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Long-term exposure to particulate matter, NO_2 and the oxidative potential of particulates and diabetes prevalence in a large national health survey☆,☆☆

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ABSTRACT

Background: The evidence from observational epidemiological studies of a link between long-term air pollution exposure and diabetes prevalence and incidence is currently mixed. Some studies found the strongest associations of diabetes with fine particles, other studies with nitrogen dioxide and some studies found no associations.
Objectives: Our aim was to investigate associations between long-term exposure to multiple air pollutants and diabetes prevalence in a large national survey in the Netherlands.
Methods: We performed a cross-sectional analysis using the 2012 Dutch national health survey to investigate the associations between the 2009 annual average concentrations of multiple air pollutants (PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, $PM_{2.5}$ absorbance, OP^{DTT}, OP^{ESR} and NO_2) and diabetes prevalence, among 289,703 adults. Air pollution exposure was assessed by land use regression models. Diabetes was defined based on a combined measure of self-reported physician diagnosis and medication prescription from an external database. Using logistic regression, we adjusted for potential confounders, including neighborhood- and individual socio-economic status and lifestyle-related risk factors such as smoking habits, alcohol consumption, physical activity and BMI.
Results: After adjustment for potential confounders, all pollutants (except $PM_{2.5}$) were associated with diabetes prevalence. In two-pollutant models, NO_2 and OP^{DTT} remained associated with increased diabetes prevalence. For NO_2 and OP^{DTT}, single-pollutant ORs per interquartile range were 1.07 (95% CI: 1.05, 1.09) and 1.08 (95% CI: 1.05, 1.10), respectively. Stratified analysis showed no consistent effect modification by any of the included known diabetes risk factors.
Conclusions: Long-term residential air pollution exposure was associated with diabetes prevalence in a large health survey in the Netherlands, strengthening the evidence of air pollution being an important diabetes risk factor. Most consistent associations were observed for NO_2 and oxidative potential of $PM_{2.5}$ measured by the DTT assay. The finding of an association with the oxidative potential of fine particles but not with $PM_{2.5}$, suggests that particle composition may be important for a potential effect on diabetes.

1. Introduction

Diabetes is an important public health concern in both developed and developing countries. A recent World Health Organization report estimated that in 2014 422 million people had diabetes, a global prevalence of 8.5% among the adult population, nearly doubled from 4.7% in 1980 (WHO 2016a). Lifestyle, in particular high body mass index (BMI) and low physical activity (PA), is a major risk factor for type 2

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diabetes (GBD 2013 Collaborators 2015).

In recent years, a number of epidemiological cohort and cross-sectional studies suggested an association between long-term exposure to air pollution and diabetes incidence and prevalence (Andersen et al. 2012; Brook et al. 2008; Chen et al. 2013; Coogan et al. 2012, 2016a, 2016b; Dijkema et al. 2011; Eze et al. 2014, 2017; Kramer et al. 2010; Park et al. 2015; Puett et al. 2011; Weinmayr et al. 2015). In a recent systematic review and meta-analysis, Eze and co-workers reported an overall positive association between air pollution and diabetes from epidemiological studies, but also noted heterogeneity of effect estimates, diversity of study designs, relatively high risk of bias and lack of evaluation of dose-response relationships (Eze et al. 2015). The plausibility of air pollution affecting diabetes is increased by a few experimental animal studies showing an increase in insulin resistance and other physiological markers relevant for development of diabetes after controlled exposure to fine particles (Sun et al. 2009). In epidemiological studies published since the Eze et al. (2015) review, evidence has been mixed as well (Table S1). Overall, we argue that the association between air pollution and diabetes has not yet been firmly established and additional large studies are needed.

Seven of the 13 published studies included only a single measure of pollution, either NO_2 or particle metrics, often $PM_{2.5}$. The remaining studies included combinations of mostly $PM_{2.5}$/PM_{10} and NO_2. No study of diabetes so far included oxidative potential (OP) of particulate matter. It has been proposed that OP may be a more health relevant metric than PM mass (Ayres et al. 2008; Borm et al. 2007), however the empirical evidence for this hypothesis is still limited. Evidence of the pollutant most consistently associated with diabetes was inconsistent across the studies. A number of studies have suggested higher hazard ratios in women (Andersen et al. 2012; Brook et al. 2008; Chen et al. 2013; Dijkema et al. 2011), whereas others suggested them to be higher in men (Eze et al. 2014; Park et al. 2015; Puett et al. 2011; Weinmayr et al. 2015). Effect modification by smoking status and PA have shown conflicting results as well (Andersen et al. 2012; Hansen et al. 2016). Some of the heterogeneity may be due to the relatively small size of some of the studies.

In the current study, our aim was to investigate the associations between long-term exposure to a number of different air pollutants and prevalence of diabetes in a large national health survey (~300,000 subjects) in the Netherlands including detailed information on lifestyle. Our second aim was to evaluate effect modification by sex, smoking, PA and other diabetes risk factors, exploiting the large size of the study population.

