The association between air pollution and type 2 diabetes in a large cross-sectional study in Leicester: The CHAMPIONS Study

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Abstract

Background: Observational evidence suggests there is an association between air pollution and type 2 diabetes; however, there is high risk of bias.
Objective: To investigate the association between air pollution and type 2 diabetes, while reducing bias due to exposure assessment, outcome assessment, and confounder assessment.
Methods: Data were collected from 10,443 participants in three diabetes screening studies in Leicestershire, UK. Exposure assessment included standard, prevailing estimates of outdoor nitrogen dioxide and particulate matter concentrations in a 1 x 1 km area at the participant's home postcode. Three-year exposure was investigated in the primary analysis and one-year exposure in a sensitivity analysis. Outcome assessment included the oral glucose tolerance test for type 2 diabetes. Confounder assessment included demographic factors (age, sex, ethnicity, smoking, area social deprivation, urban or rural location), lifestyle factors (body mass index and physical activity), and neighbourhood green space.
Results: Nitrogen dioxide and particulate matter concentrations were associated with type 2 diabetes in unadjusted models. There was no statistically significant association between nitrogen dioxide concentration and type 2 diabetes after adjustment for demographic factors (odds: 1.08; 95% CI: 0.91,1.29). The odds of type 2 diabetes was 1.10 (95% CI: 0.92, 1.32) after further adjustment for lifestyle factors and 0.91 (95% CI: 0.72, 1.16) after yet further adjustment for neighbourhood green space. The associations between particulate matter concentrations and type 2 diabetes were also explained away by demographic factors. There was no evidence of exposure definition bias.
Conclusions: Demographic factors seemed to explain the association between air pollution and type 2 diabetes in this cross-sectional study. High-quality longitudinal studies are needed to improve our understanding of the association.
Keywords: Air pollutants; Diabetes Mellitus, Type 2; Cross-Sectional Studies.

Introduction

Diabetes is one of the leading causes of death in lower-middle-income economies, upper-middle-income economies, and high-income economies (World Health Organization 2017). The global prevalence of diabetes has risen from 4.7% in 1980 to 8.5% in 2014, with the majority of cases being type 2 diabetes (World Health Organization 2016). Experimental evidence in humans and animals suggests that it is plausible that air pollution is a risk factor for type 2 diabetes (Rao et al. 2015). Exposure to the traffic-related air pollutant nitrogen dioxide (NO_2) and the associated particulate matter ≤ 2.5 μm ($PM_{2.5}$) and ≤ 10.0 μm (PM_{10}) pollutants is related to inflammation and insulin resistance (Rao et al. 2015), which are the hallmarks of type 2 diabetes (DeFronzo 2010). Experimental evidence in humans suggests that short-term exposure to low levels of $PM_{2.5}$ increases systemic insulin resistance (Brook et al. 2013). Experimental evidence in mice suggests that oxidative stress in the lungs may be an intermediate step between exposure to $PM_{2.5}$ and systemic insulin resistance (Haberzettl et al. 2016). Observational evidence also suggests that there is an association between air pollution and type 2 diabetes; however, there is a high risk of bias (Eze et al. 2015).

It is important to investigate the association between air pollution and type 2 diabetes while reducing bias. Bias due to exposure assessment, bias due to outcome assessment, and bias due to confounder assessment were addressed in the present study in Leicester, Calculating How Air Pollution Impacts Our Society (The CHAMPIONS Study).

Methods

Participants

The present study included participants from three diabetes screening studies that were conducted in Leicestershire in the United Kingdom using identical standard operating procedures: ADDITION-Leicester (ClinicalTrials.gov registration number: NCT00318032), Let's Prevent Diabetes ('Let's Prevent', NCT00677937), and Walking Away from Diabetes ('Walking Away', NCT00941954). Research ethics committees approved the studies and all participants gave written, informed consent.

