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Long-term air pollution exposure and diabetes in a population-based Swiss cohort

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ABSTRACT

Air pollution is an important risk factor for global burden of disease. There has been recent interest in its possible role in the etiology of diabetes mellitus. Experimental evidence is suggestive, but epidemiological evidence is limited and mixed. We therefore explored the association between air pollution and prevalent diabetes, in a population-based Swiss cohort.

We did cross-sectional analyses of 6392 participants of the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults [SAPALDIA], aged between 29 and 73 years. We used estimates of average individual home outdoor PM_{10} [particulate matter <10 μm in diameter] and NO_2 [nitrogen dioxide] exposure over the 10 years preceding the survey. Their association with diabetes was modeled using mixed logistic regression models, including participants' study area as random effect, with incremental adjustment for confounders.

There were 315 cases of diabetes (prevalence: 5.5% [95% confidence interval (CI): 2.8, 7.2%]). Both PM_{10} and NO_2 were associated with prevalent diabetes with respective odds ratios of 1.40 [95% CI: 1.17, 1.67] and 1.19 [95% CI: 1.03, 1.38] per 10 $\mu g/m^3$ increase in the average home outdoor level. Associations with PM_{10} were generally stronger than with NO_2, even in the two-pollutant model. There was some indication that beta blockers mitigated the effect of PM_{10}. The associations remained stable across different sensitivity analyses.

Our study adds to the evidence that long term air pollution exposure is associated with diabetes mellitus. PM_{10} appears to be a useful marker of aspects of air pollution relevant for diabetes. This association can be observed at concentrations below air quality guidelines.

1. Introduction

Ambient air pollution, indoor air pollution and hyperglycemia constitute major risks for the global burden of disease (Lim et al., 2012). Air pollution is associated with cardiovascular diseases (Auchincloss et al., 2008; Hoffmann et al., 2007), and chronic respiratory diseases (Künzli et al., 2009; Schikowski et al., 2010) and has been shown to contribute to hospitalizations and deaths among cardiac disease patients (Goldberg et al., 2013), and diabetic patients (Goldberg et al., 2013; O'Neill et al., 2005; Zanobetti and Schwartz, 2001). Type 2 diabetes is increasing globally and is already one of the major causes of death (Lim et al., 2012). Type 2 diabetes and cardiovascular diseases share similar risk factors. Air pollution could be involved in the etiology of type 2 diabetes mellitus. Postulated mechanisms of action include oxidative stress and low grade inflammation, endothelial dysfunction, visceral adipose tissue inflammation, endoplasmic reticulum stress and mitochondrial dysfunction (Liu et al., 2013; Rajagopalan and Brook, 2012) with resulting impairment in insulin signaling (Xu et al., 2013).

Animal and human biomarker studies, including sparse epidemiological studies contribute to this evidence. Animal studies suggest a contribution of fine particles to insulin resistance, especially in association with a high fat diet (Sun et al., 2009; Xu et al., 2011; Yan et al., 2011). Chuang et al. (2007) demonstrated an alteration in glycosylated hemoglobin C, blood lipids and blood pressure in young adults in Taipei, after exposure to particulate matter and ozone.

Epidemiological evidence is sparse and findings are mixed. Longitudinal studies in European and North American populations (Andersen

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et al., 2012; Chen et al., 2013; Coogan et al., 2012; Krämer et al., 2010; Puett et al., 2011), found inconsistent associations between incident diabetes mellitus and PM_{10} [particulate matter < 10 μm in diameter], NO_2 [nitrogen dioxide], NO_x [nitrogen oxides], $PM_{2.5}$ [particulate matter < 2.5 μm in diameter], $PM_{10-2.5}$ [particulate matter with diameter between 2.5 and 10 μm] and residential proximity to traffic. Although the previous studies taken together with experimental evidence support the evidence for an association between inhaled pollutants and diabetes, several aspects may contribute to uncertainties and inconsistencies. Limiting factors toward more conclusive evidence include differences in (a) exposure metrics and assessment; (b) diabetes definition; (c) population characteristics and (d) covariates considered (Papazafiropoulou et al., 2011; Rajagopalan and Brook, 2012). Two epidemiological studies have investigated the association between air pollution and prevalent type 2 diabetes, with contradictory results on NO_2 effects (Brook et al., 2008; Dijkema et al., 2011). Noise can positively correlate with air pollution (Foraster, 2013; Kim et al., 2012) and has been implicated in cardiovascular diseases (Dratva et al., 2012; Sorensen et al., 2011), as well as more recently with diabetes (Sorensen et al., 2013). The quality and quantity of sleep have been shown to be significant predictors of the risk of type 2 diabetes (Cappuccio et al., 2010). Thus, noise can be considered a potential confounder in air pollution epidemiology studies.

To add to the epidemiologic evidence base on the newly uncovered, potentially causal relationship between air pollution and diabetes, we investigated the association between ambient/traffic-related air pollution and prevalent diabetes mellitus in the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults [SAPALDIA], taking noise exposure, individual and area-level socio-economic index into consideration.

2. Materials and methods

2.1. Study population and health examinations

At baseline [SAPALDIA 1; 1991], the study population of SAPALDIA included 9561 randomly selected participants aged 18–65 years. These participants were selected from eight different areas in Switzerland, representing a wide range of environmental conditions in Switzerland. Subjects had extensive health examinations which involved computer-assisted interviews, lung function and allergy testing. At the first follow-up [SAPALDIA 2; 2002], the health assessments were repeated in 8047 participants, with more detailed interviews, including information on diabetes and other chronic non-communicable diseases, blood testing for biomarkers and genotyping. This is described in detail elsewhere (Ackermann-Liebrich et al., 2005). For the purpose of the present analysis, we had a sample of 6392 follow-up participants, aged 29–73 years, who had complete information on all the variables of interest, for assessing the association between air pollution and diabetes mellitus.

2.2. Definition of diabetes mellitus

At SAPALDIA 2, participants were asked “do you have diabetes mellitus?” and “was it diagnosed by a physician?” Participants' non-fasting blood samples were taken to measure blood markers, including non-fasting blood glucose, glycosylated hemoglobin C [HbA1c] and blood lipids. Based on the available information, we defined diabetes as present if at least one of the following conditions was met i) intake of any anti-diabetic medication; ii) self-reported, physician-diagnosed diabetes mellitus; iii) non-fasting blood glucose of >11.1 mmol/L or iv) HbA1c of >6.5% or 48 mmol/mol. Since this is an adult population [minimum age of 29 years] and >90% of diabetes in adults is of type 2, we assumed the majority of diabetic cases in this population to be type 2 diabetes mellitus.

2.3. Individual assignment of exposures

We considered markers of ambient air pollution [PM_{10}] and traffic-related air pollution [NO_2] as our air pollution exposure indicators. Estimates of mean ambient levels of these pollutants were available for the residential addresses of the participants in the years 1990 and 2000, the years before health assessments (Liu et al., 2007). They were obtained from validated dispersion models, with different emission inventories for both years. They have a spatial resolution of 200 × 200 m (Liu et al., 2007). Annual trends at fixed monitoring sites and participants' residential histories were used to estimate average ambient residential levels of the two pollutants over periods of 1 to 10 years prior to the first follow-up assessment in 2002. The dispersion model for PM_{10} provided good predictions both at background and traffic sites, whereas the model for NO_2 provided better predictions at traffic sites while underestimating levels at background sites (Liu et al., 2007). For this reason, the dispersion model for NO_2 was extended to a hybrid model involving land-use regression components (Liu et al., 2012). For this analysis, we primarily used the modeled average ambient levels of PM_{10} and NO_2 at participants' residential addresses over the 10 years preceding the first follow-up survey.

