical activity and variants near the *FTO* gene are one of the most studied GEI in T2D (Kilpelainen and Franks, 2014), demonstrating an attenuation of the effect of an *FTO* variant on BMI among the physically active compared to the inactive (Kilpelainen et al., 2011). Variants near *HNF1B* (Brito et al., 2009) and *CDKN2A* also interacted with physical activity on T2D incidence (Moore et al., 2008). The Pro12Ala variant of *PPARG* was shown to modify the association between physical activity and glucose regulation in people with (Adamo et al., 2005) and without diabetes (Kahara et al., 2003). Evidence from GEI studies on nutrition and T2D also demonstrated that the carriers of this *PPARG* variant are more responsive to the beneficial effects of unsaturated fat and less susceptible to the adverse effects of saturated fat on glucose regulation and/or body mass index (Lamri et al., 2012). Carriers of a *TCF7L2* risk variant had a lower T2D risk when they were on low glycemic diet (Cornelis et al., 2009a). An *SLC30A8* variant modified the negative relationship between zinc intake and glucose homeostasis (Kanoni et al., 2011).

Compared to single genetic variants, a combination of genetic variants may contribute more substantially to disease risk and might thus be useful to better characterize high-risk populations (Talmud et al., 2015; Vassy et al., 2014). Few studies have explored the impact of the T2D genetic risk score on its associated phenotypes such as coronary artery disease (Hamad et al., 2015), or explored its modifying effect on the diabetes association with basic risk factors including age, sex, physical activity (Langenberg et al., 2014), weight gain (Andersson et al., 2013), obesity and family history (Cornelis et al., 2009b; Langenberg et al., 2014). No study explored the interaction of the T2D genetic risk score with air pollution.

Several studies on the effects of T2D risk variants on quantitative traits of glucose metabolism have identified pathways through which some of these variants impact on T2D. Pathways through which the risk variants impact directly on T2D include the impairment of beta-cell function (BCF) and insulin resistance (IR) (Dimas et al., 2014; Harder et al., 2013; Manning et al., 2012; Perry and Frayling, 2008; Scott et al., 2012) or other pathways may confer insulin resistance indirectly through obesity risk increasing genetic variants (near *FTO* and *M4CR*) (Perry and Frayling, 2008; Scott et al., 2014).

We generated GWAS-derived polygenic risk scores and explored modification of our previously reported association between air pollutants and diabetes (Eze et al., 2014a) among participants of the Swiss cohort study on air pollution and lung and heart diseases in adults (SAPALDIA), in general and in pathway-analyses approach. Genome-wide data and detailed covariate information were available from a previous nested asthma case-control study design.

2. Materials and methods

2.1. Study population and sample selection

The SAPALDIA study has been described elsewhere (Martin et al., 1997) but in brief, the participants include 9651 population-representative adults, aged 18 to 60 years when they were recruited in 1991, from eight Swiss communities (Aarau, Basel, Davos, Geneva, Lugano, Montana, Payerne, and Wald) which represent the diverse geographic characteristics of Switzerland. At baseline (SAPALDIA1) and first follow-up in 2002 (SAPALDIA2), 8047 participants had computer-assisted interviews on health and lifestyle characteristics. Venipuncture for biomarker and genetic assays was also done at follow-up. Details of follow-up participation rates can be found elsewhere (Ackermann-Liebrich et al., 2005). Participants gave prior written informed consent (including to genetic testing). The study protocols were approved by the Swiss National Ethics Committee and the Regional Ethics Committees of the eight study centers. As part of the European asthma consortium, GABRIEL, a nested asthma case-control study was designed using the SAPALDIA2 samples and data involving 1612 participants (Moffatt et al., 2010). Participants were identified as having asthma if they responded "yes" to the question: "have you ever been diagnosed of asthma"? Corresponding controls were selected from participants who responded "no" to this question. Eligible participants in the GABRIEL study comprised 654 asthma cases and 958 randomly selected asthma controls (Moffatt et al., 2010) and underwent genome-wide typing. The present cross-sectional analyses include 1524 (615 asthma cases and 913 controls) SAPALDIA2 participants who had genome-wide data and data on other relevant variables for current research question.

2.2. Case identification

We identified participants with diabetes as having at least one of the following at follow-up: a self-report of physician-diagnosed diabetes; use of diabetes medication in the past month; non-fasting blood glucose >11.1 mmol/L or HbA1c > 0.065. HbA1c was measured only in participants with non-fasting glucose > 6.1 mmol/L (Eze et al., 2014b). We did not have information on diabetes status at baseline, thus precluding the study of incident diabetes.

2.3. Air pollution exposure assignment

Consistent with our previous publication (Eze et al., 2014a), we considered 10-year mean residential exposure to particulate matter <10 μm (PM_{10}) as our air pollution exposure measure of interest. We did not consider nitrogen dioxide (NO_2) in this study because PM_{10} showed a sustained effect on diabetes and metabolic syndrome independent of NO_2 (in adjusted two-pollutant models) in the SAPALDIA cohort (Eze et al., 2014a, 2015b). PM_{10} was assigned to participants' residential addresses in 1990 and 2000 using validated dispersion models, at a resolution of 200 m × 200 m, based on various emission inventories including road and rail traffic, agriculture and industries (Liu et al., 2007). Annual estimates of ambient residential PM_{10} levels of up to ten years of follow-up were computed using annual trends at fixed monitoring stations closest to the residential addresses, and participants' residential histories. We computed 10-year means as a marker of long-term exposure to PM_{10} (Eze et al., 2014a).

2.4. Genotyping, imputation and selection of T2D risk variants

Genomic DNA was extracted using PUREGENE™ DNA Purification Kit (GENTRA Systems, Minneapolis, USA), from EDTA-buffered whole blood (Ackermann-Liebrich et al., 2005). Whole genome genotyping was done at the Centre National de Génotypage (CNG, Evry, France) within the nested asthma case-control study (N = 1612), using Illumina Human610K Quad BeadChip (Illumina, San Diego, CA, USA) covering 567′589 autosomal single nucleotide polymorphisms (SNPs) (Moffatt et al., 2010). Following quality control, 35 participants were excluded for having low genotyping call rate (<97%), leaving 1577 participants with high quality genome-wide data for analyses. Successfully genotyped SNPs were imputed to 2.5 million SNPs using MaCH v1.0 (Li et al., 2010; Soler Artigas et al., 2015).