The original studies are described in detail elsewhere (Gray et al. 2012b; Webb et al. 2010; Yates et al. 2012). Briefly, ADDITION-Leicester (2004-2009) was a population-based study in which people were screened for type 2 diabetes (Webb et al. 2010). Individuals selected at random from participating general practices who met the eligibility criteria were invited to participate. Eligibility criteria included age 40-75 years (white Europeans) or 25-75 years (other ethnicities) and no diagnosis of diabetes; thus, all type 2 diabetes cases were screen-detected. Let's Prevent (Gray et al. 2012b) (2009-2011) and Walking Away (Yates et al. 2012) (2010) used similar recruitment methods and inclusion criteria, except that individuals in Walking Away were at high risk of type 2 diabetes according to the Leicester Practice Risk Score (Gray et al. 2012a). Participants in all three studies attended a clinic visit where they provided a fasting blood sample, underwent an oral glucose tolerance test, had anthropometric measurements recorded, and completed questionnaires. Participants were excluded from the present analysis if their postcode was missing or invalid, if their postcode could not be reconciled with an air pollution value, or if their diabetes values were missing. The most recent record was used if participants took part in more than one of the studies. The original cohorts are also described in detail elsewhere; briefly, age was similar in each cohort, the proportion of males was similar, the proportion of whites was similar, physical characteristics were similar, cardiovascular disease risk factors were similar, the proportion with abnormal glucose tolerance was similar, and the proportion with type 2 diabetes was similar (Gray et al. 2012a).

Explanatory variables

The Department for Environment, Food & Rural Affairs (DEFRA) in the United Kingdom publishes 1x1 km grids of pollutant concentrations using data from around 9,000 representative roadside values (Department for Environment Food & Rural Affairs 2015). Air pollution data were derived from the DEFRA Pollution Climate Mapping (PCM) model, which is described elsewhere (Department for Environment Food & Rural Affairs 2015). There is one model per pollutant and the models are run by Ricardo Energy & Environment (Oxfordshire, UK) on behalf of DEFRA. Exposure to air pollution in the present study was defined as the three-year average, including the year in which the participant entered the study and the preceding two years. The list of participants' postcodes was run through a script which binned each postcode into a 1x1 km grid of the same size and shape as that used in the PCM model. The NO_2, $PM_{2.5}$ and PM_{10} concentrations for each of the 5,394 unique postcodes could then be combined with the diabetes data for that postcode.

Outcomes measures

Type 2 diabetes diagnoses were based on World Health Organisation 2011 criteria, using the oral glucose tolerance test (fasting glucose ≥ 7.0 $mmol \cdot L^{-1}$ or two hour glucose ≥ 11.0 $mmol \cdot L^{-1}$).

Potential confounders

We recorded age, sex, smoking habit, urban or rural location (Bibby and Shepherd 2004), and area social deprivation score [The English Indices of Deprivation 2010 provides a relative measure of deprivation at small area level across England, and its measure of multiple deprivation was used in the present study (DATA.GOV.UK 2013)]. Ethnicity was self-reported using United Kingdom census categories and grouped as white European, South Asian and other due to the small number of participants in some ethnic groups. Trained staff measured height and weight and body mass index (BMI) was calculated as weight (kg) / height (m) squared. Cholesterol concentration was measured in the fasting blood sample. Self-reported physical activity was assessed using the International Physical Activity Questionnaire

and published standards were used to calculate the number of metabolic equivalents (METs) per day for total activity (The IPAQ Group 2005). Green space was defined as the percentage of green space in the participant's home neighbourhood. The geographic information system, ArcGIS 9.3, was used (ESRI 2009). To delineate neighbourhood boundaries, each participant's postcode was geolocated using the UK Ordnance Survey Code-Point database (2004-2013) (Ordnance Survey 2016), which provides a set of coordinates depicting the average latitude and longitude of all mail delivery locations within each postcode, which contains 15 addresses on average. Neighbourhood was delineated based on distance around these coordinates. Neighbourhood was defined as the straight-line distance of 3 km, as it is thought that people will travel such a distance to access resources and be physically active (Boruff et al. 2012; Dalton et al. 2013; Hurvitz and Moudon 2012). Estimates of green space were from the Centre for Ecology and Hydrology Land Cover Map of the United Kingdom (Centre for Ecology & Hydrology 2011), which is derived from satellite images and digital cartography, and records the dominant land use type, based on a 23 class typology, per 25x25 m grid cell. Broadleaved and coniferous woodland, arable, improved grassland, semi-natural grassland, mountain, heath, bog, and freshwater (including rural Lakeland environments) were classed as green space. Each participant's exposure was computed by overlaying the mapped green space with the neighbourhood boundary in the geographic information system software to calculate the percentage of each neighbourhood area that contained these land cover types.