We obtained estimates of road traffic and railway noise from sonBASE, the Swiss national noise database (FOEN, 2009a,b). This database, developed by the Swiss Federal Office of Environment, provides average railway and road traffic noise estimates for day [0600 h–2200 h] and night [2200 h–0600 h]. Noise propagation was estimated with 10 × 10 meter grids and for individual buildings using the StL86 + emission model for road traffic noise and SEMIBEL [Swiss emission model for the estimation of railway noise] for railway noise (FOEN, 2009b). These estimates were then assigned to participants' residential addresses. From the day and night estimates, we estimated the average day–night [L_{dn}] noise exposure level by applying a penalty of 10 dB on the night noise estimates for both road traffic and railway noise. The L_{dn} value at the participant's address of the first follow-up survey was used as measure of individual noise exposure in the regression analysis.

2.4. Potential confounding variables

From the computer-assisted interviews at SAPALDIA 2, we extracted information on potential confounders. These included participants' age, sex [male, female], height and weight to compute the body mass index [BMI; kg/m^2], and educational attainment [low corresponding to primary education; intermediate corresponding to secondary, middle, or vocational school; and high corresponding to technical college or university]. Neighborhood-level socio-economic index was obtained for participants' residential areas. This index was defined using neighborhood characterization based on median rent, occupation and education of heads of households and crowding of households, combined in a principal component analysis (Panczak et al., 2012). We also extracted information on physical activity [≤0.5 h per week, 0.5–2 h per week and >2 h per week of vigorous activity], smoking [never, former, current and pack years smoked], environmental tobacco smoking in the past 12 months [never smoker, and former smoker] and alcohol consumption [never, ≤once a day, and >once a day], and occupational exposure to gases, dusts and fumes [yes/no]. In addition, we extracted information on consumption of raw vegetables [never, ≤3 days per week, and >3 days per week], consumption of citrus fruits [never, ≤3 days per week, and >3 days per week] and consumption of other fruits [never, ≤3 days per week, and >3 days per week]. We also extracted information on some existing co-morbidities including hypertension [yes/no], and chronic obstructive pulmonary disease [COPD; defined by GOLD standard: forced expiratory volume in 1 s (FEV_1) ÷ forced vital capacity (FVC) < 0.7; yes/no].

Since the parameter of air pollution exposure was the mean ambient residential level over the ten years preceding the first follow-up survey, we also considered some baseline exposure characteristics, as potential

confounders. We extracted information on baseline smoking history [never, former, current and pack years smoked], environmental tobacco smoking in the past 12 months [never smoker, former smoker] and occupational exposure to gases, dusts or fumes [yes/no].

2.5. Statistical analysis

We included 6392 participants with complete information on the variables of interest in this analysis. First, we estimated the prevalence of diabetes mellitus among the study sample. We then evaluated the distribution of various characteristics among participants, stratified by diabetes status.

Second, we assessed the association between air pollution and prevalent type 2 diabetes mellitus using mixed logistic regression models, with a random intercept for the different study areas. We selected potential confounders based on literature review and plausibility and added them to the model in an incremental manner. Our fully-adjusted model included age, sex, BMI, educational status, neighborhood socio-economic index, smoking status, pack years of cigarettes smoked, environmental tobacco smoking status, occupational exposure to gases, dusts or fumes, consumption of alcohol, raw vegetables, citrus fruits and other fruits, and average railway and road traffic noise exposure. In some exploratory analyses, we additionally adjusted for self-reported hypertension, inflammatory markers including high sensitivity C-reactive protein and dyslipidemia. We assessed this association singly for each pollutant [single pollutant model] and in combination [two-pollutant model].

Third, we assessed potential effect modifiers. The pre-selected candidates included age group [≤50 years, and >50 years], sex, obesity [BMI > 30 kg/m^2], educational level [low, intermediate, and high], physical activity [low, medium, and high], COPD [yes/no], hypertension [yes/no] and intake of beta-blockers [yes/no]. Beta-blockers have been shown to be protective on the cardiac effects of

Table 1
Background characteristics of participants by diabetes status.

Characteristic (%)	Diabetes mellitus N = 315	No diabetes mellitus N = 6077	p-Value [chi-square]
Females	34.6	52.2	<0.001
Smoking status [yes/no]			<0.001
Never	35.6	43.9	
Former	42.5	31.0	
Current	21.9	25.1	
ETS [yes/no]			0.768
Never smoker	7.0	6.6	
Former smoker	6.0	6.5	
Physical activity [yes/no]			<0.001
<0.5 h/week	58.1	37.7	
0.5–2 h/week	23.8	34.2	
>2 h/week	18.1	28.1	
Educational level [yes/no]			<0.001
Low	11.4	5.9	
Intermediate	65.4	65.6	
High	23.2	28.5	
Work exposure to gas/dusts/fumes [yes/no]	25.7	27.6	0.474
Alcohol consumption [yes/no]			<0.001
Never	14.6	8.9	
≤Once/day	71.4	82.3	
>Once/day	14.0	8.8	
Raw vegetable consumption [yes/no]			0.288
Never	0.3	0.6	
≤3 days/week	20.3	18.8	
>3 days/week	79.4	80.6	
Citrus fruits consumption [yes/no]			0.045
Never	12.7	8.2	
≤3 days/week	54.0	56.2	
>3 days/week	33.4	35.7	
Other fruits consumption [yes/no]			0.053
Never	1.9	1.8	
≤3 days/week	25.7	33.6	
>3 days/week	72.4	64.6	
Duration of residence < 10 years	30.8	42.4	<0.001
Duration of residence ≥ 10 years	69.1	57.6	
Self-reported hypertension [yes/no]	52.4	17.7	<0.001
COPD (FEV_1/FVC < 0.7) [yes/no]	22.5	19.7	0.209
Dyslipidemia [yes/no]	73.7	46.6	<0.001
High hs-CRP [yes/no]	72.4	48.8	<0.001
Mean (SD)			T-test
Age [years]	60.8 (8.1)	51.7 (11.4)	<0.001
BMI [kg/m^2]	30.3 (5.1)	25.6 (4.3)	<0.001
Pack-years of smoking	16.4 (25.1)	10.5 (17.9)	<0.001
Neighborhood socio-economic index	63.6 (10.1)	62.1 (10.4)	0.005
10-year mean PM_{10} [μg/m^3]	24.4 (7.2)	22.2 (7.4)	<0.001
10-year mean NO_2 [μg/m^3]	29.2 (10.5)	26.7 (11)	<0.001
Mean railway noise [dB]	11.6 (13.5)	10.3 (13.0)	0.076
Mean street noise [dB]	49.9 (9.0)	49.4 (8.8)	0.365

ETS: Environmental tobacco smoking; COPD: chronic obstructive pulmonary disease. FEV_1: forced expiratory volume in 1 s, FVC: forced vital capacity. hs-CRP: high sensitivity C-reactive protein. High hs-CRP is defines as hs-CRP ≥ 1.0 mmol/L, the median hs-CRP. Dyslipidemia defined as triglyceride ≥ 1.7 mmol/L and/or high density lipoprotein ≤ 1.03 mmol/L in men or ≤1.29 mmol/L in women. Low education corresponds to primary school level, intermediate corresponds to secondary, middle, or vocational school, and high education corresponds to technical college or university. IQR: Inter-quartile range.

$PM_{2.5}$ (Folino et al., 2009; Lotti, 2011). Non-selective beta blockers have also been shown to improve insulin sensitivity among cardiac and diabetic patients (Hara et al., 2003; Kveiborg et al., 2006), possibly through their anti-atherogenic, anti-inflammatory and oxygen perfusion improvement properties (Bell, 2004). We generated interaction terms between each of the potential effect modifiers and the variables of PM_{10} and NO_2 exposure, and added these interaction terms to the fully-adjusted model one by one. We estimated separate effects of the respective air pollutant variable for the groups compared, from the same model. Heterogeneity of these separate estimates was assessed using the likelihood ratio test and the p-values were noted. Finally, we did some sensitivity analyses, using the fully-adjusted single-pollutant model, to check the robustness of the estimated association of air pollution on the prevalence rate of diabetes mellitus. In the first sensitivity analysis, we restricted the analysis to those who had lived in the same residence between SAPALDIA 1 and SAPALDIA 2, since our noise data was from a single measurement during follow-up. Next, we excluded participants with any heart disease from the model. In another sensitivity analysis, we excluded cases that reportedly started anti-diabetic medication before or at baseline. We also restricted the diabetes definition to each of the diagnostic criterion used to identify diabetes cases, excluding the diabetes cases not matching the criterion, from the controls. We also adjusted for participation bias using the inverse probability weighting (ignoring area as a random effect). We did this by deriving a model for the probability of participation based on informative predictor variables assessed at baseline, i.e., age, sex, BMI, nationality, educational status, chronic disease status and lifestyle characteristics. We then weighted each participant based on their probabilities and added it to the fully adjusted model. Lastly, we tested linearity of association by introducing quadratic terms of the exposure variables to the model.