T2D risk variants were selected if they were identified or confirmed as achieving genome-wide significance ($P < 5 \times 10^{-8}$) irrespective of population ancestry. A recent meta-analysis identified 65 T2D variants reaching genome-wide significance (Morris et al., 2012). We included 63 T2D in our GRS. Genotype data on two variants (rs6819243 near gene *MAEA* and rs4458523 near *WFS1*) on chromosome 4 (including proxies with $R^2 \geq 0.8$) were not captured on the Illumina 610 K Quad BeadChip, thus, the genetic risk scores computed for this study were based on 63 T2D SNPs each representing the top GWAS-identified variant of one T2D associated locus.

2.5. Genetic risk scores

We computed two polygenic risk scores, "count-GRS" and "weighted-GRS", based on the 63 selected SNPs. We calculated the count-GRS by summing up the number of risk alleles across the 63 SNPs, giving a minimum of 52 risk alleles and a maximum of 82 risk alleles. Count-GRS assumes that alleles contribute to disease risk in an additive manner, i.e., with a value of 0 for non-risk and 1 for each risk allele (Cornelis et al., 2009b). The additive model is more plausible when the genetic model is unknown (Balding, 2006). We calculated the weighted-GRS by first, weighting by size of the beta-coefficients derived from the largest genome-wide meta-analysis on T2D (Morris et al., 2012). We weighted the SNPs by multiplying the number of risk alleles of each SNP (i.e., 0, 1, and 2) by the reported beta-coefficient associated with the SNP. Next, we summed up the products across the 63 SNPs. To facilitate interpretation of effect size per risk allele, and enable comparison with count-GRS, we standardized the weighted-GRS by dividing it by 5.34 (the sum of the beta-coefficients) and multiplying by 63 (the possible maximal number of risk variants) (Cornelis et al., 2009b). The minimum and maximum weighted-GRS were 49.9 and 84.6 risk alleles respectively.

We also computed count- and weighted-GRS, using the same procedure, for the major pathway markers of T2D pathology including insulin resistance (count-GRS_{IR}; weighted-GRS_{IR}; involving variants near *GCKR*, *GRB14*, *IRS1*, *PPARG*, *ANKRD55*, *KLF14*, *HMGA2*, *FTO*, *M4CR* and *PEPD*) and beta-cell function (count-GRS_{BCF}; weighted-GRS_{BCF}; involving variants near *PROX1*, *THADA*, *UBE2E2*, *ADCY5*, *IGF2BP2*, *CDKAL1*, *DGKB*, *GCK*, *ANK1*, *SLC30A8*, *GLIS3*, *CDKN2A/B*, *CDC123*, *HHEX/IDE*, *TCF7L2*, *KCNQ1*, *KCNJ11*, *ARAP1*, *MTNR1B*, *C2CD4A* and *BCAR1*) or of related traits likely to mediate insulin resistance based on two T2D GWAS variants, one near *FTO* and one in the *M4CR* gene.

2.6. Potential confounders

Similar to our previous publication on air pollution and diabetes (Eze et al., 2014a), we considered the following potential confounders: age (years; continuous), sex, body mass index (kg/m^2; continuous), years of formal education (≤9; >9), neighborhood socio-economic index (expressed as a percentage; developed from a principal component analysis involving occupation and educational level of household head, median rent and number of persons in a household (Panczak et al., 2012)). Additionally we considered active smoking history (never, former, current; and pack-years), exposure to passive smoke (yes/no) and occupational vapors, gases, dusts and fumes (yes/no), as well as nutritional habits like alcohol consumption (including beers, wines, spirits and liquors: never; ≤1 glass/day; >1 glass/day); consumption of at least one portion of fruits and raw vegetables respectively (never; ≤3 days/week; >3 days/week) and moderate physical activity (defined as at least 150 min/week of participation in activities that make one out of breath). All models were adjusted for genome-wide population stratification.

2.7. Statistical analyses

We summarized characteristics at follow-up of participants with and without diabetes and contrasted them to follow-up participants not included in the current analysis. We assessed risk allele frequency (RAF) and Hardy-Weinberg equilibrium of the selected risk variants. We explored associations of diabetes with GRS and with ambient air pollution in this sample.

We first assessed interactions between PM_{10} and each of the 63 T2D genetic risk variants on diabetes. Then we fitted interaction terms between the GRS and PM_{10}, on a continuous scale to assess potential risk dependent effect modification. We also explored associations between PM_{10} and diabetes across quartiles of GRS. For the pathway-related genetic risk, we fitted interaction terms between count- and weighted-GRS, and PM_{10} for insulin resistance, obesity-mediated insulin resistance and beta cell function pathway separately (count-GRS_{IR} and count-GRS_{BCF}) to explore their specific interaction with PM_{10} on diabetes. In sensitivity analyses, we repeated all analyses with weighted-GRS by i) stratifying our analyses by asthma status, ii) omitting BMI from covariates, iii) assessing impact of selection bias by applying inverse probability weighting (IPW) to the models and iv) performing models with study center as fixed effect. All analyses were performed with STATA version 14 [STATA Corporation, Texas, USA] and involved mixed logistic regression models, with random intercepts by study area.

3. Results

Characteristics at the first follow-up (SAPALDIA2) of participants and non-participants in the presented analyses and comparison of the included participants with and without diabetes are presented in Table 1.