Statistical analysis

The distributions of the air pollutants were considered using histograms (not shown). The odds of type 2 diabetes were investigated using generalized estimating equations, with pollutant concentrations expressed per 10 $\mu g \cdot m^3$. It has been argued that models should include variables that are thought to be important from the literature, whether or not they reach statistical significance in a particular data set (Collins et al. 2011). The models in the present study included variables that Eze and colleagues (2015) identified as potential confounders of the association between air pollution and type 2 diabetes. Neighbourhood green space was also added because we recently found that neighbourhood green space was inversely associated with

screen-detected type 2 diabetes in Leicester (Bodicoat et al. 2014). Four models were fitted for each air pollution measure. Model 1 was unadjusted. Model 2 was adjusted for demographic factors, including ethnicity, sex, smoking (current or not), and urban/rural location as categorical variables and for age and area of social deprivation score as continuous variables. Model 3 was further adjusted for lifestyle factors, BMI and physical activity (both continuous variables). Model 4 was adjusted for the variables in Model 2 and Model 3 plus neighbourhood green space as a continuous variable. Three interactions were investigated using *a priori* assumptions about air pollution and type 2 diabetes (Bodicoat et al. 2014; Eze et al. 2015): the interaction between air pollution and socioeconomic status; the interaction between air pollution and BMI; and the interaction between air pollution and neighbourhood green space. Missing data were imputed in the primary analyses. Missing area of social deprivation scores, BMI values, and physical activity values were imputed as the mean value. Missing ethnic group, smoking status, and location were imputed as the modal values in the study sample: white European, non-smoker, and urban, respectively. A sensitivity analysis was performed using the complete case sample; that is, missing data were not imputed. Another sensitivity analysis was performed using one-year pollution averages; that is, the year in which the participant entered the study. Statistical significance was set at 5% and all p values were two-sided. Statistical analyses were performed using STATA (version 14.0).

Results

A total of 11,032 people were screened in the three studies, including 6,749 in ADDITION-Leicester, 3,450 in Let's Prevent, and 833 in Walking Away. Three hundred people were excluded from the present study because their post code was missing (all ADDITION-Leicester) and 12 because it was invalid (6 ADDITION-Leicester, 5 Let's Prevent, 1 Walking Away). A total of 244 people participated in more than one study, 20 postcodes could not be reconciled with an air pollution value, and 13 diabetes diagnoses were missing; therefore, the present study included 10,443 participants. Table 1 shows participants' characteristics according to study. The mean age was 59 years, 47% were female, and 18% were of South Asian origin. Concentrations of NO_2, $PM_{2.5}$ and PM_{10} and percentages of neighbourhood green space were similar in each of the three studies. The proportion with type 2 diabetes was 6.2% in ADDITION-Leicester, 10.9% in Let's Prevent, and 9.4% in Walking Away, reflecting the high-risk nature of the two latter samples.

Table 2 shows the average level of air pollution according to participant characteristics. Nitrogen dioxide, $PM_{2.5}$ and PM_{10} concentrations differed according to age, sex, ethnicity, urban or rural location, area social deprivation score, and neighbourhood green space. Nitrogen dioxide concentrations also differed by smoking status. There were inverse associations between green neighbourhood space and NO_2 (r = -0.84, p < 0.001), $PM_{2.5}$ (r = -0.56, p < 0.001), and PM_{10} (r = -0.44, p < 0.001). Table 3 shows type 2 diabetes prevalence according to air pollution quartiles. Type 2 diabetes prevalence was 5.97% in the lowest, 6.77% in the second, 8.91% in the third, and 10.37% in the highest NO_2 quartile. Type 2 diabetes prevalence also increased across $PM_{2.5}$ and PM_{10} quartiles.