2. Methods

2.1. Study population

The Public Health Monitor is a national health survey carried out in 2012 by 28 Public Health Services (GGD), Statistics Netherlands (CBS) and National Institute for Public Health and the Environment (RIVM). The Monitor population was selected across the Netherlands with both major cities, smaller towns and rural areas sampled and a response rate of 45–50%. The survey was carried out mostly in Dutch language. The Monitor includes information on 387,195 citizens aged ≥ 19 and covers a range of issues related to physical and mental health status, socio-economic situation (*e.g.*, education, paid occupation, marital status), lifestyle (*e.g.*, smoking, alcohol consumption, PA, BMI) and other individual characteristics. Specification of variables used in our analysis are presented in the data analysis section. CBS has further enriched the Monitor with information on ethnicity and standardized household income on an individual level. Elderly (≥ 65 years) subjects were overrepresented by design. We have linked the Monitor dataset with information on socio-economic status (SES) at a neighborhood level (four-digit postal code). This continuous indicator represents educational, occupational and economical status of the neighborhood and is measured every four years by The Netherlands Institute for Social Research (Sociaal en Cultureel Planbureau) (Knol 1998); we used the latest available data, being the 2006 SES score and categorized the score into quantiles, with the lowest quantile representing the highest SES. To examine the representativeness of the Monitor for the general adult Dutch population we have used the 2012 information from the electronic databank of Statistics Netherlands (http://statline.cbs.nl). Further, we linked each individual in the Monitor with information on individual diabetes medication prescription for the year 2012 from an external database. Exposure information was available for 386,831 participants, but due to missing values on potential confounders, information on 289,703 participants was available for the analysis.

2.2. Outcome definition

The Public Health Monitor included a question on diabetes not specifying its type. The main question is: “Do you have diabetes?”, with a follow-up question: “In the last 12 months, have you been treated for diabetes by a GP or a specialist?”. We have chosen the follow-up question for our analyses as it refers to actual medical treatment of diabetes; 92% of positive answers for the main question were also positive in the follow-up question.

Additionally, using an external database, we used the prescription of diabetes medication ATC codes A10A - “Insulins and analogues”, and A10B - “Blood glucose lowering drugs, excl. insulins” (WHO 2016b) as a second definition of diabetes. The database contains all medication that is paid for by all insurance companies in the framework of the national obligatory basic health insurance for all residents of the Netherlands. The database is maintained by Health Care Netherlands (Zorginstituut Nederland). We used a prescription of any of the two types of medication in our analyses.

As the main outcome of our analysis, we created a combined measure of diabetes prevalence by consolidating the answers for the “self-reported doctor-diagnosed diabetes” question with the information on diabetes medication prescription. If any of the two was positive, then the combined measure was assigned “yes”; if both were negative, then the combined measure was assigned “no”. Using the combined measure increases the sensitivity of outcome definition and limits the risk of false negatives. We further analyzed the self-reported diabetes and the use of diabetes medication as separate outcomes in additional analyses.

2.3. Air pollution exposure assessment

We used land use regression (LUR) models to assess long-term average air pollution exposure at the home addresses. The models have originally been developed within the framework of the ESCAPE project for the Netherlands and provided annual average concentration data on PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$ (the coarse fraction of PM), absorbance of $PM_{2.5}$ (a measure of black carbon particles) and NO_2 (Beelen et al. 2013; Eeftens et al. 2012). The models were based on measurements in 2009, preceding the current survey. In the Netherlands, simultaneous measurements of NO_2 and NO_X took place at 80 locations and PM at 40 locations, over three two-week campaigns spread over a year. The three measurements were then averaged, adjusting for temporal trends using continuous data from an ESCAPE background reference monitoring site. $PM_{10-2.5}$ was calculated as difference of PM_{10} and $PM_{2.5}$; absorbance was measured on $PM_{2.5}$ filters. Predictor variables (*e.g.*, traffic variables, land use, population and household density) were then derived from the Geographic Information Systems (GIS) to explain the spatial variation in measured annual average air pollution concentrations. The Dutch ESCAPE LUR models explained 86% of the variability in the annual NO_2 concentrations, 68% variability in the PM_{10} concentrations, 67% in the $PM_{2.5}$ concentrations, 51% in the $PM_{10-2.5}$ concentrations, and 92% in the absorbance concentrations.

Further, we used the recently developed $PM_{2.5}$ OP LUR models, including two OP metrics – electron spin resonance (OP^{ESR}) and

dithiothreitol (OP^{DTT}) (Yang et al. 2015). The ESR method is based on the ability of PM to generate hydroxyl radicals (•OH) in the presence of hydrogen peroxide (H_2O_2), and 5,5-dimethyl-1-pyrroline-N-oxide (DMPO; spin trap) (Shi et al. 2003). OP^{ESR} is reported as the average of the total amplitudes of the DMPO-OH and is expressed in arbitrary units (A.U.) per sample volume. The DTT method measures the presence of reactive oxygen species (ROS) due to transfer of electrons from DTT to oxygen (Cho et al. 2005). OP^{DTT} is reported as the rate of DTT depletion and is expressed in nmol DTT per minute per sample volume. The OP LUR models were developed using exactly the same methodology as the ESCAPE LUR models and explained > 60% of the variability in the annual average OP concentrations. Home-address concentrations of all the included air pollutants were calculated by applying the LUR models in the PCRaster environmental modelling software using grids of 5 × 5 m (Karssenberg et al. 2010). The air pollution estimates at home addresses were then assigned a unique, unintelligible address identifier by CBS (keeping four-digit postal code available) to preserve confidentiality. Using this identifier, we have then merged the air pollution estimates with the Public Health Monitor data in the secure remote access environment of CBS.

2.4. Statistical analyses

We used logistic regression models to obtain the odds ratios (OR) and 95% confidence intervals (CI) of the associations between long-term exposure to PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, absorbance, NO_2, OP^{DTT} and OP^{ESR} and the combined measure of diabetes prevalence (see *Outcome definition*). Air pollution was entered as a linear term. In an additional analysis, we entered deciles of pollutants, with the lowest decile as a reference, to evaluate the shape of the association.