Overall, the participant characteristics were similarly distributed between the included (no diabetes) and excluded participants, despite a low inclusion rate of ~20% (Table 1). Among included participants, diabetes prevalence was 4.6%, and highly comparable to the diabetes prevalence in the non-participants (4.7%); and mean PM_{10} exposure was 22.1 μg/m^3 in participants and 22.5 μg/m^3 in non-participants. Compared to participants without diabetes, diabetes cases were more likely to be male, of lower social status, obese, smokers and consumed more alcohol. Moreover, they were exposed to higher PM_{10} concentrations. Prevalent asthma and mean count- and weighted GRS were also significantly higher among participants with diabetes (Table 1). Mean (SD) count-GRS was 67 (4.8) risk alleles whereas mean (SD) weighted-GRS was 66.5 (5.3) risk alleles. Both GRS were normally distributed in the study population (0.4 ≤ P-value of Shapiro-Wilk test ≤0.8). Table 2 describes all included SNPs, indicating chromosomal location, nearby gene, risk allele and its frequency. All SNPs were in Hardy-Weinberg Equilibrium ($P > 0.01$), with risk allele frequency (RAF) ≥3%.

The previously published positive association between PM_{10} and diabetes (Eze et al., 2014a) persisted in this smaller sample in both crude (odds ratio (OR): 1.23 (0.88, 1.73) per 10μg/m^3 exposure to PM_{10}) and adjusted models (OR: 1.35 (0.92, 1.97)). Additional adjustment for count-GRS (while adjusting for BMI), and removal of BMI (while adjusting for count-GRS) only increased the odds of diabetes by 2% and 6% respectively.

Table 1
Characteristics of participants at first follow-up of SAPALDIA study, included and excluded from present study.

Characteristics (% or mean (SD))	Diabetes N = 70	No diabetes N = 1454	Excluded % or mean (SD); N
Age (years)	60.7 (8.4)	51.5 (11.3)[a]	52.1 (11.6); 6156
Females	33.8	51.7[a]	52.1; 6156
Body mass index (kg/m^2)	30.6 (5.2)	25.7 (4.3)[a]	25.9 (4.5); 5074
Formal education ≤9 years	15.5	6.1[a]	8.7; 6145[b]
Neighborhood socio-economic index (%)	60.9 (9.8)	63.6 (10.2)[a]	63.3 (10.3); 6466
Ever-smokers	70.4	56.1[a]	58.1; 6523
Pack-years smoked	16.6 (27.4)	9.9 (17.6)[a]	11.3 (18.7); 5972
Exposure to passive smoke	54.9	47.5	47.6; 6523
Occupational exposure to vapors, gases, dusts and fumes	48.6	43.0	31.0; 6523[b]
Alcohol consumption >1 glass/day	11.4	8.2	9.4; 5038
Consumption of fruits - never/seldom	7.0	8.9	8.9; 5036
Consumption of raw vegetables - Never/seldom	4.2	2.0	2.0; 5040
150 min of moderate physical activity /week	51.4	46.8	49.9; 5019
Asthma cases	52.1	39.9[a]	43.4; 53
Diabetes cases	100	0[a]	4.7
10-year mean PM_{10} (μg/m^3)	23.1 (7.0)	22.0 (7.0)	22.5 (7.5); 6052
Total count-GRS	68.5 (4.8)	66.9 (4.7)[a]	67.3 (3.9); 53
Total weighted-GRS	68.2 (5.2)	66.4 (5.3)[a]	66.6 (4.4); 53
Insulin resistance count-GRS	10.8 (2.1)	10.4 (1.9)	10.4 (1.8); 53
Insulin resistance weighted-GRS	10.7 (2.2)	10.4 (2.0)	10.4 (2.0); 53
Beta-cell function count-GRS	24.1 (3.1)	23.5 (3.2)	20.7 (2.7); 53
Beta-cell function weighted-GRS	20.7 (2.7)	19.9 (3.1)[a]	2.2 (0.3); 53
Insulin resistance (obesity variants) count-GRS	1.6 (0.9)	1.4 (0.9)	1.6 (1.0); 53
Insulin resistance (obesity variants) weighted-GRS	1.7 (1.0)	1.4 (1.0)[a]	1.6 (1.0); 53

GRS: genetic risk score; PM_{10}: particulate matter <10 μm in diameter; SAPALDIA: Swiss cohort study on air pollution and lung and heart diseases in adults.
[a] Significant difference in proportion or mean between diabetes cases and participants without diabetes ($P < 0.05$).
[b] Significant difference in proportions or means between participants and non-participants of the presented analyses ($P < 0.05$).

The direction of association of 41 alleles agrees with that of published risk alleles on T2D, despite perfect agreement in the RAFs (Supplementary Table 1). We observed positive associations between count- and weighted-GRS and diabetes in our sample. In the crude model, odds of diabetes was increased by 7% (2, 12%) and 6% (2, 11%) per unit of count- and weighted-GRS respectively. Adjusted models, which did not depend on adjustment for BMI or PM_{10}, showed similar results (Table 2).

Table 2 also shows the results of the single SNP interactions with PM_{10} on the odds of diabetes. Interaction with only five variants (near *GRB14*, *UBE2E2*, *PTPRD*, *VPS26A* and *KCNQ1*) showed nominal significance ($P < 0.05$). Although nominally non-significant, we observed strong interaction signals with variants near *THADA*, *PPARG*, *KLF14*, *ZMIZ1*, *DUSP8*, *ARAP1*, *PRC1* and *FTO* (Table 2). No single variant interaction remained significant following Bonferroni correction at $P < 0.0016$ (0.1/63), false discovery rate $P < 0.0016$ ($0.1 * 1/63$) or family-wise error rate $P < 0.0016$ ($1-(1-0.1)^{1/63}$).

Looking at the combination of T2D variants, we observed a significant positive interaction between 10-year mean PM_{10} and 63-loci GRS (Table 2). The association between PM_{10} and diabetes increased across quartiles of count-GRS, being strongest among those in the highest quartile of genetic risk (Table 3). Compared to those at lowest genetic risk (Q1), odds of diabetes (per 10 μg/m^3 exposure to PM_{10}) increased by 106% among those at highest risk (Q4). Interactions between PM_{10} and weighted-GRS on odds of diabetes were similar, and sometimes stronger, compared to those observed with count-GRS (Table 3).

Fig. 1 shows interaction odds ratios for PM_{10} and pathway-specific GRS. Odds of diabetes (per 10μg/m^3 exposure to PM_{10}) increased by 22% (95% CI: 0, 49%) per T2D risk allele of insulin resistance GRS (count-GRS_{IR}).