We investigated interactions between air pollution and socioeconomic status, air pollution and BMI, and air pollution and neighbourhood green space. Thirty-three interactions were investigated and there was little statistically significant evidence of interaction (data not shown): there were only interactions between $PM_{2.5}$ and green space and between PM_{10} and green space in the unadjusted models. Therefore, we could not justify adding interaction terms to the main analyses. The figure shows the association between air pollution and type 2 diabetes using three-year air pollution

averages. There was a statistically significant association between NO_2 concentration and type 2 diabetes in the unadjusted analysis (model 1) (odds: 1.48; 95% confidence interval, CI: 1.32, 1.66). There was no statistically significant association between NO_2 concentration and type 2 diabetes after adjustment for demographic factors (model 2) (odds: 1.08; 95% CI: 0.91,1.29). The odds for type 2 diabetes was 1.10 (95% CI: 0.92, 1.32) after further adjustment for lifestyle factors (model 3) and 0.91 (95% CI: 0.72, 1.16) after yet further adjustment for neighbourhood green space (model 4). There were also statistically significant associations between $PM_{2.5}$ concentration, PM_{10} concentration and type 2 diabetes in the unadjusted models. These associations were also explained away by demographic factors. Figure A1 in the appendix shows that the associations between air pollution and type 2 diabetes was similar in the complete case analysis. Figure A2 in the appendix shows that the association between air pollution and type 2 diabetes was similar using one-year air pollution averages. Table A1 in the appendix shows that the nature of the association between air pollution and type 2 diabetes was similar in each of the cohorts. The confidence intervals were wider because of the smaller sample sizes.

Discussion

The purpose of this study was to investigate the association between air pollution and type 2 diabetes while reducing bias. Exposure assessment included three-year and one-year pollutant concentrations and there was no evidence of exposure definition bias. Outcome assessment included the oral glucose tolerance test for diagnosing type 2 diabetes. Confounder assessment included a wide range of potential confounders. The results suggested that air pollution was associated with type 2 diabetes; however, demographic factors seemed to explain the association.

The present study has three major strengths that ~~minimize~~ reduce the risk of bias. First, standard and prevailing estimates of pollutant concentrations were used and three-year and one-year exposures were investigated to rule out exposure definition bias. Second, outcome assessment included the oral glucose tolerance test for diagnosing type 2 diabetes. Third, confounder assessment included demographic factors (age, sex, ethnicity, smoking, area social deprivation, urban or rural location), lifestyle factors (BMI and physical activity), and neighbourhood green space. The present study also has some limitations. The cross-sectional design of the study means that causal relationships cannot be inferred. Exposure to air pollution was based on residential location and may not reflect actual exposure. The association between air pollution and type 2 diabetes was not adjusted for other potential confounders that were not assessed in all our studies, such as indoor air pollution, environmental tobacco smoke, diet and alcohol, individual deprivation, and noise exposure (Eze et al. 2015). The social deprivation score used in the present study includes a measure of air pollution; therefore, the possibility of over-adjustment exists. Missing data are a potential source of bias (European Agency for the Evaluation of Medicinal Products 2001); however, the proportion of missing data was small and the absence of data seemed to be random. The main reasons to impute missing data are to decrease bias and to increase statistical power in the presence of confounding variables (European Agency for the Evaluation of Medicinal Products 2001). Imputation was restricted to known confounding variables in the main analysis in present study. Furthermore, the results of the main analysis and the complete case analysis were similar. The use of data from diabetes screening studies might be regarded as a strength because of the accurate assessment of type 2 diabetes.

The use of such data might also be regarded as a limitation because the results are generalizable to those who might enter screening studies, not the entire population.