We specified five models *a priori*, with an increasing level of adjustment for potential confounders. Model 1 was adjusted for sex and age only. Model 2a added to model 1 individual socio-economic characteristics (highest achieved education level, paid occupation, household income, marital status, and ethnicity). Model 3a added neighborhood SES score to model 2a. Models 2b and 3b added lifestyle risk factors (smoking habits, alcohol consumption, PA, and BMI) to models 2a and 3a, respectively. We *a priori* chose model 3b as our main confounder model. All confounders were specified as categorical variables (categories are shown in Table 1) except for the number of cigarettes smoked and alcohol consumption, which were entered as continuous variables.

Using the main confounder model, we also performed stratified analyses to study effect modification by known diabetes risk factors, *i.e.*, sex, age, education, income, ethnicity, smoking habit, PA, and BMI. For the effect modification analysis, we have used the same categories of included confounders as in the main analysis (see Table 1).

To study the individual associations of different pollutants with diabetes prevalence, we specified two-pollutant models (based on the main confounder model) with all possible combinations of the included pollutants. Models in which a variance inflation factor (VIF) was larger than 3 were not interpreted, due to possible multicollinearity issues.

Since we excluded nearly 100,000 participants of the Public Health Monitor due to missing values on potential confounders, we analyzed the potential selection bias in our study by comparing the results for the full population of the Public Health Monitor and our study population using the ORs obtained from model 1 (*i.e.*, with no potential confounders missing).

For PA, we included activities with Metabolic Equivalent of Task (MET) score ≥ three, *i.e.*, moderate-intensity PA. MET scores range from "1" for inactivity (*e.g.*, sitting or lying quietly) to "18" for running at 17.5 km/h (3.4 min/km) (Ainsworth et al. 2000). Activities which we included were walking or cycling to commute, leisure time walking or cycling, gardening, doing odd jobs in the home, leisure sports (up to four, only those ≥ 3 MET included), and vigorous activities in the home, work or school.

Table 1
Public Health Monitor population characteristics.

Characteristic	Full population *N = 289,703*	Diabetes[a] *n = 23,097*	Self-reported physician-diagnosed diabetes *n = 20,635*	Diabetes medication prescription *n = 19,986*
Diabetes	8.1	100.0	100.0	100.0
Self-reported physician-diagnosed diabetes	7.2	94.4	100.0	93.5[c]
Diabetes medication prescription	6.9	86.5	84.9[b]	100.0
Female	52.6	44.9	44.9	43.6
Age (years)				
19–40	20.9	2.2	2.2	2.2
41–64	41.3	27.2	28.0	27.1
65–74	24.6	41.9	42.0	42.1
≥ 75	13.2	28.7	27.9	28.6
Education				
Primary or less	7.4	18.0	17.2	18.0
Lower-secondary	32.9	44.0	44.1	43.8
Higher-secondary	29.7	21.0	21.4	21.3
University	29.9	17.0	17.2	16.9
Paid occupation	50.4	19.8	20.2	19.8
Household income				
< €15,200	9.2	11.0	10.7	11.0
€15,200–19,400	16.5	26.2	25.8	26.3
€19,400–24,200	21.1	23.4	23.4	23.4
€24,200–31,000	25.1	20.9	21.1	21.0
≥€31,000	28.2	18.6	18.9	18.4
Marital status				
Married/living together	73.1	69.4	69.8	69.7
Unmarried/never married	12.3	5.6	5.6	5.6
Divorced	6.3	8.0	7.9	8.0
Widowed	8.3	17.0	16.7	16.8
Ethnicity				
Moroccan	0.6	1.2	1.1	1.3
Turkish	0.8	1.1	1.1	1.1
Surinamese	0.9	2.0	1.8	2.1
Dutch Antillean & Aruban	0.4	0.4	0.4	0.4
Other non-Western	1.6	1.5	1.4	1.4
Other Western	8.4	10.0	10.1	9.9
Dutch	87.4	83.7	84.1	83.8
Neighborhood SES score[d]				
< 30	21.6	18.0	18.1	18.1
30–34	21.9	20.4	20.6	20.3
34–38	20.6	20.6	20.4	20.3
38–43	17.5	17.9	18.0	17.8
≥ 43	18.4	23.2	22.9	23.5
Smoking habit				
Current	19.0	15.8	15.7	15.6
Former	40.5	52.9	53.3	53.3
Never	40.6	31.4	31.0	31.2
Alcohol consumption				
Current	83.3	68.4	68.9	67.8
Former	6.0	12.8	12.8	13.2
Never	10.7	18.8	18.3	19.0
Physical activity (≥ 3 MET)				
< 375 min/week	25.0	39.4	38.9	39.7
375–750 min/week	25.1	21.8	21.9	21.7
750–1440 min/week	25.4	21.6	21.7	21.5
≥ 1440 min/week	24.5	17.3	17.5	17.1
BMI				
Underweight	1.3	0.4	0.4	0.4
Normal range	47.4	23.5	23.4	22.8
Overweight	38.2	43.6	43.8	43.4

(continued on next page)

Table 1 *(continued)*

Characteristic	Full population *N = 289,703*	Diabetes[a] *n = 23,097*	Self-reported physician-diagnosed diabetes *n = 20,635*	Diabetes medication prescription *n = 19,986*
Obese	13.2	32.5	32.5	33.4
Number of cigarettes/day for current smokers [mean (SD)]	10.2 (8.3)	12.0 (9.6)	12.0 (9.7)	12.0 (9.7)
Number of alcohol glasses/week for current alcohol consumers [mean (SD)]	8.5 (9.5)	8.3 (10.0)	8.3 (10.0)	8.2 (9.9)

Unless otherwise stated, values are frequency (%).