We observed a positive and weaker interaction with beta cell function GRS (count-GRS_{BCF}), the odds of diabetes (per 10 μg/m^3 exposure to PM_{10}) increased by 6% (−8, 22%) per T2D risk allele of count-GRS_{BCF} (Fig. 1). Interactions with weighted-GRS were almost identical to those observed with count-GRS for both pathways (Supplementary Table 2), and were insensitive to BMI in the interaction model.

Interactions with 63-loci GRS were comparable between asthma cases and controls, but pathway-specific GRS_{IR} showed stronger significant interactions with PM_{10} among asthma cases (Fig. 2).

When considering only obesity-dependent variants in the count-GRS_{IR}, asthma cases had a more than twofold increased odds of diabetes (per 10 μg/m^3 exposure to PM_{10} and per T2D risk variant) (Fig. 2). These observations were also very consistent with weighted-GRS (Supplementary Table 2) and were insensitive to BMI. When comparing participants by asthma status, significant differences were only observed for age, BMI, alcohol consumption and diabetes status (Supplementary Table 3).

Sensitivity analyses proved robust results. In particular, interactions were not sensitive to body mass index. Adjusting the analyses for selection bias or treating study area as fixed effect also did not change the results of PM_{10}-GRS interactions (Table 4).

4. Discussion

This is the first study to show a positive interaction between T2D polygenic risk and particulate matter, on prevalent diabetes. Individuals at higher genetic risk for diabetes were more susceptible to PM_{10}. This was especially true for genetic variants functionally related to T2D through alteration of insulin sensitivity. Our findings, which remained robust across sensitivity analyses, also indicate that stronger associations may be observed in pathway-based analyses, providing a promising handle to disentangle the complex disease etiology by assessing gene-environment interactions.

Similar to our finding of a positive relationship between T2D polygenic risk and diabetes and its modifiability by air pollution, in the Health Professionals Follow-up and Nurses' Health Study, a ten-SNP score-associated risk of T2D was higher among the obese and persons with family history of diabetes (Cornelis et al., 2009b). Another study of a GRS of 49 SNPs also showed the positive association with incident T2D to be modified by age and obesity (Langenberg et al., 2014). A study by Andersson et al (Andersson et al., 2013) showed a polygenic risk score of 46 SNPs to predict T2D especially among weight gainers (Andersson et al., 2013). A 65-loci GRS was associated with prevalent

Table 2
Interactions of PM_{10} with candidate SNPs and genetic risk scores on the odds of diabetes in the SAPALDIA study.