In most analyses, participants' study area was treated as a random effect [except in some sensitivity analyses]. This is to account for the gradient between health outcomes and exposure levels across study areas, and not exclusively focusing only on within-area gradients, which leads to loss of some statistical power.

We used STATA statistical software version 12 (StataCorporation, 2011) for all statistical analyses and defined statistical significance at the 5% level.

3. Results

3.1. Characteristics of study population

The prevalence of diabetes mellitus in the study sample was 5.5% [95% confidence interval (CI): 2.8, 7.2%]. The mean age of the participants was 52 years and about 50% of them were females (Table 1). Males constituted 65% of the diabetics, were more overweight/obese [64% vs. 43%], smoked twice the pack-years of females [14 vs. 7.7] and were more often current smokers [27% vs. 22%], but mean age was the same for males and females. The mean PM_{10} exposure in the study population was 22.3 $\mu g/m^3$ [WHO air quality guideline: 20 $\mu g/m^3$ (WHO, 2006)] whereas mean NO_2 exposure was 26.8 $\mu g/m^3$ [WHO: 40 $\mu g/m^3$ (WHO, 2006)]. The mean railway noise exposure was 10.4 dB whereas the mean road traffic noise was 49.5 dB. Participants with diabetes were older, had higher body mass index, smoked more and were more likely exposed to environmental tobacco smoke. Furthermore, diabetic subjects were less educated, and consumed less fruits but more alcohol. In addition, diabetic subjects had higher exposures to PM_{10} and NO_2 and were more likely to remain in the same residential area over the course of follow-up. Diabetic subjects were also more likely to be hypertensive and have COPD [Table 1]. Table A1 summarizes excluded subjects vs. included subjects based on the background characteristics and shows no substantial differences between these groups. Fig. A1 shows the identification of diabetes cases for this study.

3.2. Association between air pollution and diabetes mellitus

For every 10 $\mu g/m^3$ increase in home outdoor PM_{10} or NO_2, the fully adjusted odds ratio for prevalent diabetes mellitus was 1.40 [95% CI: 1.17, 1.67] and 1.19 [95% CI: 1.03, 1.38], respectively. The unadjusted odds ratio for prevalent diabetes mellitus was 1.46 [95% CI: 1.20, 1.77] and 1.20 [95% CI: 1.03, 1.39] respectively [Table 2]. Additional adjustment for neither age and sex nor educational level and neighborhood-level socio-economic index appreciably changed the estimates. Additional adjustment for lifestyle characteristics such as physical activity, diet, smoking and alcohol consumption, reduced the home outdoor PM_{10} estimate by 11% [OR: 1.35 (95% CI: 1.12, 1.63)]; and NO_2 estimate by 3% [OR: 1.17 (95% CI: 1.02, 1.36)]. The effect estimate for home outdoor NO_2 and PM_{10} increased by 4% [OR: 1.21 (95% CI: 1.05, 1.39)] and 9% [OR: 1.40 (1.21, 1.71)] respectively, upon additional adjustment for body mass index. Additional adjustment for noise further reduced the effect estimates, but these estimates remained stable all through the adjustments, including hypertension, high sensitivity C-reactive protein (hs-CRP) and dyslipidemia [Table 2].

For the multi-pollutant model, the unadjusted odds ratio for home outdoor PM_{10} and NO_2 was 1.37 [95% CI: 1.02, 1.84] and 1.02 [95% CI: 0.84, 1.25] respectively. These estimates remained fairly stable following additional adjustments [Table 3].

A multivariate comparison across study areas, showed a consistent association between adjusted diabetes prevalence rates and the community air pollution levels ($r = 0.88$ and 0.70 for PM_{10} and NO_2 respectively). Areas with higher air pollution levels tended to have higher rates of diabetes [Figs. A2 and A3]. Also, the effect estimates did not substantially change when we removed one area at a time in our model [result not shown].

Table 2
Association between home outdoor air pollution and diabetes mellitus [single pollutant models].

	NO_2 OR [95% CI]	PM_{10} OR [95% CI]
Unadjusted	1.20 [1.03, 1.39]	1.46 [1.20, 1.77]
Adjusted for age and gender	1.23 [1.06, 1.43]	1.43 [1.18, 1.74]
+ adjusted for educational level and neighborhood SEI	1.22 [1.05, 1.41]	1.45 [1.23, 1.72]
+ adjusted for lifestyle characteristics[a]	1.17 [1.02, 1.36]	1.35 [1.12, 1.63]
+ adjusted for body mass index	1.21 [1.05, 1.39]	1.44 [1.21, 1.71]
+ adjusted for noise	1.19 [1.03, 1.38]	1.40 [1.17, 1.67]
+ adjusted for hypertension	1.17 [1.01, 1.36]	1.37 [1.14, 1.65]
+ adjusted for high hs-CRP and dyslipidemia	1.21 [1.04, 1.40]	1.41 [1.17, 1.69]

SEI: socio-economic index. OR: odds ratio. OR values represent % increase in diabetes prevalence per 10 $\mu g/m^3$ increase in PM_{10} or NO_2. CI: confidence interval. hs-CRP: high sensitivity C-reactive protein. High hs-CRP defined as CRP level > sample median (1.0 mmol/L). Dyslipidemia defined as triglyceride ≥ 1.7 mmol/L and/or high density lipoprotein ≤ 1.03 mmol/L in men or ≤1.29 mmol/L in women. Area was treated as a random effect in all models. + indicates additional adjustment. N = 6392 at all levels of adjustment except for hs-CRP and dyslipidemia where N = 6111.

[a] Include alcohol consumption, smoking, passive smoking, work exposure to dust gas and fumes, consumption of alcohol, fruits and raw vegetables and physical activity.

Table 3
Association between home outdoor air pollution and diabetes mellitus [two-pollutant models].

	NO_2 OR [95% CI]	PM_{10} OR [95% CI]
Unadjusted	1.03 [0.83, 1.27]	1.41 [1.02, 1.96]
Adjusted for age and gender	1.10 [0.87, 1.37]	1.28 [0.90, 1.82]
+ adjusted for educational level and neighborhood SEI	1.03 [0.84, 1.28]	1.40 [1.03, 1.90]
+ adjusted for lifestyle characteristics[a]	1.03 [0.83, 1.28]	1.31 [0.95, 1.79]
+ adjusted for body mass index	1.04 [0.86, 1.27]	1.37 [1.02, 1.85]
+ adjusted for noise	1.02 [0.84, 1.25]	1.37 [1.02, 1.84]
+ adjusted for hypertension	1.02 [0.82, 1.26]	1.35 [0.99, 1.84]
+ adjusted for high hs-CRP and dyslipidemia	1.04 [0.84, 1.29]	1.35 [0.99, 1.84]

SEI: socio-economic index. OR: odds ratio. OR values represent % increase in diabetes prevalence per 10 μg/m^3 increase in PM_{10} or NO_2. CI: confidence interval. hs-CRP: high sensitivity C-reactive protein. High hs-CRP defined as CRP level > sample median (1.0 mmol/L). Dyslipidemia defined as triglyceride ≥ 1.7 mmol/L and/or high density lipoprotein ≤ 1.03 mmol/L in men or ≤1.29 mmol/L in women. Area was treated as a random effect in all models. + indicates additional adjustment. N = 6392 at all levels of adjustment except for hs-CRP and dyslipidemia where N = 6111.