[a] Combined measure of diabetes prevalence obtained by consolidating the answers for the "self-reported doctor-diagnosed diabetes" question with the information on diabetes medication prescription (see *Outcome definition*).

[b] 84.9% of population with self-reported diabetes has also been prescribed diabetes medication.

[c] 93.5% of population with prescribed diabetes medication have positively answered the survey question about having a physician diagnosis of diabetes.

[d] The lowest score represents neighborhoods with the highest SES.

The OR and 95% CI were expressed per interquartile range (IQR) of the respective pollutants (Table 2), to allow comparison of ORs between air pollutants. Additionally, for some pollutants we expressed them per 10 μg/m^3 to facilitate comparison with other studies. Analyses were carried out with SAS 9.4 (SAS Institute Inc., Cary, NC, USA) in a secured remote access environment of CBS.

3. Results

The characteristics of the 289,703 adult participants of the Public Health Monitor are presented in Table 1. The data is skewed towards the elderly population, with nearly 38% being 65 years or older, whereas in the general Dutch population only 16% is ≥65 years (http://statline.cbs.nl/), consistent with the Public Health Monitor design. People of Dutch origin are overrepresented in the Public Health Monitor (87% compared with 79% in the general Dutch population), whereas people in the lowest household income quintile are underrepresented (9% compared with 20% in the general Dutch population), probably due to differential response rates. The amount of PA per day may seem big, however it is not unrealistic in the Dutch population, where cycling is the main mode of transport. There was a good agreement between self-reported physician-diagnosed diabetes and diabetes medication prescription – nearly 85% of the population with self-reported physician diagnosis of diabetes in the past 12 months has also been prescribed diabetes medication (Table 1). There was almost no difference in population characteristics between the combined and the two separate measures of diabetes prevalence (Table 1). Subjects with diabetes differed from the overall population in most characteristics. Diabetes cases were especially older, less educated, had lower income, were less physically active and more obese.

3.1. Air pollution concentrations

Home-address concentrations of the seven air pollutants are presented in Table 2. Contrast of exposure was more limited for $PM_{2.5}$ and PM_{10} (IQR 0.81 and 1.20 μg/m^3, respectively) than for the other metrics. Correlations between the air pollutants were mostly moderate (Spearman R 0.22–0.60) (Table S2). Correlations between NO_2, PM_{10}, $PM_{10-2.5}$ and absorbance were high (0.69–0.86).

3.2. Air pollution associations with diabetes prevalence

Long-term residential exposure to nearly all the investigated air pollution components was positively associated with diabetes prevalence after adjustment for individual and area-level confounders in the main model 3b (Table 3). Only $PM_{2.5}$ was not associated with diabetes: OR 1.01 (95% CI: 0.99, 1.03). The associations were stronger in model 1, when only adjusted for age and sex. Associations were reduced especially by adjustment for individual socio-economic characteristics (Model 2a). Further decreases in effect estimates were found after adjustment for area-level SES (Model 3a), and to a lesser extent after adjustment for lifestyle-related risk factors (Models 2b and 3b). We observed the strongest associations with NO_2 and OP^{DTT}: 1.07 (95% CI: 1.05, 1.09) and 1.08 (95% CI: 1.05, 1.10), respectively. An analysis with deciles of pollutant concentrations suggested no important deviation from a linear association (Fig. 1).

We observed similar associations between air pollution and prevalence of diabetes when investigating self-reported physician diagnosis of diabetes and diabetes medication prescription as separate outcomes (Table S3).

Results of the associations with diabetes in two-pollutant models are presented in Table 4. Associations with NO_2 and OP^{DTT} remained after adjustment for all other pollutants. Both associations decreased after adjusting for one another and their effect could not be disentangled, despite their fairly moderate correlation (0.55). In some models (*e.g.*, NO_2 and absorbance), confidence intervals were widened compared to single-pollutant models, reflecting the correlation between pollutants. Consistent with the moderate correlation of OP^{DTT} with other pollutants, confidence intervals were less inflated in two-pollutant models with OP. None of the other pollutants had consistent associations in the two-pollutant models.

Analysis of the potential selection bias in our study because of excluding nearly 100,000 participants due to missing potential confounder showed no effect of the exclusion – model 1 ORs were nearly identical between the full population of the Public Health Monitor and our study population (Table S4).

3.3. Subgroup analyses

Subgroup analyses based on the main confounder model showed

Table 2
Air pollution characteristics of the Public Health Monitor population (*N* = 289,703).

	Mean (SD)	IQR	Min	P5	P25	P75	P95	Max
PM_{10} (μg/m^3)	24.76 (1.11)	1.20	23.73	23.76	23.96	25.16	27.02	34.75
$PM_{2.5}$ (μg/m^3)	16.72 (0.69)	0.81	14.86	15.55	16.33	17.14	17.68	21.50
$PM_{10-2.5}$ (μg/m^3)	8.30 (0.75)	0.79	7.60	7.63	7.77	8.56	9.91	14.16
Absorbance (10^{-5}/m)	1.28 (0.22)	0.24	0.85	0.99	1.15	1.39	1.69	3.14
NO_2 (μg/m^3)	23.88 (6.06)	7.76	9.11	15.47	19.60	27.36	34.69	138.11
OP^{DTT} (nmol DTT/min/m^3)	1.18 (0.20)	0.28	0.48	0.81	1.05	1.33	1.48	2.18
OP^{ESR} (A.U./m^3)[a]	0.91 (0.15)	0.18	0.65	0.72	0.80	0.98	1.15	2.05

[a] A.U. is arbitrary unit.