RS number	CHR	Gene$_{(pathway)}$[a]	Risk/other allele	Risk allele frequency	Association with diabetes[b]	Increase in odds of diabetes per 10 μg/m^3 increase in PM_{10}[b]
					OR (95% CI)	OR (95% CI)
rs10923931	1	*NOTCH2*	T/G	0.09	0.89 (0.46, 1.71)	0.73 (0.29, 1.87)
rs2075423	1	*PROX1*$_{(BCF)}$	G/T	0.64	0.71 (0.49, 1.04)	1.15 (0.66, 1.99)
rs780094	2	*GCKR*$_{(IR)}$	C/T	0.54	1.07 (0.74, 1.55)	0.77 (0.46, 1.27)
rs10203174	2	*THADA*$_{(BCF)}$	C/T	0.89	2.20 (1.02, 4.71)[c]	0.35 (0.11, 1.13)
rs243088	2	*BCL11A*	T/A	0.48	0.95 (0.66, 1.37)	0.71 (0.43, 1.19)
rs7569522	2	*RBMS1*	A/G	0.47	1.16 (0.78, 1.73)	0.76 (0.43, 1.32)
rs13389219	2	*GRB14*$_{(IR)}$	C/T	0.62	0.85 (0.58, 1.24)	2.19 (1.26, 3.80)[c]
rs2943640	2	*IRS1*$_{(IR)}$	C/A	0.66	1.19 (0.80, 1.17)	1.33 (0.74, 2.38)
rs1801282	3	*PPARG*$_{(IR)}$	C/G	0.89	0.75 (0.42, 1.33)	0.55 (0.23, 1.28)
rs1496653	3	*UBE2E2*$_{(BCF)}$	A/G	0.82	0.80 (0.49, 1.31)	1.98 (1.01, 3.90)[c]
rs12497268	3	*PSMD6*	G/C	0.84	0.95 (0.56, 1.61)	1.28 (0.55, 2.96)
rs6795735	3	*ADAMTS9*	C/T	0.56	1.27 (0.85, 1.88)	0.69 (0.40, 1.21)
rs11717195	3	*ADCY5*$_{(BCF)}$	T/C	0.80	1.35 (0.83, 2.20)	0.65 (0.31, 1.37)
rs4402960	3	*IGF2BP2*$_{(BCF)}$	T/G	0.31	1.25 (0.84, 1.86)	1.17 (0.65, 2.12)
rs17301514	3	*ST64GAL1*	A/G	0.10	1.51 (0.86, 2.63)	0.97 (0.42, 2.26)
rs459193	5	*ANKRD55*$_{(IR)}$	G/A	0.74	0.99 (0.63, 1.57)	1.11 (0.60, 2.07)
rs6878122	5	*ZBED3*	G/A	0.30	1.00 (0.67, 1.49)	1.00 (0.56, 1.79)
rs7756992	6	*CDKAL1*$_{(BCF)}$	G/A	0.28	1.24 (0.82, 1.88)	1.20 (0.65, 2.21)
rs4299828	6	*ZFAND3*	A/G	0.72	0.96 (0.61, 1.50)	1.06 (0.55, 2.06)
rs3734621	6	*KCNK16*	C/A	0.03	1.03 (0.37, 2.88)	1.20 (0.34, 4.24)
rs17168486	7	*DGKB*$_{(BCF)}$	T/C	0.15	0.98 (0.58, 1.66)	1.85 (0.83, 4.15)
rs849135	7	*JAZF1*	G/A	0.50	0.87 (0.60, 1.25)	1.27 (0.76, 2.14)
rs10278336	7	*GCK*$_{(BCF)}$	A/G	0.60	1.01 (0.68, 1.49)	1.13 (0.64, 1.99)
rs17867832	7	*GCC1*	T/G	0.92	0.89 (0.44, 1.79)	1.01 (0.36, 2.81)
rs13233731	7	*KLF14*$_{(IR)}$	G/A	0.54	1.46 (0.99, 2.15)	1.61 (0.91, 2.83)
rs516946	8	*ANK1*$_{(BCF)}$	C/T	0.73	1.05 (0.69, 1.60)	0.75 (0.41, 1.39)
rs7845219	8	*TP53INP1*	T/C	0.50	1.06 (0.74, 1.52)	0.90 (0.53, 1.53)
rs3802177	8	*SLC30A8*$_{(BCF)}$	G/A	0.73	0.88 (0.59, 1.31)	1.38 (0.75, 2.53)
rs10758593	9	*GLIS3*$_{(BCF)}$	A/G	0.42	1.07 (0.74, 1.55)	1.00 (0.58, 1.74)
rs16927668	9	*PTPRD*	T/C	0.24	1.26 (0.83, 1.91)	0.50 (0.28, 0.92)[c]
rs10811661	9	*CDKN2A/B*$_{(BCF)}$	T/C	0.80	1.54 (0.92, 2.58)	0.86 (0.42, 1.79)
rs17791513	9	*TLE4*	A/G	0.94	1.57 (0.63, 3.94)	0.95 (0.20, 4.41)
rs2796441	9	*TLE1*	G/A	0.61	1.08 (0.73, 1.59)	1.01 (0.58, 1.73)
rs11257655	10	*CDC123*$_{(BCF)}$	T/C	0.20	0.86 (0.54, 1.37)	1.23 (0.62, 2.43)
rs12242953	10	*VPS26A*	G/A	0.93	0.79 (0.41, 1.53)	2.96 (1.04, 8.41)[c]
rs12571751	10	*ZMIZ1*	A/G	0.54	1.01 (0.69, 1.48)	1.52 (0.90, 2.57)
rs1111875	10	*HHEX/IDE*$_{(BCF)}$	C/T	0.61	1.03 (0.71, 1.51)	1.30 (0.77, 2.21)
rs7903146	10	*TCF7L2*$_{(BCF)}$	T/C	0.33	1.33 (0.91, 1.94)	0.81 (0.47, 1.40)
rs2334499	11	*DUSP8*	T/C	0.40	0.80 (0.55, 1.15)	1.59 (0.92, 2.75)
rs163184	11	*KCNQ1*$_{(BCF)}$	G/T	0.47	1.16 (0.80, 1.69)	1.87 (1.09, 3.20)[c]
rs5215	11	*KCNJ11*$_{(BCF)}$	C/T	0.37	0.87 (0.59, 1.28)	1.00 (0.56, 1.77)
rs1552224	11	*ARAP1*$_{(BCF)}$	A/C	0.86	1.79 (0.90, 3.55)	0.50 (0.18, 1.37)
rs10830963	11	*MTNR1B*$_{(BCF)}$	G/C	0.27	1.28 (0.79, 2.07)	0.68 (0.34, 1.37)
rs11063069	12	*CCND2*	G/A	0.18	1.93 (1.12, 3.33)[a]	1.40 (0.64, 3.08)
rs10842994	12	*KLHDC5*	C/T	0.82	1.26 (0.75, 2.12)	1.10 (0.53, 2.30)
rs2261181	12	*HMGA2*$_{(IR)}$	T/C	0.12	0.81 (0.43, 1.51)	1.47 (0.59, 3.66)
rs7955901	12	*TSPAN8*	C/T	0.47	1.24 (0.85, 1.81)	1.25 (0.73, 2.13)
rs12427353	12	*HNF1A* (*TCF1*)	G/C	0.80	1.39 (0.81, 2.37)	1.34 (0.63, 2.88)
rs1359790	13	*SPRY2*	G/A	0.73	0.96 (0.63, 1.44)	1.16 (0.66, 2.05)
rs4502156	15	*C2CD4A*$_{(BCF)}$	T/C	0.57	1.12 (0.77, 1.64)	0.99 (0.58, 1.72)
rs7177055	15	*HMG20A*	A/G	0.70	1.02 (0.68, 1.53)	0.90 (0.51, 1.60)
rs11634397	15	*ZFAND6*	G/A	0.65	1.24 (0.82, 1.86)	1.41 (0.77, 2.59)
rs2007084	15	*AP3S2*	G/A	0.93	1.26 (0.58, 2.74)	0.65 (0.19, 2.20)
rs12899811	15	*PRC1*	G/A	0.31	1.00 (0.67, 1.50)	1.64 (0.94, 2.86)
rs9936385	16	*FTO*$_{(IR)}$	C/T	0.42	1.35 (0.93, 1.96)	1.59 (0.92, 2.73)
rs7202877	16	*BCAR1*$_{(BCF)}$	T/G	0.90	2.31 (1.06, 5.03)[c]	0.52 (0.17, 1.60)
rs2447090	17	*SRR*	A/G	0.64	0.83 (0.57, 1.21)	0.82 (0.46, 1.44)
rs11651052	17	*HNF1B* (*TCF2*)	G/A	0.49	0.92 (0.63, 1.33)	1.47 (0.86, 2.53)
rs12970134	18	*MC4R*$_{(IR)}$	A/G	0.28	1.08 (0.72, 1.63)	0.95 (0.52, 1.72)
rs10401969	19	*CILP2*	C/T	0.07	0.15 (0.03, 0.87)[c]	1.07 (0.07, 15.6)
rs8182584	19	*PEPD*$_{(IR)}$	T/G	0.38	1.20 (0.81, 1.76)	0.87 (0.50, 1.51)
rs8108269	19	*GIPR*	G/T	0.32	1.02 (0.68, 1.51)	1.07 (0.59, 1.95)
rs4812829	20	*HNF4A*	A/G	0.18	1.16 (0.72, 1.89)	0.71 (0.35, 1.44)
Count genetic risk score					1.08 (1.02, 1.14)[c]	1.10 (1.01, 1.20)[c]
Weighted genetic risk score					1.09 (1.03, 1.14)[c]	1.07 (0.99, 1.16)[d]

BCF: Beta-cell function; CI: confidence intervals; IR: Insulin resistance; OR: Odds ratio; PM_{10}: particulate matter <10 μm in diameter; SAPALDIA: Swiss cohort study on air pollution and lung and heart diseases in adults; SNPs: Single nucleotide polymorphisms.