[a] Include alcohol consumption, smoking, passive smoking, work exposure to dust gas and fumes, consumption of alcohol, fruits and raw vegetables and physical activity.

3.3. Effect modification

We did not find any statistically significant interaction term with the selected potential modifiers [Table 4]. Intake of beta-blocker may be protective for PM_{10} with OR 0.23 [95% CI: 0.02, 3.32] vs. 1.41 [95% CI: 1.18, 1.69] for those not taking the medication.

3.4. Sensitivity analyses

Restricting the analysis to subjects who did not change their residential address between baseline and follow-up assessments and to persons without self-reported heart disease did not substantially alter the association between air pollution and diabetes [Table 5]. Excluding participants who reported diabetes medication intake before baseline assessment increased the estimates of association by 2% for both pollutants [Table 5]. Associations remained positive and significant when we narrowed diabetes definition to each criterion used for case identification except for narrowing the definition of diabetes to reported intake of anti-diabetic medication where associations remained positive but statistically insignificant [Table A2]. This may imply under-reporting of diabetic medication intake among those we identified as diabetic. The mean probability of participation in this study (from baseline) was 66.2%; therefore, we adjusted for participation bias (IPW) which gave adjusted odds ratios of 1.39 [95% CI: 1.15, 1.67] and 1.18 [95% CI: 1.05, 1.34] per 10 μg/m^3 increase in PM_{10} and NO_2 respectively [Table 5]. There was evidence that associations might be slightly non-linear. The coefficients of the quadratic terms of NO_2 and PM_{10} were negative (−0.00152 and −0.00144), with respective p-values of 0.004 and 0.164. This might imply attenuation of effects at higher levels of exposure. When treating area as a fixed effect, no significant association between air pollution exposure and diabetes mellitus could be seen anymore and the 95% CI of these effect estimates got wide [Table A3]. We did not observe strong heterogeneity in area-specific effects of PM_{10} and NO_2.

4. Discussion

In this analysis, we found that long-term exposure to PM_{10} and NO_2 were positively associated with prevalent diabetes mellitus in the SAPALDIA cohort, at concentrations below the air quality guidelines. As mentioned earlier, we assume the diabetes cases to be predominantly type 2, since >90% of adult diabetes is type 2 diabetes. The associations were independent of traffic-related noise exposure, individual and area-level socioeconomic status. They were in fact remarkably insensitive to adjustment for potential confounders. Based on evidence and physical properties, $PM_{2.5}$ could be a better predictor of health effects of air pollution than PM_{10}, but the associations would essentially be the same due to the high spatial and temporal correlations in the SAPALDIA study areas (measured at a later point), given their ratio of ~0.80.

In contrast to the results for NO_2, those for PM_{10} were very different when area was controlled as a fixed instead of a random effect. The absence of significant associations within areas, shown by the fixed effect estimates, could have several reasons. First, power to detect within-area associations is clearly lower for PM_{10} due to its low spatial variation within these rather small geographic areas. NO_2 has instead larger contrasts within areas as it picks up the local contrasts of traffic related pollution. Second, PM_{10} is known to have different compositions across areas. Depending on the PM_{10} composition, the diabetogenic toxicity may vary, thus, adding to the heterogeneity in the within-area effects. Instead, NO_2 is generally an indicator of local traffic-related pollution, which is a comparable source all across Switzerland. Lastly, the prevalence of possible susceptibility factors varied across areas, for instance the proportion of high physical activity and alcohol intake > once/day varied from 8.1 to 42% and 1.7 to 21.9% respectively. However, effect estimates for PM_{10} and NO_2 remained quite stable when we additionally considered interaction terms between these factors and the exposure variables or study area. Thus, variation in susceptibility factors is unlikely to explain the observed difference in the associations within and across study areas. Since associations between air pollution and diabetes across areas might be confounded by lifestyle characteristics at the area level, we conducted additional sensitivity analyses including area means of socio-demographic and lifestyle characteristic. Again, effect estimates of PM_{10} and NO_2 remained remarkably stable.

This study adds to the growing, but still inconsistent evidence on the cross-sectional and longitudinal association between air pollution and possible type 2 diabetes. Brook et al. (2008) found a positive association between NO_2 and prevalent diabetes mellitus in women, but not men, who attended respiratory clinics in Hamilton and Toronto, Canada [OR: 1.04; 95% CI: 1.00, 1.08 for every 1 ppb increase in NO_2]. Dijkema et al. did not find any association of diabetes with NO_2 and traffic proximity estimates (Dijkema et al., 2011). In a purely ecologic comparison, Pearson et al. (2010) found a positive association between $PM_{2.5}$ and diabetes prevalence at the county level.

The longitudinal studies on incident diabetes were a bit more consistent. Kraemer et al. found the hazard of diabetes to be increased by 15–42% per interquartile range (IQR) of PM or traffic-related exposure measured as NO_2 in a German cohort of 1775 adult females (Krämer et al., 2010). Chen et al. reported a hazard ratio of 1.11 [95% CI: 1.02, 1.21], for diabetes as recorded in the Ontario diabetes database, per 10 μg/m^3 increase in 6-year average $PM_{2.5}$ in a Canadian cohort of 62,012 adults (Chen et al., 2013). In a Danish registry-based study involving 51,818 participants (Andersen et al., 2012), NO_2 was also associated with confirmed diabetes cases [HR = 1.04; 95% CI: 1.00, 1.08 per 2.6 ppb interquartile range of NO_2]. Coogan et al. studied 3992 African–American women in Los Angeles and reported an incidence risk ratio of 1.25 [95% CI: 1.07, 1.46] per 12.4 ppb IQR of NO_x and 1.63 [95% CI: 0.78, 3.44] per 10 μg/m^3 increase in $PM_{2.5}$ (Coogan et al.,

Table 4
Modification of the association between air pollution and diabetes mellitus.

Variable	Categories	NO_2 OR [95% CI]	PM_{10} OR [95% CI]
Age	≤50 years	1.22 [0.87, 1.71]	1.34 [0.81, 2.20]
	>50 years	1.18 [1.01, 1.38]	1.42 [1.18, 1.71]
	Interaction (p-value)	0.925	0.813
Sex	Males	1.25 [1.06, 1.48]	1.53 [1.29, 1.90]
	Females	1.11 [0.91, 1.36]	1.18 [0.89, 1.58]
	Interaction (p-value)	0.300	0.146
Obesity (BMI > 30 kg/m^2)	No	1.19 [1.00, 1.40]	1.37 [1.10, 1.67]
	Yes	1.13 [0.93, 1.34]	1.28 [0.99, 1.70]
	Interaction (p-value)	0.639	0.702
Hypertension	No	1.14 [0.90, 1.43]	1.34 [0.98, 1.84]
	Yes	1.19 [1.01, 1.41]	1.38 [1.12, 1.71]
	Interaction (p-value)	0.687	0.881
COPD ($FEV_1/FVC < 0.7$)	No	1.15 [0.98, 1.35]	1.32 [1.08, 1.61]
	Yes	1.31 [1.02, 1.67]	1.61 [1.11, 2.34]
	Interaction (p-value)	0.326	0.331
Educational level	Low	1.13 [0.83, 1.55]	1.32 [0.78, 2.48]
	Medium	1.22 [1.03, 1.44]	1.46 [1.18, 1.79]
	High	1.17 [0.91, 1.51]	1.23 [0.84, 1.79]
	Interaction (p-value)	0.885	0.698
Physical activity	Low	1.14 [0.96, 1.35]	1.37 [1.11, 1.70]
	Medium	1.23 [0.94, 1.60]	1.31 [0.90, 1.90]
	High	1.38 [1.03, 1.86]	1.73 [1.07, 2.80]
	Interaction (p-value)	0.456	0.618
Intake of Beta-blockers	No	1.19 [1.03, 1.38]	1.41 [1.18, 1.69]
	Yes	1.83 [0.52, 6.39]	0.23 [0.02, 3.32]
	Interaction (p-value)	0.388	0.185

