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

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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.

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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).