[a] SNPs were genotyped using Illumina Human610Kquad BeadChip and imputations done using MaCH v1.0 software.

[b] All models adjusted for age, sex, educational level, neighborhood socio-economic index, smoking status and pack years, passive smoke exposure, consumption of alcohol, fruits and vegetables, physical activity, body mass index and genome-wide population stratification.

[c] $P < 0.05$.

[d] $P < 0.1$.

Table 3
Associations between PM_{10} and quartiles of count-GRS on the odds of diabetes in the SAPALDIA study.

	Quartile	N	Range of risk alleles	Association with diabetes[a]	Increase in odds of diabetes per 10 μg/m^3 increase in PM_{10}[b]
Count-GRS				OR (95% CI)	OR (95% CI)
	Q_1	385	51.67–63.83	Reference	0.82 (0.41, 1.65)
	Q_2	378	63.84–67.09	0.93 (0.40, 2.14)	0.92 (0.55, 1.54)
	Q_3	381	67.10–70.22	1.66 (0.76, 3.61)	1.54 (0.95, 2.49)[d]
	Q_4	380	70.23–82.33	1.86 (0.86, 3.99)	1.97 (1.00, 3.87)[c]
	Q_4 vs. Q_1	765	51.67–82.33	2.31 (1.03, 5.19)[c]	2.06 (0.69, 6.19)
Weighted-GRS					
	Q_1	381	49.92–62.84	Reference	0.83 (0.39, 1.74)
	Q_2	382	62.85–66.49	1.28 (0.55, 2.99)	1.04 (0.62, 1.73)
	Q_3	380	66.50–70.13	1.40 (0.60, 3.28)	1.21 (0.73, 1.99)
	Q_4	381	70.14–84.62	3.28 (1.48, 7.27)[c]	2.01 (1.04, 3.88)[c]
	Q_4 vs. Q_1	762	49.92–84.62	3.61 (1.55, 8.42)[c]	2.53 (0.82, 7.76)

Abbreviations: CI, confidence intervals; GRS, genetic risk score; OR, Odds ratio; PM_{10}, particulate matter < 10 μm in diameter; SAPALDIA, Swiss cohort study on air pollution and lung and heart diseases in adults.
[a] ORs and 95%CIs represent increase in odds of diabetes per risk allele.
[b] ORs and 95%CIs represent increase in odds of diabetes per 10 μg/m^3 increase in exposure to PM_{10}.
[c] $P < 0.05$.
[d] $P < 0.1$.

T2D among people with European ancestry (Talmud et al., 2015) whereas a 62-loci GRS equally predicted T2D in both blacks and whites (Vassy et al., 2014).

Experimental and epidemiologic evidence have demonstrated the contribution of fine particulate matter to insulin resistance. $PM_{2.5}$ was shown to enhance insulin resistance in a mouse model of diet-induced obesity (Sun et al., 2009). Kelishadi and colleagues found $PM_{2.5}$ to be associated with markers of insulin resistance among Iranian children (Kelishadi et al., 2009). On the other hand, NO_2 was also associated with insulin resistance among two cohorts of German children (Thiering et al., 2013). In a study of 25 healthy adults, Brook and colleagues found an association between a sub-acute exposure to $PM_{2.5}$ and insulin resistance (Brook et al., 2013). Postulated mechanisms for the observed association include systemic inflammation, alteration of insulin signaling following oxidative stress, endothelial vasoconstriction, hypothalamic-adrenal stress response and augmentation of sympathetic activity (Liu et al., 2013; Rajagopalan and Brook, 2012).

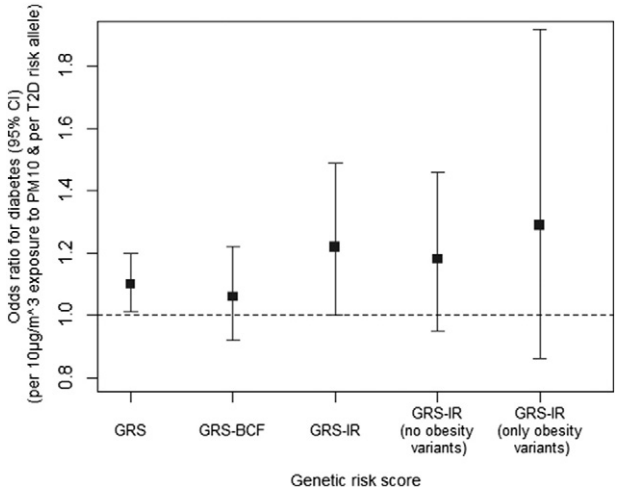

Fig. 1. Interactions between PM_{10} and count-GRS on prevalent diabetes in the SAPALDIA study. GRS: total genetic risk score; GRS-BCF: beta-cell function genetic risk score; GRS-IR: insulin resistance genetic risk score; GRS-IR (no obesity variants): insulin resistance genetic risk score excluding polymorphisms on *FTO* and *M4CR* with primary effect on obesity; GRS-IR (only obesity variants): insulin resistance genetic risk score including only polymorphisms on *FTO* and *M4CR* with primary effect on obesity; PM_{10}: particulate matter < 10 μm in diameter; SAPALDIA: Swiss cohort study on air pollution and lung and heart diseases in adults. Count-GRS was computed by summation of risk alleles. Odds ratios represent increase in odds of diabetes per 10 μg/m^3 exposure to PM_{10} and per risk allele. All associations were adjusted for obesity, age, sex, socio-economic status, smoking habits, consumption of alcohol, fruits and vegetables, physical activity and genome-wide population stratification. Study area was treated as a random effect in all models.