OR values represent % increase in diabetes prevalence per 10 $\mu g/m^3$ increase in PM_{10} or NO_2; OR: odds ratio, CI: confidence interval; kg/m^2: kilogram per meter squared; COPD: chronic obstructive pulmonary disease, FEV_1: forced expiratory volume in 1 s, FVC: forced vital capacity. OR values represent % increase in diabetes prevalence per 10 $\mu g/m^3$ increase in PM_{10} or NO_2 in each category. Area was treated as a random effect in all models. The odds ratio of each category represents a stratified analysis for the category. Odds ratio in each category represents the effect in that group whereas the p-value of interaction term represents the p-value of the likelihood ratio test. All models were adjusted for age, sex, educational status, neighborhood socio-economic index, smoking status, pack-years of smoking, environmental tobacco smoking, occupational exposure to dusts, gases and fumes, consumption of alcohol, raw vegetables and fruits, physical activity, body mass index and noise. Low education corresponds to primary school level, intermediate corresponds to secondary, middle, or vocational school, and high education corresponds to technical college or university.

2012) whereas Puett et al., in the Health Professionals Follow-up Study and Nurses' Health Study, found an association only among female nurses living <50 m from a roadway [HR: 1.14, 95% CI: 1.03, 1.27] (Puett et al., 2011).

In our two-pollutant model, there was an attenuation of the effect of NO_2 from 1.19 [95% CI: 1.03, 1.38] to 1.02 [0.84, 1.25]. The Black Women Health Study reported a similar pattern with the attenuation of NO_x coefficient in the model that included $PM_{2.5}$ (Coogan et al., 2012). Unlike some studies that found a stronger effect in women (Brook et al., 2008; Chen et al., 2013), we did not find any substantial gender differences in our analysis. One of the reasons for observing a gender difference, apart from chance or hormonal differences, is potential exposure misclassification, because exposure estimates were based on residential addresses and women are believed to stay more around the home than men (Brook et al., 2008). Our exposure estimates were also based on the residential addresses and we found a slightly weaker effect in women, which might be a chance finding. Similar to the Canadian cohort (Chen et al., 2013) and the Danish cohort (Andersen et al., 2012), we did not find any significant interactions with any co-morbidities. Unlike the Danish study (Andersen et al., 2012), we did not find any interaction with physical activity, even though we observed stronger effects among the physically active for both pollutants. Whereas Kraemer et al. found a higher effect of living near a busy road in women of low education [HR: 2.54; 95% CI: 1.31–4.91, p = 0.006], we did not find any interaction with educational level.

4.1. Biological mechanisms linking air pollution to development of diabetes mellitus

Air pollution causes subclinical inflammation and appears to mediate components of the metabolic syndrome including impaired vascular endothelial function, and alterations in the central autonomic tone, visceral and brown adipose tissue, with mitochondrial and hepatic insulin receptor dysfunction (Liu et al., 2013; Rajagopalan and Brook, 2012). Apart from the experimental studies on mouse models which showed insulin resistance among rats, regardless of the type of diet given (Sun et al., 2009; Xu et al., 2011), human epidemiological studies have also demonstrated insulin resistance after air pollution exposure. Thiering et al. found a positive association between long-term exposure to NO_2 and PM_{10}, and homeostatic model assessment (HOMA) of insulin resistance among 10-year old children in Germany. Insulin resistance increased by 17% [95% CI: 5.0, 30.3] and 18.7% [95% CI: 2.9, 36.9] for every 2SD increase in NO_2 and PM_{10} respectively (Thiering et al., 2013). Similarly, Kelishadi and colleagues found positive associations between exposure to PM_{10}, and NO_2 [and other markers of air pollution], and insulin resistance [and other markers of inflammation and oxidative stress] among children in Iran (Kelishadi et al., 2009).

4.2. Strengths and limitations of this study

This study draws from the extensive database of the SAPALDIA study. This is the first cross-sectional study assessing this association with detailed confounding adjustment, including several lifestyle characteristics, health status as well as noise exposure. Our air pollution estimates were derived annually, over the 10 years preceding the first follow-up. This provided reliable estimates for cumulative exposure of the participants in this study. To limit outcome misclassification, we tried to identify undiagnosed cases through tests for non-fasting blood glucose and HbA1c, the gold standard for diagnosis of diabetes mellitus.

One major limitation of this study was the inclusion of all cases of self-reported, physician-diagnosed diabetes in the analysis irrespective of time of diagnosis. We did not have this information for all diabetes cases. However, we had information on some who reported

Table 5
Sensitivity analyses.

	N [cases/controls]	NO_2 OR [95% CI]	PM_{10} OR [95% CI]
Subjects living in same residence over 10-year follow-up period	3719 [218/3719]	1.17 [1.00, 1.37]	1.36 [1.09, 1.70]
Subjects without self-reported heart disease	5951 [259/5692]	1.21 [1.04, 1.41]	1.41 [1.16, 1.71]
Exclusion of diabetes reported at or before baseline assessment	6373 [296/6077]	1.21 [1.04, 1.41]	1.42 [1.17, 1.72]
Adjustment for participation bias (Inverse probability weighting)	6392 [315/6077]	1.18 [1.05, 1.34]	1.39 [1.15, 1.67]

OR values represent % increase in diabetes prevalence per 10 $\mu g/m^3$ increase in PM_{10} or NO_2. OR: odds ratio, CI: confidence interval. Area was treated as a random effect in all models. All models were adjusted for age, sex, educational status, neighborhood socio-economic index, smoking status, pack-years of smoking, environmental tobacco smoking, occupational exposure to dusts, gases and fumes, consumption of alcohol, raw vegetables and fruits, physical activity, body mass index and noise. All sensitivity analyses were done using the fully-adjusted single-pollutant models.

starting anti-diabetic medication, 90% of whom started taking the medication after the baseline examination. We also performed a sensitivity analysis, excluding those who reported taking diabetes medication before baseline. Another limitation was that air pollution was modeled at participants' residences. We did not have estimates for exposure at work and at other places where outdoor activities may take place. We expect this misclassification to be mostly non-systematic, thus, leading to bias toward the null. Fortunately, attenuation due to ignoring exposure at work is expected to be small (some 10%), because people spend more of their time at home. Nevertheless, we adjusted for occupational exposure to vapor, dust and fumes, which is unlikely to confound our main findings because it is not really correlated with our exposure of interest.

To the best of our knowledge, this is the first epidemiological study to consider noise exposure as a potential confounder of the association between diabetes and ambient air pollution exposure. Experimental evidence associating noise with diabetes mellitus (Spiegel et al., 2005; Tasali et al., 2009) postulates mechanisms through sleep deprivation, imbalance of the autonomic nervous system with a relative increase in sympathetic tone, release of stress hormones and consequent increase in blood pressure, blood lipids, glucose level, clotting and viscosity. Our consideration of noise could be a strength and a limitation. As discussed above, one may hypothesize interrelated pathways where both noise and air pollution may be relevant, thus, as in the case of cardiovascular outcomes, taking noise into account in air pollution–diabetes research is a strength (Tetreault et al., 2013). On the other side, we had only outdoor noise estimates available. As discussed by Foraster, outdoor noise estimates may not be a good proxy for personal exposure to noise, thus, it is not clear to what degree our models were able to properly control for independent effects of noise (Foraster, 2013). Finally, we had only one noise exposure estimate, at participants' residences for the entire follow-up period. To address this limitation, we also did a sensitivity analysis restricting the analysis to participants having lived in the same residence between baseline and follow-up.