Table 3
Odds ratios (95% CI) for the associations (per IQR increase[a]) between air pollution and diabetes prevalence depending on the level of confounder adjustment.

	Model 1	Model 2a	Model 2b	Model 3a	(Main) Model 3b
PM_{10}	1.11 (1.10, 1.13)	1.07 (1.05, 1.08)	1.06 (1.04, 1.07)	1.04 (1.03, 1.06)	1.04 (1.02, 1.06)
$PM_{2.5}$	1.05 (1.03, 1.06)	1.03 (1.02, 1.05)	1.02 (1.00, 1.04)	1.02 (1.00, 1.03)	1.01 (0.99, 1.03)
$PM_{10-2.5}$	1.12 (1.10, 1.13)	1.06 (1.05, 1.08)	1.05 (1.04, 1.07)	1.04 (1.02, 1.06)	1.04 (1.02, 1.05)
Absorbance	1.11 (1.09, 1.12)	1.07 (1.05, 1.08)	1.05 (1.04, 1.07)	1.04 (1.03, 1.06)	1.04 (1.02, 1.06)
NO_2	1.17 (1.15, 1.19)	1.10 (1.08, 1.12)	1.08 (1.06, 1.10)	1.08 (1.06, 1.10)	1.07 (1.05, 1.09)
OP^{DTT}	1.23 (1.20, 1.25)	1.14 (1.11, 1.16)	1.09 (1.07, 1.12)	1.11 (1.09, 1.13)	1.08 (1.05, 1.10)
OP^{ESR}	1.09 (1.07, 1.11)	1.05 (1.04, 1.07)	1.04 (1.03, 1.06)	1.04 (1.02, 1.05)	1.03 (1.02, 1.05)

Model 1: adjusted for sex and age; Model 2a: model 1 + individual SES characteristics; Model 2b: model 2a + lifestyle risk factors; Model 3a: model 2a + neighborhood SES score; Models 3b: model 3a + lifestyle risk factors.

[a] PM_{10} IQR = 1.20 μg/m^3, $PM_{2.5}$ IQR = 0.81 μg/m^3, $PM_{10-2.5}$ IQR = 0.79 μg/m^3, Absorbance IQR = $0.24 * 10^{-5}$/m, NO2 IQR = 7.76 μg/m^3, OP^{DTT} IQR = 0.28 nmol DTT/min/m^3, OP^{ESR} IQR = 0.18 A.U./m^3.

small differences in associations between pollutants and diabetes by sex, age, education, income, smoking habit and BMI groups (Fig. 2 and Fig. S1). Associations between air pollution and diabetes prevalence were substantially stronger in subjects reporting higher PA (Fig. 2 and Fig. S1). For NO_2 and OP^{DTT}, differences among categories of PA were nearly statistically significant ($p = 0.063$ and $p = 0.051$, respectively; Fig. 2).

4. Discussion

The results of this study showed that air pollution was positively associated with diabetes prevalence, based on the combined measure of self-reporting and diabetes medication prescription from external database, in a large population of adults living in the Netherlands. We observed the strongest associations with NO_2 and the OP of fine particles, as represented by DTT. We found little evidence for effect modification, with the exception of a stronger associations in physically more active persons.

4.1. Comparison with previous studies of air pollution and diabetes

Our finding of consistent associations between NO_2 and diabetes prevalence is in agreement with the meta-analytical HR estimate of 1.08 (95% CI: 1.00, 1.17) per 10 μg/m^3 NO_2 (Eze et al. 2015). Since the meta-analysis was published, three more studies reported positive associations with prevalence or incidence of diabetes (Eze et al. 2014; Hansen et al. 2016; Park et al. 2015) and two studies reported no increased risk (Coogan et al. 2016a; Eze et al. 2017) (Table S1). The effect estimate in our study, per 10 μg/m^3, was 1.09 (95% CI: 1.06, 1.12; Table S5). Our confidence intervals were thus substantially smaller than confidence intervals of the meta-analytic estimate. Differences in effect estimates across studies were large (Table S1), to some extent due to random variation related to several relatively small studies. In the Eze meta-analysis, heterogeneity was statistically significant for NO_2 but not for $PM_{2.5}$ (Eze et al. 2015). Differences in study area, exposure assessment methods and presence of co-pollutants may have contributed to heterogeneity of effect estimates as well.

We found no statistically significant association between diabetes prevalence and $PM_{2.5}$ in contrast to the meta-analytical HR estimate of 1.10 (95% CI: 1.02, 1.18) per 10 μg/m^3 (Eze et al. 2015). The effect estimate in our study, per 10 μg/m^3, was 1.12 (95% CI: 0.91, 1.38; Table S5), very close to the meta-analytical HR. The relatively wide CI is likely due to the small contrast in exposure for $PM_{2.5}$. The meta-analytic estimate was based upon three studies, with a Canadian study contributing 78% of the weight (Chen et al. 2013). Since the Eze et al. (2015) review, three studies reported positive associations with larger but less precise effect estimates (Hansen et al. 2016; Park et al. 2015; Weinmayr et al. 2015) (Table S1). One US study found no association (Coogan et al. 2016b). We do not have a clear explanation of the lack of a significant association with $PM_{2.5}$ in our study. The relatively small contrast in $PM_{2.5}$ exposure could play a role, but the exposure contrast for PM_{10} and coarse particles was small as well and significant associations were found with these pollutants in single pollutant models, although also with wide CIs related to the small contrast in exposure for these components. We can speculate that $PM_{2.5}$ mass did not reflect the impact of health relevant components in fine particles well in our and previous studies. It is likely but difficult to document that the use of $PM_{2.5}$ mass in study areas with different particle composition introduces some heterogeneity in effect estimates.