Our results also suggest that individuals with pre-existing inflammation like asthma or at risk of obesity are potentially most susceptible to air pollution increasing the risk for developing diabetes. We observed a stronger interaction of PM_{10} with insulin resistance variants among asthma cases which was even stronger when we restricted the score to the *FTO* and *M4CR* variants which are known to be causally related to higher BMI over the course of life (Perry and Frayling, 2008; Scott et al., 2014) (Fig. 1). Air pollution exposure has been linked to both asthma and obesity (Eze et al., 2015b; Jacquemin et al., 2015; Jerrett et al., 2014), and studies have linked asthma to obesity and insulin resistance (Husemoen et al., 2008; Sanchez Jimenez et al., 2014; Singh et al., 2013). While there is a consensus that obesity-related systemic inflammation likely contributes to the asthma etiology, epidemiological evidence on the relationship between asthma and diabetes is limited and conflicting. Some studies reported a link between asthma and diabetes (Ehrlich et al., 2010; Mueller et al., 2013) especially in obese people (Mueller et al., 2013), others did not (Rana et al., 2004).

While asthma and obesity are recognized inflammatory conditions and with experimental data from animal models corroborating that visceral adiposity-related inflammation may act as mediator for $PM_{2.5}$ to increase the risk for insulin resistance (Sun et al., 2009), other studies have shown discordance between systemic inflammation and severity of symptoms in obese asthmatics (Beuther et al., 2006; Haldar et al., 2008). Other lines of evidence suggest that non-inflammatory pathways might also link PM to insulin resistance (Brook et al., 2013), with experimental animal models providing evidence for insulin resistance in muscle tissues resulting from lipid and protein oxidation by-products upon acute exposure to ozone (Kodavanti, 2015; Vella et al., 2015). Hence, despite the strong evidence for a central role of pre-existing inflammation, e.g., due to asthma or being at genetic risk of obesity, other non-inflammation based mechanisms cannot be ruled out to underlie or contribute to the air pollution-diabetes association.

There is some evidences on the impact of environmental pollutants (including organophosphorus compounds, persistent organic pollutants and metals) on various aspects of beta-cell dysfunction that lead to diabetes (Hectors et al., 2011), but there is to date no experimental evidence on the impact of air pollutants on BCF. Although interactions with the polygenic risk involving the BCF variants in the 63-loci GRS were not significant, we observed some positive signals among non-asthmatics in the BCF pathway (Fig. 2) and nominally significant

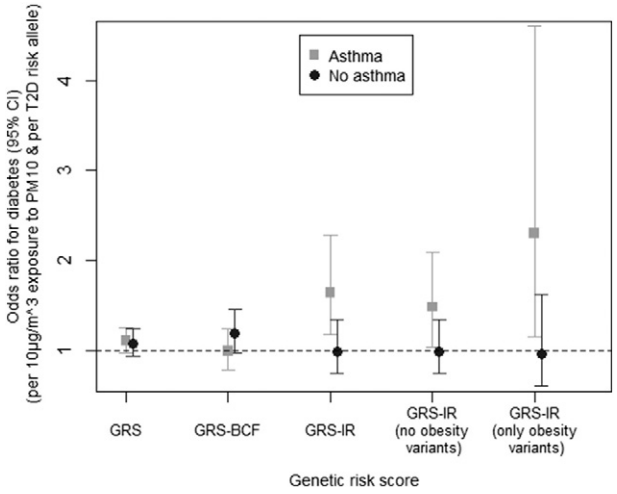

Fig. 2. Interactions between PM_{10} and count-GRS on prevalent diabetes in the SAPALDIA study, stratified by asthma status. GRS: total genetic risk score; GRS-BCF: beta-cell function genetic risk score; GRS-IR: insulin resistance genetic risk score; GRS-IR (no obesity variants): insulin resistance genetic risk score excluding polymorphisms on *FTO* and *M4CR* with primary effect on obesity; GRS-IR (only obesity variants): insulin resistance genetic risk score including only polymorphisms on *FTO* and *M4CR* with primary effect on obesity; PM_{10}: particulate matter <10 μm in diameter; SAPALDIA: Swiss cohort study on air pollution and lung and heart diseases in adults. Count-GRS was computed by summation of risk alleles. Odds ratios represent increase in odds of diabetes per 10μg/m^3 exposure to PM_{10} and per risk allele. All associations were adjusted for obesity, age, sex, socio-economic status, smoking habits, consumption of alcohol, fruits and vegetables, physical activity and genome-wide population stratification. Study area was treated as a random effect in all models. N (asthma) = 615; N (no asthma) = 909.

interactions with single variants in the BCF pathway (Table 2). This might indicate that PM may also have some impact on T2D through some alterations in the BCF.

This study has several strengths. It provides comprehensive evidence on the modifying effect of a polygenic risk score (including pathway-related components) on the association between ambient air pollution and DM. The SAPALDIA study contains a rich data set on well characterized participants including a large number of phenotypes and lifestyle characteristics, in addition to genomic data. We attempted to identify undiagnosed diabetes, using non-fasting blood tests, to limit outcome misclassification. Our estimates of air pollution derive from validated models, which have been applied to other SAPALDIA studies. These estimates were assigned to participants' residential address history, thus limiting exposure misclassification.

Despite these strengths, our study has also limitations. First is our inability to distinguish T1D and T2D. We assumed most of our diabetes cases to be type 2, since >90% of adult diabetes is type 2 (Alberti and Zimmet, 1998). We observed strong associations between the confirmed T2D risk alleles and our diabetes cases, in the range of published literature, thus strengthening our assumption of T2D. Moreover, when we limited the diabetes definition to either medication use or those without a diagnosis but increased non-fasting glucose levels, the associations with GRS remained unchanged. We had limited sample size (62% statistical power) for this analysis due to lacking genome-wide data. Assuming the observed effect is identical to the true effect, we would have needed twice the size of our sample to achieve 90% power for detecting this effect at the usual significance level of 5%. However, we made some salient findings, and IPW revealed no effect of potential selection bias in our study. This was a cross-sectional analysis, precluding any causal inferences. To limit this design bias, we focused on the 10-year mean of PM_{10} exposure, rather than on the mean during the year preceding the health assessment. Our study of genetic variation also limits this design bias to some extent considering that genetic variants remain unchanged throughout life. Furthermore, we studied PM_{10}, instead of $PM_{2.5}$, which may have stronger health effects due to its physical properties. Modeled $PM_{2.5}$ was not available for our study, but there is a high correlation between both pollutants across SAPALDIA study areas (R = 0.8) (Eze et al., 2014a). We would expect similar, if not stronger associations with $PM_{2.5}$. Lastly, our observations may be biased by the relationship between asthma (and its treatment) and diabetes, but we did not observe substantial differences in interactions between PM_{10} and total genetic risk, on stratification by asthma status.