The potential bias due to differential non-participation deserves further investigation. Analyses involving IPW help to correct at least some of the bias, but some bias may persist. All longitudinal studies on diabetes determinants face this challenge. Diabetic individuals with more advanced disease and disease-related handicaps are more likely to die or no longer participate. Air pollution is thought to contribute to the progression of diabetes and to susceptibility for cardiovascular events (Rajagopalan and Brook, 2012). Also, our finding of effect attenuation at higher rather than lower levels of exposure (opposing the usual threshold thinking), deserves further investigation. This calls for extension of air pollution research to areas with higher pollution levels and larger contrasts as observed in many developing countries.

In conclusion, this study adds to the evidence for a moderate and independent association between air pollution and diabetes. The results point to the need of future studies to consider the composition of PM. The observed association at concentrations below air quality standards parallels associations with mortality and points to continuous needs in air quality regulation.

Conflict of interest

All authors declare no actual or potential conflict of financial or other interests.

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All authors contributed equally to the development of this manuscript.

Appendix A

Table A1
Characteristics of participants included/excluded from the study.

Variables (%)	Baseline participants excluded only (N = 1604)	Follow-up participants excluded (N = 1655)	Participants Included (N = 6392)	N of baseline participants excluded/N of follow-up participants excluded/N included in the analysis
Females	45.3	54.5	51.3	1604/1655/6392
Smoking status at baseline				
Never smoker	35.6	40.1	46.9	1602/1648/6392
Ex-smoker	22.4	20.6	23.2	
Current smoker	42.0	39.3	29.9	
Smoking status at follow-up				0/1642/6392
Never smoker		37.5	43.5	
Ex-smoker		30.6	31.6	
Current smoker		31.9	24.9	
ETS in never smokers				
Baseline	12.4	13.2	13.3	1602/1648/6392
Follow-up		5.3	6.7	0/1261/6392
ETS in ex-smokers				
Baseline	8.2	7.5	7.2	1602/1648/6392
Follow-up		6.3	6.4	0/1261/6392
Occupational exposure to dust/gases/fumes				
Baseline	36.6	31.3	30.6	1600/1628/6392
Follow-up		26.3	27.5	0/171/6392
Physical activity[a]				0/141/6392
<0.5 h/week		45.4	38.7	
0.5–2 h/week		31.2	33.7	
>2 h/week		23.4	27.6	
Educational level at baseline				1594/1643/6390
Low	27.4	19.0	13.7	
Intermediate	57.6	65.7	68.9	
High	15.0	15.3	17.5	
Educational level at follow-up				0/1649/6392
Low		18.5	6.2	
Intermediate		64.5	65.6	
High		17.0	28.2	
Alcohol consumption[a]				0/170/6392
Never		10.6	9.2	
≤Once a day		75.9	81.8	
>Once a day		13.5	9.0	
Raw vegetable consumption[a]				0/172/6392
Never		0	0.6	
≤3 days/week		16.9	18.8	
>3 days/week		83.1	80.6	
Citrus fruits consumption[a]				0/172/6392
Never		7.1	8.4	
≤3 days/week		52.9	56.1	
>3 days/week		40.0	35.5	
Other fruits consumption[a]				0/168/6392
Never		1.2	1.8	
≤3 days/week		31.6	33.2	
>3 days/week		67.3	65.0	
Areas[a]: Basel		15.1	12.9	0/195/824
Wald		17.9	18.1	0/231/1154
Davos		7.6	8.0	0/98/512
Lugano		16.1	14.5	0/208/928
Montana		5.8	9.2	0/75/589
Payerne		18.5	13.8	0/238/885
Aarau		3.4	15.1	0/44/968
Geneva		15.5	8.3	0/199/532
Diabetes cases[a]		4.9	4.9	0/1045/6392
COPD (FEV1/FVC < 0.7) cases[a]		22.7	19.8	0/185/6392
Hypertension cases[a]		15.6	19.3	0/1025/6392
Dyslipidemias[a]		48.5	47.9	0/206/6111
High hs-CRP[a]		57.8	53.4	0/206/6111
Mean (SD)				
Age at baseline (years)	40.7 (12.0)	40.7 (12.1)	41.3 (11.4)	1604/1655/6392
Age at follow-up (years)		51.8 (12.1)	52.2 (11.4)	0/1655/6392
BMI at baseline (kg/m^2)	24.4 (4.3)	24.1 (4.1)	23.8 (3.6)	1571/1618/6363
BMI at follow-up (kg/m^2)		26.6 (5.4)	25.9 (4.4)	0/206/6392
Neighborhood SEI[a]		62.7 (10.7)	63.5 (10.1)	0/1598/6392
10-year mean PM_{10} (μg/m^3)[a]		22.7 (7)	22.3 (7.4)	0/1532/6392

Table A1 (*continued*)

Variables (%)	Baseline participants excluded only (N = 1604)	Follow-up participants excluded (N = 1655)	Participants Included (N = 6392)	N of baseline participants excluded/N of follow-up participants excluded/N included in the analysis
10-year mean NO_2 ($\mu g/m^3$)[a]		28.3 (11.4)	26.8 (11)	0/1532/6392
Mean smoking pack-years		12.4 (19.9)	10.8 (18.4)	0/1493/6392
Mean railway noise (dB)[a]		10.5 (13.1)	10.4 (13.1)	0/1595/6392
Mean street noise (dB)[a]		49.7 (9.4)	49.5 (8.8)	0/1595/6392

ETS: Environmental tobacco smoking; COPD: chronic obstructive pulmonary disease. FEV_1: forced expiratory volume in 1 s, FVC: forced vital capacity. hs-CRP: high sensitivity C-reactive protein. High hs-CRP is defines as hs-CRP ≥ 1.0 mmol/L, the median hs-CRP. Dyslipidemia defined as triglyceride ≥ 1.7 mmol/L and/or high density lipoprotein ≤ 1.03 mmol/L in men or ≤1.29 mmol/L in women. Low education corresponds to primary school level, intermediate corresponds to secondary, middle, or vocational school, and high education corresponds to technical college or university. SEI: socio-economic index. IQR: inter-quartile range.

[a] Measured only at follow-up.

Table A2
Association between air pollution and diabetes mellitus, stratified by case definition criteria.

	Self-reported, physician-diagnosed diabetes		Non-fasting blood glucose ≥ 11.1 mmol/L or HbA1c ≥ 0.065.		Self-reported diabetes medication	
	NO_2	PM_{10}	NO_2	PM_{10}	NO_2	PM_{10}
OR [95% CI]	1.18 [0.99,1.40] N = 6306; Cases = 229	1.31 [1.02, 1.67]	1.26 [1.09, 1.45] N = 6298; Cases = 221	1.48 [1.19, 1.82]	1.19 [0.96, 1.48] N = 6224; Cases = 147	1.12 [0.84, 1.51]

OR values represent % increase in diabetes prevalence per 10 $\mu g/m^3$ increase in PM_{10} or NO_2. OR: odds ratio, CI: confidence interval. Area was treated as a random effect in all models. All models were adjusted for age, sex, educational status, area socio-economic index, smoking status, pack-years of smoking, environmental tobacco smoking, occupational exposure to dusts, gases and fumes, consumption of alcohol, raw vegetables and fruits, physical activity, body mass index and noise. Diabetes cases not matching the criterion were excluded from the controls.

Table A3
Association between air pollution and diabetes with fixed effect models.

	NO2 OR [95% CI]	PM10 OR [95% CI]
Fully adjusted model treating study area as a fixed effect	1.11 [0.87, 1.40]	0.86 [0.47, 1.60]
Fully adjusted model ignoring study area	1.21 [1.07,1.36]	1.40 [1.17, 1.68]

OR values represent % increase in diabetes prevalence per 10 $\mu g/m^3$ increase in PM_{10} or NO_2. OR: odds ratio, CI: confidence interval. Area was treated as a fixed effect in all models. All models were adjusted for age, sex, educational status, area socio-economic index, smoking status, pack-years of smoking, environmental tobacco smoking, occupational exposure to dusts, gases and fumes, consumption of alcohol, raw vegetables and fruits, physical activity, body mass index and noise. N = 6392 at all levels of adjustment.