The latter speculation is supported by the very consistent

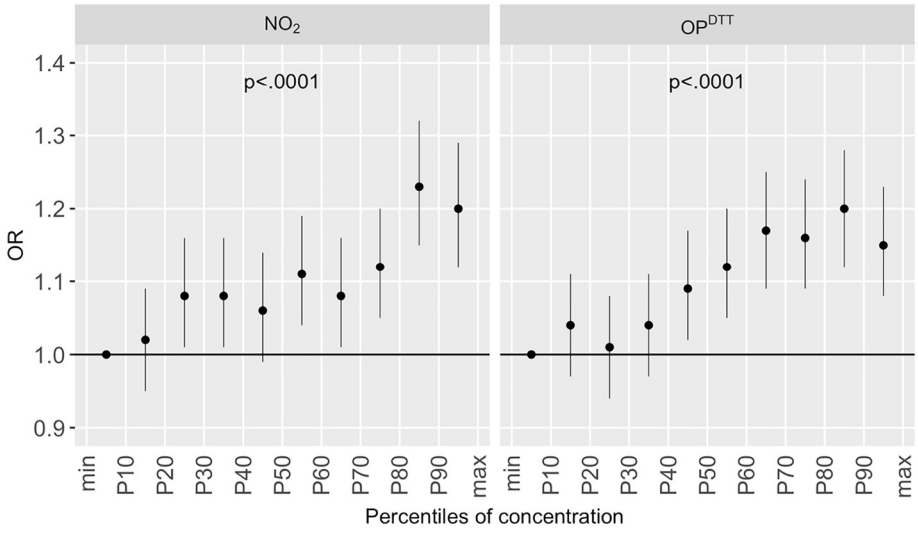

Fig. 1. Assessment of linearity of the association between NO_2, OP^{DTT} and diabetes.
Note: Based on percentiles of pollutants (in brackets).

Table 4
Odds ratios (95% CI) for the associations (per IQR increase[a]) between air pollution and diabetes prevalence in two-pollutant models.

	PM_{10}	$PM_{2.5}$	$PM_{10-2.5}$	Absorbance	NO_2	OP^{DTT}	OP^{ESR}
PM_{10}	**1.04 (1.02, 1.06)**	1.05 (1.03, 1.07)	1.03 (1.00, 1.05)	1.03 (0.99, 1.07)	1.00 (0.97, 1.02)	1.02 (1.01, 1.04)	1.03 (1.01, 1.05)
$PM_{2.5}$	0.99 (0.97, 1.01)	**1.01 (0.99, 1.03)**	1.00 (0.98, 1.02)	0.96 (0.94, 0.99)	0.99 (0.97, 1.01)	0.98 (0.97, 1.00)	0.99 (0.97, 1.01)
$PM_{10-2.5}$	1.02 (0.99, 1.04)	1.04 (1.02, 1.05)	**1.04 (1.02, 1.05)**	1.02 (1.00, 1.04)	0.99 (0.97, 1.02)	1.02 (1.00, 1.04)	1.03 (1.01, 1.05)
Absorbance	1.01 (0.98, 1.05)	1.07 (1.04, 1.09)	1.03 (1.00, 1.05)	**1.04 (1.02, 1.06)**	0.99 (0.96, 1.02)	1.01 (0.99, 1.03)	1.03 (1.01, 1.05)
NO_2	1.07 (1.04, 1.10)	1.07 (1.05, 1.09)	1.07 (1.04, 1.10)	1.08 (1.05, 1.11)	**1.07 (1.05, 1.09)**	1.04 (1.02, 1.07)	1.07 (1.05, 1.10)
OP^{DTT}	1.07 (1.04, 1.09)	1.08 (1.06, 1.11)	1.07 (1.05, 1.09)	1.07 (1.04, 1.09)	1.05 (1.03, 1.08)	**1.08 (1.05, 1.10)**	1.07 (1.05, 1.09)
OP^{ESR}	1.02 (1.00, 1.04)	1.04 (1.02, 1.06)	1.02 (1.00, 1.04)	1.01 (0.99, 1.04)	0.99 (0.97, 1.02)	1.02 (1.00, 1.04)	**1.03 (1.02, 1.05)**

Each row represents ORs (95% CIs) of one pollutant adjusted for another pollutant (given in column). Diagonally in bold: ORs (95% CIs) from the single-pollutant (main) model 3b. Grey shading: VIF > 3, suggesting possible multicollinearity.
[a] PM_{10} IQR = 1.20 μg/m^3, $PM_{2.5}$ IQR = 0.81 μg/m^3, $PM_{10-2.5}$ IQR = 0.79 μg/m^3, Absorbance IQR = $0.24 * 10^{-5}$/m, NO2 IQR = 7.76 μg/m^3, OP^{DTT} IQR = 0.28 nmol DTT/min/m^3, OP^{ESR} IQR = 0.18 A.U./m^3.

associations we found with the oxidative potential of $PM_{2.5}$ measured by the DTT assay. It has been suggested that OP may be a more health relevant metric than particle mass, integrating differences in particle composition, size and bio-availability (Ayres et al. 2008; Borm et al. 2007). We previously reported consistent associations between OP^{DTT} and asthma symptoms and lung function in a Dutch birth cohort study, also in the absence of associations with $PM_{2.5}$ and presence of associations with NO_2 (Yang et al. 2016). The inconsistent associations between PM and diabetes in previous studies and our findings of robust association with the OP of $PM_{2.5}$ may suggest that effects of particles on diabetes may differ with composition. A study in Germany reporting much higher effect estimates for traffic fine particles compared to total $PM_{2.5}$ provides further support for this hypothesis (Weinmayr et al. 2015).