Future studies should explore the possible role of air pollution in the impairment of BCF, and explore the role of unclassified T2D variants in disease etiology. Our present findings need confirmation and follow-up in diabetes cohort consortia. Consideration should also be given to ultra-fine particles, which can penetrate even further into the respiratory tract than $PM_{2.5}$ or PM_{10}.

In conclusion, our results indicate that polygenic risk of T2D may modify the effects of air pollutants on the risk of diabetes through alteration of insulin sensitivity among people with some existing background inflammation. This study is relevant given the need for the knowledge of genetic risk in disease prevention, and the importance of genotypes as research instrument in disentangling complexities and mechanisms in causality of modifiable risks.

Table 4
Sensitivity analyses using inverse probability weighting to assess for potential selection bias, and testing study area as a fixed effect, in the modification of associations between PM_{10} and diabetes by GRS in the SAPALDIA study.

Model	Interactions between PM_{10} and count-GRS on prevalent diabetes[a]	Interactions between PM_{10} and weighted-GRS on prevalent diabetes[a]
Inverse probability weighting for selection bias	OR (95% CI)	OR (95% CI)
63-loci GRS	1.10 (1.02, 1.20)[b]	1.08 (1.00, 1.16)[b]
GRS-beta cell function	1.07 (0.95, 1.20)	1.04 (0.93, 1.15)
GRS-insulin resistance	1.25 (1.03, 1.51)[b]	1.23 (1.03, 1.47)[b]
GRS-insulin resistance excluding obesity variants	1.21 (0.96, 1.53)	1.20 (0.95, 1.52)
GRS-insulin resistance (only obesity variants)	1.25 (0.86, 1.83)	1.54 (0.50, 4.69)
Study area as a fixed effect		
63-loci GRS	1.10 (1.01, 1.20)[b]	1.07 (0.99, 1.15)[b]
GRS-beta cell function	1.06 (0.92, 1.22)	1.03 (0.91, 1.15)
GRS-insulin resistance	1.22 (1.00, 1.50)[b]	1.21 (1.00, 1.48)[b]
GRS-insulin resistance excluding obesity variants	1.18 (0.95, 1.47)	1.17 (0.93, 1.47)
GRS-insulin resistance (only obesity variants)	1.29 (0.87, 1.91)	1.32 (0.90, 1.92)

Abbreviations: CI, confidence intervals; GRS, genetic risk score; OR, Odds ratio; PM_{10}, particulate matter <10 μm in diameter; SAPALDIA, Swiss cohort study on air pollution and lung and heart diseases in adults.

[a] ORs and 95%CIs represent increase in odds of diabetes per 10 μg/m^3 increase in exposure to PM_{10} and per unit risk allele. All models were mixed logistic regression with random intercepts for study areas, and adjusted for age, sex, educational attainment, neighborhood socio-economic index, smoking status, exposure to passive smoke and occupational vapors, dusts, gases and fumes, consumption of alcohol, fruits and vegetables, physical activity, body mass index and genome-wide population stratification.

[b] $P < 0.05$.

5. Current SAPALDIA team

Study directorate: NM Probst-Hensch (PI; e/g); T Rochat (p), C Schindler (s), N Künzli (e/exp), JM Gaspoz (c).

Scientific team: JC Barthélémy (c), W Berger (g), R Bettschart (p), A Bircher (a), C Brombach (n), PO Bridevaux (p), L Burdet (p), Felber Dietrich D (e), M Frey (p), U Frey (pd), MW Gerbase (p), D Gold (e), E de Groot (c), W Karrer (p), F Kronenberg (g), B Martin (pa), A Mehta (e), D Miedinger (o), M Pons (p), F Roche (c), T Rothe (p), P Schmid-Grendelmeyer (a), D Stolz (p), A Schmidt-Trucksäss (pa), J Schwartz (e), A Turk (p), A von Eckardstein (cc), E Zemp Stutz (e).

Scientific team at coordinating centers: M Adam (e), I Aguilera (exp), S Brunner (s), D Carballo (c), S Caviezel (pa), I Curjuric (e), A Di Pascale (s), J Dratva (e), R Ducret (s), E Dupuis Lozeron (s), M Eeftens (exp), I Eze (e), E Fischer (g), M Foraster (e), M Germond (s), L Grize (s), S Hansen (e), A Hensel (s), M Imboden (g), A Ineichen (exp), A Jeong (g), D Keidel (s), A Kumar (g), N Maire (s), A Mehta (e), R Meier (exp), E Schaffner (s), T Schikowski (e), M Tsai (exp).

(a) allergology, (c) cardiology, (cc) clinical chemistry, (e) epidemiology, (exp) exposure, (g) genetic and molecular biology, (m) meteorology, (n) nutrition, (o) occupational health, (p) pneumology, (pa) physical activity, (pd) pediatrics, (s) statistics.

Local fieldworkers: Aarau: S Brun, G Giger, M Sperisen, M Stahel, Basel: C Bürli, C Dahler, N Oertli, I Harreh, F Karrer, G Novicic, N Wyttenbacher, Davos: A Saner, P Senn, R Winzeler, Geneva: F Bonfils, B Blicharz, C Landolt, J Rochat, Lugano: S Boccia, E Gehrig, MT Mandia, G Solari, B Viscardi, Montana: AP Bieri, C Darioly, M Maire, Payerne: F Ding, P Danieli A Vonnez, Wald: D Bodmer, E Hochstrasser, R Kunz, C Meier, J Rakic, U Schafroth, A Walder.

Administrative staff: N Bauer Ott, C Gabriel, R Gutknecht.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2016.04.032.

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