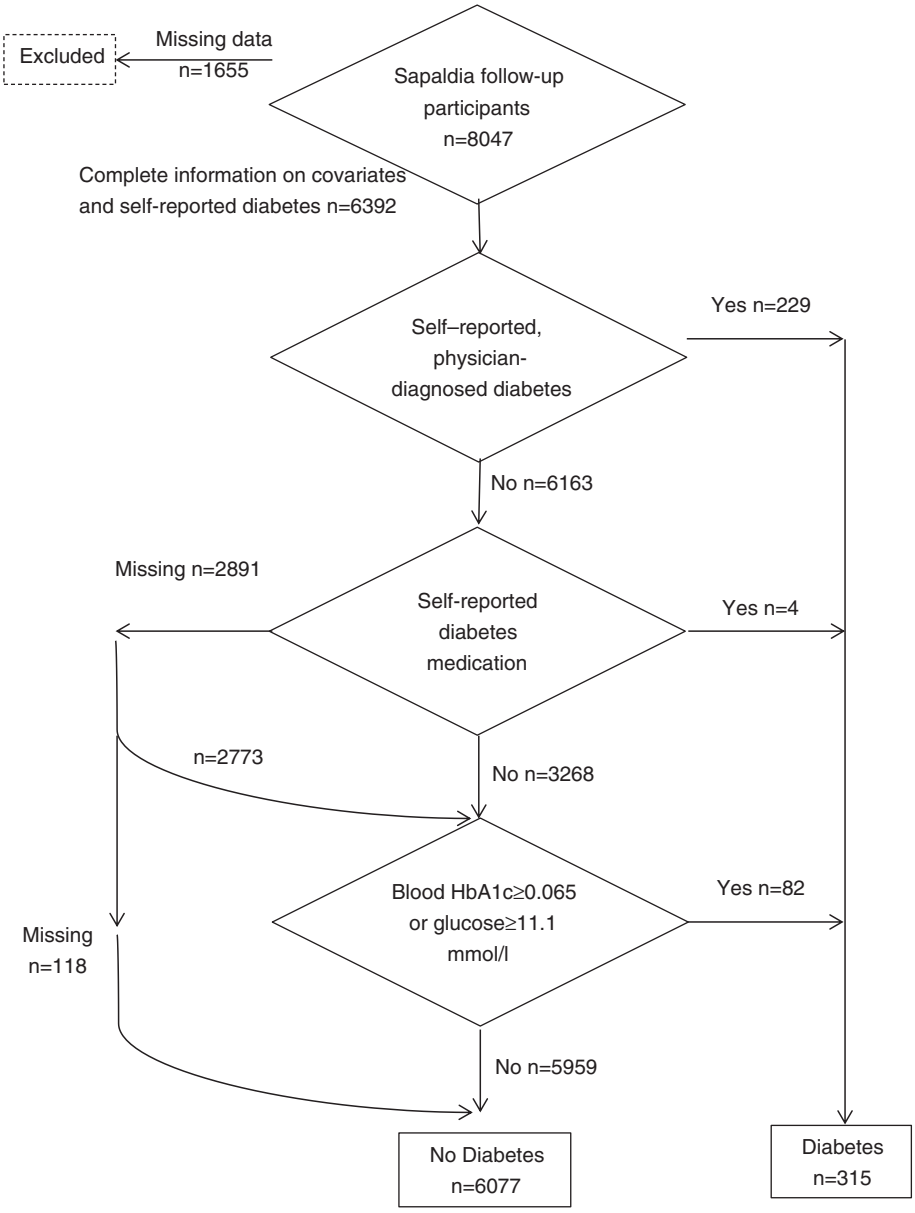

Fig. A1 Diabetes case identification flow chart.

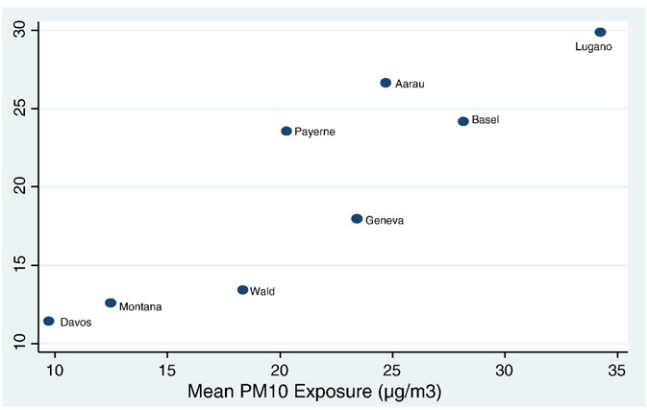

Fig. A2 Correlation between adjusted diabetes prevalence and mean PM_{10} by area.

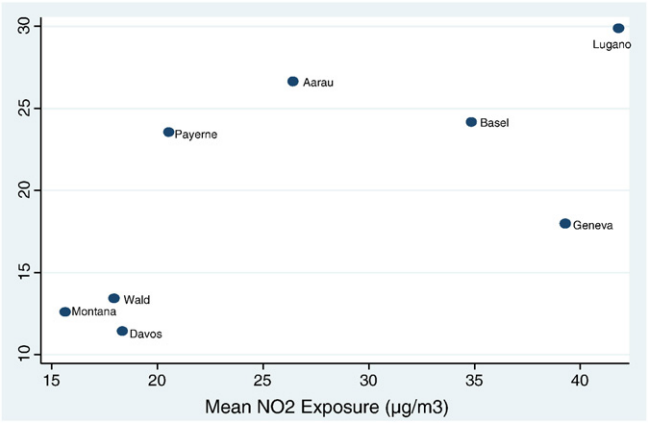

Fig. A3 Correlation between adjusted diabetes prevalence and mean NO_2 by area.

References

Ackermann-Liebrich U, Kuna-Dibbert B, Probst-Hensch NM, Schindler C, Felber Dietrich D, Stutz EZ, et al. Follow-up of the Swiss cohort study on air pollution and lung diseases in adults (SAPALDIA 2) 1991–2003: methods and characterization of participants. Soz Praventivmed 2005;50:245–63.

Andersen ZJ, Raaschou-Nielsen O, Ketzel M, Jensen SS, Hvidberg M, Loft S, et al. Diabetes incidence and long-term exposure to air pollution: a cohort study. Diabetes Care 2012;35:92–8.

Auchincloss AH, Diez Roux AV, Dvonch JT, Brown PL, Barr RG, Daviglus ML, et al. Associations between recent exposure to ambient fine particulate matter and blood pressure in the multi-ethnic study of atherosclerosis (MESA). Environ Health Perspect 2008;116:486–91.

Bell DS. Advantages of a third-generation beta-blocker in patients with diabetes mellitus. Am J Cardiol 2004;93:49B–52B.

Brook RD, Jerreft M, Brook JR, Bard RL, Finkelstein MM. The relationship between diabetes mellitus and traffic-related air pollution. J Occup Environ Med 2008;50:32–8.

Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. Diabetes Care 2010;33:414–20.

Chen H, Burnett RT, Kwong JC, Villeneuve PJ, Goldberg MS, Brook RD, et al. Risk of incident diabetes in relation to long-term exposure to fine particulate matter in Ontario, Canada. Environ Health Perspect 2013;121:804–10.

Chuang KJ, Chan CC, Su TC, Lee CT, Tang CS. The effect of urban air pollution on inflammation, oxidative stress, coagulation, and autonomic dysfunction in young adults. Am J Respir Crit Care Med 2007;176:370–6.

Coogan PF, White LF, Jerrett M, Brook RD, Su JG, Seto E, et al. Air pollution and incidence of hypertension and diabetes mellitus in black women living in Los Angeles. Circulation 2012;125:767–72.