In a meta-analysis including three cross-sectional studies and four prospective studies published up to 3 February 2014, Eze and colleagues (2015) found that air pollution was positively associated with type 2 diabetes risk. For example, NO_2 and $PM_{2.5}$ were positively associated with type 2 diabetes after adjustment for age, sex, BMI, smoking and socioeconomic status [1.08 (95% CI: 1.00 to 1.17) and 1.10 (95% CI: 1.02 to 1.08) respectively, per 10 $\mu g \cdot m^3$ increase in exposure] (Eze et al. 2015). The review of Eze and colleagues (2015) suggests that the present study is one of the largest cross-sectional studies of air pollution and type 2 diabetes. Type 2 diabetes risk is higher in South Asians than whites (Hippisley-Cox et al. 2009), and, to the best of our knowledge, this is the only study of air pollution and type 2 diabetes to include a substantial number of adults of South Asian ethnic origin. Park and colleagues (2015) investigated air pollution and type 2 diabetes prevalence in a multiethnic sample of 5,839, including men and women of white (19.1 %), black (37.6 %), Hispanic (31.0 %), and Chinese (12.2%) ethnic origins. Park and colleagues (2015) found that $PM_{2.5}$ and nitrogen oxides were positively associated with type 2 diabetes prevalence after adjustment for age, sex, ethnicity, family history of diabetes, educational level, smoking status, alcohol consumption, physical activity level, neighbourhood socioeconomic status, and BMI [odds ratios: 1.09 (95% CI: 1.00 to 1.17) and 1.18 (95% CI: 1.01 to 1.38) respectively, per interquartile range increase in exposure].

Seven million premature deaths per year are linked to air pollution, according to the World Health Organisation (2014). Outdoor air pollution is thought to explain 40% of ischaemic heart disease deaths, 40% of stroke deaths, 11% of chronic obstructive pulmonary disease deaths, and 6% of lung cancer deaths (World Health Organisation 2014). The association between air pollution and type 2 diabetes was not statistically significant after adjustment for potential confounders in the present cross-sectional study. Longitudinal studies are beginning to show that outdoor air pollution is associated with diabetes-related morbidity (Eze et al. 2015) and mortality (Raaschou-Nielsen et al. 2013) independent of potential confounders. If more high-quality longitudinal studies were to show that air pollution was associated with type 2

317 diabetes, the case for intervention would be even stronger. Combustion engines are
318 a major source of NO_2 and particulate matter air pollution (World Health Organisation
319 2016) and one way for the United Kingdom to reduce air pollution and to save lives
320 would be to adopt Danish levels of cycling (British Cycling 2014).

Conclusions

There was a positive association between air pollution and type 2 diabetes in this cross-sectional study; however, demographic factors seemed to explain the association. Lifestyle factors and neighbourhood green space did not explain the association. High-quality longitudinal studies are needed to improve our understanding of the association between air pollution and type 2 diabetes.

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Conflicts of interests

The authors have no conflicts of interest to declare.

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Figure. Associations of NO_2 concentration (top), $PM_{2.5}$ concentration (middle), and PM_{10} concentration (bottom) with type 2 diabetes. Pollutant concentrations are three year averages from 10,443 adults. Circles are odds and error bars are 95% confidence intervals (CI). From left to right: ‘reference’, model 1, model 2, model 3, and model 4. Model 1 is unadjusted. Model 2 is adjusted for demographic factors (age, sex, ethnicity, smoking, area deprivation score, and urban or rural location). Model 3 is adjusted for all variables in model 2 plus BMI and physical activity [total METs (metabolic equivalents)]. Model 4 is adjusted for all variables in model 3 plus neighbourhood green space (three km circular area around the participant’s home postcode).

Table 1. Participants' characteristics by study and for the entire sample combined.

Variable	ADDITION-Leicester (n=6,171)	Let's Prevent Diabetes (n=3,442)	Walking Away from Diabetes (n=830)	All (n=10,443)
Age, years	56.2 (10.8)	63.2 (8.1)	63.1 (8.2)	59.0 (10.4)
Area social deprivation score	19.7 (14.1)	17.3 (15.0)	20.2 (16.3)	19.0 (14.6)
Physical activity, METs	3375.2 (3579.1)	2291.9 (3037.9)	3388.1 (3952.2)	3005.8 (3474.9)
BMI, $kg \cdot m^{-2}$	28.0 (5.0)	32.5 (5.7)	32.4 (5.6)	29.9 (5.7)
Fasting glucose, $mmol \cdot L^{-1}$	5.2 (0.9)	5.3 (0.8)	5.3 (0.8)	5.2 (0.9)
Two-hour glucose, $mmol \cdot L^{-1}$	6.0 (2.4)	6.6 (2.5)	6.5 (2.4)	6.3 (2.5)
HbA1C, %	5.7 (0.6)	5.9 (0.5)	5.9 (0.6)	5.8 (0.6)
Total cholesterol, $mmol \cdot L^{-1}$	5.5 (1.1)	5.1 (1.0)	5.1 (1.1)	5.4 (1.1)
Female, %	53.1	39.1	36.5	47.1
White, %	74.0	86.7	88.6	79.4
South Asian, %	23.5	10.7	8.1	17.9
Other ethnicity, %	2.6	2.6	3.4	2.6
Smoker, %	27.5	8.0	9.2	19.1
Rural location, %	11.6	24.5	17.5	16.3
Type 2 diabetes, %	6.2	10.9	9.4	8.0