As in the Yang et al. (2016) study, we did not find consistent associations with OP measured by the ESR assay. The two OP assays respond to different PM components – the ESR assay is more sensitive to transition metals, whereas the DTT assay responds mainly to organic components (Yang et al. 2016), and thus complement each other in providing information on the oxidative properties of particles (Janssen et al. 2014). There is no external evidence why organic components would be more associated with diabetes than the transition metals.

4.2. Mechanisms

The association of air pollution with diabetes is likely due to systemic inflammation and/or oxidative stress induced by particles and/or NO_2, with subsequent impact on metabolic pathways (Brook et al. 2010; Rajagopalan and Brook 2012). Animal studies have supported the plausibility of diabetes associations, by documenting an increase in insulin resistance and other physiological markers relevant for development of diabetes after controlled exposure to fine particles (Sun et al. 2009; Yan et al. 2011). Our finding of a robust association with the oxidative potential of fine particles as measured by the DTT assay is consistent with the oxidative stress pathway. Associations with another assay of oxidative potential (ESR), were however not robust to adjustment for, especially, NO_2.

4.3. Differences in response to air pollution

Women have been suggested to have increased risk of diabetes associated with air pollution exposure (Andersen et al. 2012; Brook et al. 2008; Chen et al. 2013; Dijkema et al. 2011). In the recent meta-analysis by Eze et al. (2015), combined effect estimates for both NO_2 and $PM_{2.5}$ were higher for women than for men. The published studies since then, however, found stronger effects in men in Switzerland, the US and Germany (Eze et al. 2014; Park et al. 2015; Weinmayr et al. 2015). In none of these studies, associations differed significantly between men and women. Despite the large study population, we have not observed significantly different risk of diabetes between men and women in relation to air pollution exposure (Fig. 2 and Fig. S1).

The finding of stronger associations with air pollution in subjects with higher PA, is in agreement with the findings of the Danish Diet, Cancer, and Health cohort study (Andersen et al. 2012). The explanation is not obvious, but could include higher air pollution doses due to increased minute ventilation in subjects with higher PA, smaller air pollution exposure misclassification due to more time spent outdoors, or easier detection of a small effect in subjects without major risk for diabetes than high-risk subjects or subjects with pre-existing disease. Before more longitudinal studies have confirmed this finding, we do not want to attach too much interpretation to this observation. Extensive literature has documented that the main effect of PA is protective: more PA reduces the likelihood of diabetes risk, as also found in our study population (Table 1).

Reported PA levels were high, either as a result of over-reporting of PA levels in a survey or because Dutch citizens frequently use bicycles, an activity listed as moderate PA.

4.4. Potential biases

The high agreement between self-reported diabetes diagnoses and diabetes medication prescription taken from an external database supports validity of the self-reports. A study comparing self-reported diabetes with blood glucose and medication data, reported very high specificity and moderate sensitivity of self-reports of diabetes