Dijkema MB, Mallant SF, Gehring U, van den Hurk K, Alssema M, van Strien RT, et al. Long-term exposure to traffic-related air pollution and type 2 diabetes prevalence in a cross-sectional screening-study in the Netherlands. Environ Health 2011;10:76.

Dratva J, Phuleria HC, Foraster M, Gaspoz JM, Keidel D, Kunzli N, et al. Transportation noise and blood pressure in a population-based sample of adults. Environ Health Perspect 2012;120:50–5.

FOEN. Noise pollution in Switzerland. Results of the SonBase National Noise Monitoring Programme. State of the environment no 0907. Bern, Switzerland: Federal Office for the Environment; 2009a.

FOEN. SonBase — the GIS noise database of Switzerland. Technical bases. State of the environment no 0908. Bern: Federal Office for the Environment; 2009b.

Folino AF, Scapellato ML, Canova C, Maestrelli P, Bertorelli G, Simonato L, et al. Individual exposure to particulate matter and the short-term arrhythmic and autonomic profiles in patients with myocardial infarction. Eur Heart J 2009;30:1614–20.

Foraster M. Is it traffic-related air pollution or road traffic noise, or both? Key questions not yet settled! Int J Public Health 2013;58:647–8.

Goldberg MS, Burnett RT, Stieb DM, Brophy JM, Daskalopoulou SS, Valois MF, et al. Associations between ambient air pollution and daily mortality among elderly persons in Montreal, Quebec. Sci Total Environ 2013;463–464:931–42.

Hara Y, Hamada M, Shigematsu Y, Ohtsuka T, Ogimoto A, Higaki J. Effect of beta-blockers on insulin resistance in patients with dilated cardiomyopathy. Circ J 2003;67:701–4.

Hoffmann B, Moebus S, Mohlenkamp S, Stang A, Lehmann N, Dragano N, et al. Residential exposure to traffic is associated with coronary atherosclerosis. Circulation 2007;116:489–96.

Kelishadi R, Mirghaffari N, Poursafa P, Gidding SS. Lifestyle and environmental factors associated with inflammation, oxidative stress and insulin resistance in children. Atherosclerosis 2009;203:311–9.

Kim KH, Ho DX, Brown RJ, Oh JM, Park CG, Ryu IC. Some insights into the relationship between urban air pollution and noise levels. Sci Total Environ 2012;424:271–9.

Krämer U, Herder C, Sugiri D, Strassburger K, Schikowski T, Ranft U, et al. Traffic-related air pollution and incident type 2 diabetes: results from the SALIA cohort study. Environ Health Perspect 2010;118:1273–9.

Künzli N, Bridevaux PO, Liu LJ, Garcia-Esteban R, Schindler C, Gerbase MW, et al. Traffic-related air pollution correlates with adult-onset asthma among never-smokers. Thorax 2009;64:664–70.

Kveiborg B, Christiansen B, Major-Petersen A, Torp-Pedersen C. Metabolic effects of beta-adrenoceptor antagonists with special emphasis on carvedilol. Am J Cardiovasc Drugs 2006;6:209–17.

Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2224–60.

Liu C, Ying Z, Harkema J, Sun Q, Rajagopalan S. Epidemiological and experimental links between air pollution and type 2 diabetes. Toxicol Pathol 2013;41:361–73.

Liu LJ, Curjuric I, Keidel D, Heldstab J, Kunzli N, Bayer-Oglesby L, et al. Characterization of source-specific air pollution exposure for a large population-based Swiss cohort (SAPALDIA). Environ Health Perspect 2007;115:1638–45.

Liu SL, Tsai M-Y, Keidel D, Gemperli A, Ineichen A, Hazenkamp-von Arx M, et al. Long-term exposure models for traffic related NO_2 across geographically diverse areas over separate years. Atmos Environ 2012;46:460–71.

Lotti M. Individual exposure to particulate matter and heart rate variability (HRV) in patients with previous myocardial infarction. J Biomed Nanotechnol 2011;7:28.

O'Neill MS, Veves A, Zanobetti A, Sarnat JA, Gold DR, Economides PA, et al. Diabetes enhances vulnerability to particulate air pollution-associated impairment in vascular reactivity and endothelial function. Circulation 2005;111:2913–20.

Panczak R, Galobardes B, Voorpostel M, Spoerri A, Zwahlen M, Egger M. A Swiss neighbourhood index of socioeconomic position: development and association with mortality. J Epidemiol Community Health 2012;66:1129–36.

Papazafiropoulou AK, Kardara MS, Pappas SI. Environmental pollution and diabetes mellitus. Recent Pat Biomark 2011;1:44–8.

Pearson JF, Bachireddy C, Shyamprasad S, Goldfine AB, Brownstein JS. Association between fine particulate matter and diabetes prevalence in the U.S. Diabetes Care 2010;33:2196–201.

Puett RC, Hart JE, Schwartz J, Hu FB, Liese AD, Laden F. Are particulate matter exposures associated with risk of type 2 diabetes? Environ Health Perspect 2011;119:384–9.

Rajagopalan S, Brook RD. Air pollution and type 2 diabetes: mechanistic insights. Diabetes 2012;61:3037–45.

Schikowski T, Ranft U, Sugiri D, Vierkotter A, Bruning T, Harth V, et al. Decline in air pollution and change in prevalence in respiratory symptoms and chronic obstructive pulmonary disease in elderly women. Respir Res 2010;11:113.

Sorensen M, Hvidberg M, Hoffmann B, Andersen ZJ, Nordsborg RB, Lillelund KG, et al. Exposure to road traffic and railway noise and associations with blood pressure and self-reported hypertension: a cohort study. Environ Health 2011;10:92.

Sorensen M, Andersen ZJ, Nordsborg RB, Becker T, Tjonneland A, Overvad K, et al. Long-term exposure to road traffic noise and incident diabetes: a cohort study. Environ Health Perspect 2013;121:217–22.

Spiegel K, Knutson K, Leproult R, Tasali E, Van Cauter E. Sleep loss: a novel risk factor for insulin resistance and type 2 diabetes. J Appl Physiol 2005;99:2008–19.

StataCorporation. Stata statistical software: release 12. College Station, Texas: StataCorp LP; 2011.

Sun Q, Yue P, Deiuliis JA, Lumeng CN, Kampfrath T, Mikolaj MB, et al. Ambient air pollution exaggerates adipose inflammation and insulin resistance in a mouse model of diet-induced obesity. Circulation 2009;119:538–46.

Tasali E, Leproult R, Spiegel K. Reduced sleep duration or quality: relationships with insulin resistance and type 2 diabetes. Prog Cardiovasc Dis 2009;51:381–91.

Tetreault LF, Perron S, Smargiassi A. Cardiovascular health, traffic-related air pollution and noise: are associations mutually confounded? A systematic review. Int J Public Health 2013;58:649–66.

Thiering E, Cyrys J, Kratzsch J, Meisinger C, Hoffmann B, Berdel D, et al. Long-term exposure to traffic-related air pollution and insulin resistance in children: results from the GINIplus and LISAplus birth cohorts. Diabetologia 2013;56:1696–704.

WHO. Who air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide. Global update 2005. Summary of risk assessment. Geneva, Switzerland: World health Organization; 2006.

Xu X, Liu C, Xu Z, Tzan K, Zhong M, Wang A, et al. Long-term exposure to ambient fine particulate pollution induces insulin resistance and mitochondrial alteration in adipose tissue. Toxicol Sci 2011;124:88–98.

Xu X, Jiang SY, Wang TY, Bai Y, Zhong M, Wang A, et al. Inflammatory response to fine particulate air pollution exposure: neutrophil versus monocyte. PLoS One 2013;8:e71414.

Yan Y-H, Chou CCK, Lee C-T, Liu J-Y, Cheng T-J. Enhanced insulin resistance in diet-induced obese rats exposed to fine particles by instillation. Inhal Toxicol 2011;23:507–19.

Zanobetti A, Schwartz J. Are diabetics more susceptible to the health effects of airborne particles? Am J Respir Crit Care Med 2001;164:831–3.