NO_2, $\mu g \cdot m^3$	21.7 (6.1)	20.8 (5.3)	21.5 (5.0)	21.4 (5.8)
$PM_{2.5}$, $\mu g \cdot m^3$	12.1 (0.8)	11.8 (0.7)	11.8 (0.7)	12.0 (0.8)
PM_{10}, $\mu g \cdot m^3$	16.5 (1.0)	16.2 (1.0)	16.2 (0.9)	16.4 (1.0)
Neighbourhood green space, %	55 (25)	59 (26)	56 (24)	57 (26)

Data are mean (SD) or percentage.

Missing data: 0 age, sex, type 2 diabetes, NO_2, $PM_{2.5}$, PM_{10}, and neighbourhood green space; 21 Social deprivation score; 1474 total METS; 207 BMI; 21 fasting glucose; 70 two-hour glucose; 136 HbA1C; 96 total cholesterol; 189 ethnicity; 224 smoker; 21 rural location.

METs, metabolic equivalents. BMI, body mass index. HbA1C, glycated haemoglobin.

Table 2. Average levels of air pollution by participant characteristics

Variable	Category	N	Mean (SD) NO_2, $\mu g \cdot m^3$	P value[a]	Mean (SD) $PM_{2.5}$, $\mu g \cdot m^3$	P value[a]
Age, years	<55	3191	22.7 (6.3)		12.2 (0.8)	
	55-64	3541	21.0 (5.6)		12.0 (0.8)	
	≥65	3711	20.5 (5.2)	<0.001	11.8 (0.7)	<0.001
Sex	Male	5520	21.1 (5.7)		12.0 (0.8)	
	Female	4923	21.6 (5.8)	<0.001	12.1 (0.8)	<0.001
Ethnicity	White European	8144	20.0 (5.1)		11.9 (0.7)	
	South Asian	1839	26.3 (5.1)		12.5 (0.9)	
	Other	271	27.4 (6.2)	<0.001	12.7 (1.0)	<0.001
Smoker	No	8229	21.5 (5.8)		12.0 (0.8)	
	Yes	1990	20.7 (5.7)	<0.001	12.0 (0.8)	0.568
Location	Urban	8720	22.5 (5.5)		12.1 (0.8)	
	Rural	1702	15.4 (2.9)	<0.001	11.5 (0.7)	<0.001

Area social deprivation score	Low	5331	18.4 (3.9)		11.7 (0.6)	
	High	5091	24.4 (5.8)	<0.001	12.4 (0.8)	<0.001
Neighbourhood green space*	Low	4517	26.3 (4.4)		12.4 (0.8)	
	Medium	698	22.0 (3.0)		11.8 (0.4)	
	High	5228	17.0 (3.0)	<0.001	11.7 (0.7)	<0.001

[a]P values test for a difference in the percentage of air pollution across the categories and were estimated using two sample t-test or one-way analysis of variance. *Low neighourhood green space defined as green space one standard deviation below the mean amount; medium neighbourhood green space defined as green space at the mean amount; high neighbourhood green space defined as green space one standard deviation above the mean amount.

Table 3. Number and prevalence of type 2 diabetes cases by air pollution quartiles (n=10,433)

Pollutant	Number of cases (prevalence)			
	Lowest	Quartile 2	Quartile 3	Highest
NO_2	156 (5.97%)	177 (6.77%)	239 (8.91%)	263 (10.37%)
$PM_{2.5}$	190 (6.99%)	189 (7.45%)	211 (7.69%)	245 (10.04%)
PM_{10}	188 (7.19%)	194 (7.40%)	198 (7.55%)	255 (9.88%)

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