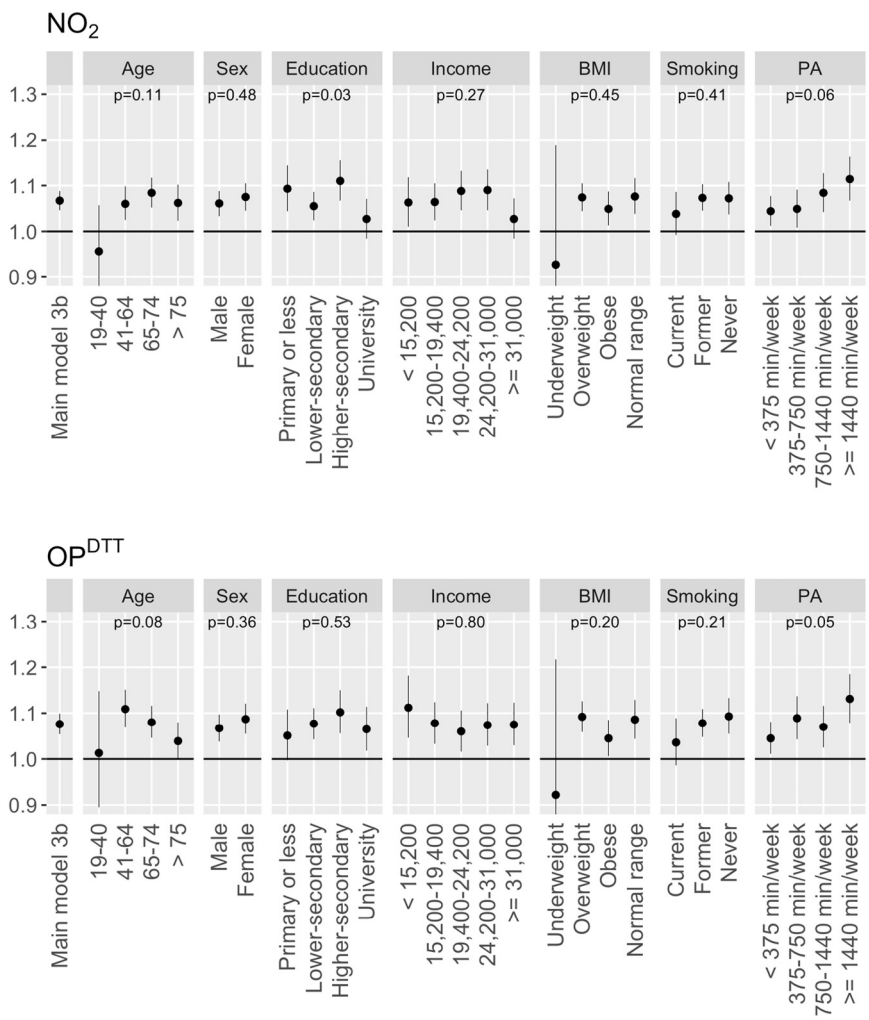

Fig. 2. Subgroup analysis of the associations between NO_2, OP^{DTT} and diabetes.[a]

[a]Results of the subgroup analysis for the remaining air pollutants are presented in Fig. S1.

(Molenaar et al. 2006). Furthermore, there was virtually no difference between air pollution effect estimates for diabetes prevalence based on self-reporting of a physician's diagnosis and on the information obtained from the medication prescription database. Data from the latter is intrinsically more objective.

Exposures generated by the LUR models (year 2009) preceded the year of health outcome ascertainment (2012), as opposed to most previous applications of the ESCAPE LUR models to cohorts recruited 10–15 years before the year of exposure assessment. For a chronic condition, such as diabetes, one would prefer to assess exposure some years before the outcome assessment. In the current study, we used prevalent diabetes, with no information on the date when diabetes has developed. Some of our cases will have developed diabetes prior to the year of exposure assessment. As argued in previous ESCAPE papers (*e.g.*, Beelen et al. 2014), spatial distribution of air pollution is generally stable over periods of 10–15 years (Eeftens et al. 2011; Gulliver et al. 2011), supporting the use of an annual average of a single year to assess long-term exposure. We did not have information about moving history of the subjects, which may have led to some likely non-differential misclassification of exposure.

We adjusted for a wide range of potential confounders, including major risk factors for diabetes. Effect estimates were reduced moderately but remained after adjustment, particularly for socio-economic factors at the individual and area level.

The use of prevalence of diabetes instead of incidence may be a limitation, as subjects may have changed lifestyle as a result of their disease. It is unlikely that air pollution exposure is associated with change in lifestyle. We, furthermore, did find the well-established associations between especially obesity and low PA with diabetes in our survey (Table 1). Several studies have also assessed prevalence (Brook et al. 2008; Dijkema et al. 2011; Eze et al. 2014; Park et al. 2015) with effect estimates as heterogeneous as those of the cohort studies on incidence. In the MESA study, $PM_{2.5}$ and NO_2 were associated with prevalence but not incidence of diabetes (Park et al. 2015).

Inability to distinguish between Type 1 and Type 2 diabetes is a limitation of the study, as in virtually all previous studies. Air pollution may affect Type 1 and 2 diabetes differently. Cohort studies evaluating incidence of diabetes in adults have argued that the majority of cases were likely to be Type 2 diabetes (*e.g.*, Andersen et al. 2012; Hansen et al. 2016). In our study, we evaluated prevalent diabetes. The age distribution of diabetes prevalence, with very low prevalence below 40 years of age suggests that also in our study the majority of cases are likely Type 2 diabetes.

Recently, transportation noise has been suggested as an important factor in the development of diabetes (Eze et al. 2017; Sorensen et al. 2013). Unfortunately, due to unavailability of noise exposure data for the current analysis, we were not able to investigate noise as a potential confounder of the observed association between air pollution and diabetes.

Our study population differed from the general Dutch adult population, by design (age) and by differential response rates (household income, ethnicity). The response rate at 45–50% was only moderate. Unfortunately, it was not possible to test whether the moderate response rate resulted in bias as there was no information on non-responders available. We note that bias only occurs if the non-responders have a larger or smaller response to air pollution than the responders. The lack of consistent effect modification found in this study, reduces the likelihood of bias.

4.5. Strengths and limitations

Strengths of this study include the large population size and the fine spatial scale at which exposure to different pollution metrics was assessed. To our knowledge, this is the largest epidemiological study so far to investigate the association between long-term exposure to air pollution and diabetes prevalence, with > 23,000 diabetes cases in the study population of nearly 290,000 individuals. A strength of our study is that we were able to evaluate this association with seven different air pollutants, as well as to investigate the strength of individual associations of different pollutants in two-pollutant models. Additionally, this is the first study to assess this association with OP of PM. Our observation of a nearly linear concentration-response using decile analysis strengthens our results and provides further support for a potential effect. No studies have previously evaluated the concentration-response relationship for diabetes (Eze et al. 2015).

Most relevant limitations, as discussed in *Potential biases* section, include a cross-sectional nature of the study, inability to distinguish between Type 1 and 2 diabetes, and unavailability of noise exposure data.

5. Conclusions

Long-term residential air pollution exposure was associated with diabetes prevalence in a large health survey in the Netherlands, strengthening the evidence of air pollution being an important diabetes risk factor. Most consistent associations were observed for NO_2 and oxidative potential of $PM_{2.5}$ measured by the DTT assay. The finding of an association with the oxidative potential of fine particles but not with $PM_{2.5}$, suggests that particle composition may be important for a potential effect on diabetes.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2017.08.017.

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