Environment International 91 (2016) 243–250

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Full length article

Long-term exposure to fine particulate matter and incidence of diabetes in the Danish Nurse Cohort

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ARTICLE INFO

Article history:
Received 19 November 2015
Received in revised form 5 February 2016
Accepted 29 February 2016
Available online 16 March 2016

Keywords:
Diabetes
Air pollution
Fine particles
$PM_{2.5}$

ABSTRACT

Aims/hypothesis: It has been suggested that air pollution may increase the risk of type 2 diabetes but data on particulate matter with diameter < 2.5 µm ($PM_{2.5}$) are inconsistent. We examined the association between long-term exposure to $PM_{2.5}$ and diabetes incidence.
Methods: We used the Danish Nurse Cohort with 28,731 female nurses who at recruitment in 1993 or 1999 reported information on diabetes prevalence and risk factors, and obtained data on incidence of diabetes from National Diabetes Register until 2013. We estimated annual mean concentrations of $PM_{2.5}$, particulate matter with diameter < 10 µm (PM_{10}), nitrogen oxides (NO_x) and nitrogen dioxide (NO_2) at their residence since 1990 using a dispersion model and examined the association between the 5-year running mean of pollutants and diabetes incidence using a time-varying Cox regression.
Results: Of 24,174 nurses 1137 (4.7%) developed diabetes. We detected a significant positive association between $PM_{2.5}$ and diabetes incidence (hazard ratio; 95% confidence interval: 1.11; 1.02–1.22 per interquartile range of 3.1 µg/m^3), and weaker associations for PM_{10} (1.06; 0.98–1.14 per 2.8 µg/m^3), NO_2 (1.05; 0.99–1.12 per 7.5 µg/m^3), and NO_x (1.01; 0.98–1.05 per 10.2 µg/m^3) in fully adjusted models. Associations with $PM_{2.5}$ persisted in two-pollutant models. Associations with $PM_{2.5}$ were significantly enhanced in never smokers (1.24; 1.09–1.42), and augmented in obese (1.25; 1.06–1.47) and subjects with myocardial infarction (1.32; 0.86–2.02), but without significant interaction.
Conclusions/interpretation: Fine particulate matter may the most relevant pollutant for diabetes development among women, and non-smokers, obese women, and heart disease patients may be most susceptible.

1. Introduction

Air pollution is among the leading causes of morbidity and mortality worldwide, accounting for 4.5% of the Global Disability Adjusted Life Year in 2010 (Lim et al., 2012). The global type 2 diabetes epidemic is a major public health challenge worldwide, and one of the greatest contributors to the global burden of disease, with an estimated 65% increase in diabetics by 2025, to 380 millions (World Health Organization. Global Status Report on Noncommunicable Diseases, 2014). Experimental studies have provided biological plausibility for a link between air pollution and type 2 diabetes risk by showing how exposure to particulate matter with diameter <2.5 µm ($PM_{2.5}$) among obese mice provoked insulin resistance and adiposity, with systemic inflammation as the key mechanism (Sun et al., 2009). This has led to a rise in epidemiological studies of long-term exposure to air pollution and type 2 diabetes, and several recent meta-analyses conclude that air pollution is likely a risk factor (Balti et al., 2014; Eze et al., 2015; Wang et al., 2014; Esposito et al., 2015; Thiering & Heinrich, 2015). However, the results from epidemiological studies are not fully consistent, with a study published after meta-analyses (Balti et al., 2014; Eze et al., 2015; Wang et al.,

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http://dx.doi.org/10.1016/j.envint.2016.02.036
0160-4120/

2014; Esposito et al., 2015; Thiering & Heinrich, 2015), failing to detect an association between $PM_{2.5}$ and diabetes incidence (Park et al., 2015). Of the twelve epidemiological studies on long-term exposure to air pollution and diabetes, five studied prevalence (Brook et al., 2008; Pearson et al., 2010; Dijkema et al., 2011; Eze et al., 2014; To et al., 2015), six incidence (Krämer et al., 2012; Puett et al., 2011; Andersen et al., 2012; Coogan et al., 2012; Chen et al., 2013; Weinmayr et al., 2015), and one both (Park et al., 2015). Two studies on diabetes prevalence and NO_2 found no associations (Brook et al., 2008; Pearson et al., 2010; Dijkema et al., 2011), while four detected associations with at least one pollutant studied: particulate matter with diameter <10 μm (PM_{10}) (Eze et al., 2014), $PM_{2.5}$ (Park et al., 2015; Pearson et al., 2010; To et al., 2015), nitrogen dioxide (NO_2)[13] or nitrogen oxides (NO_x)[9]. Of the seven cohort studies, six (Krämer et al., 2012; Andersen et al., 2012; Coogan et al., 2012; Chen et al., 2013; Weinmayr et al., 2015) detected associations between diabetes incidence and at least one pollutant in the study: two with PM_{10} (Krämer et al., 2012; Weinmayr et al., 2015), two with NO_2 (Krämer et al., 2012; Andersen et al., 2012), one with $PM_{2.5}$ (Chen et al., 2013), and one with NO_x (Coogan et al., 2012). However, US studies with data from three large cohorts, American Nurse Health Study (Puett et al., 2011), Health Professionals Study (Puett et al., 2011), and Multi Ethnic Study of Atherosclerosis (MESA) (Park et al., 2015) all failed to detect significant associations between diabetes incidence and air pollution, specifically $PM_{2.5}$ (Park et al., 2015; Puett et al., 2011), PM_{10} (Puett et al., 2011), and NO_x (Park et al., 2015). Furthermore, five studies with data on $PM_{2.5}$ (Park et al., 2015; Puett et al., 2011; Coogan et al., 2012; Chen et al., 2013; Weinmayr et al., 2015) and diabetes incidence report mixed results, with only one, by Chen et al. (2013), detecting significant positive associations (hazard ratio (HR); 95% confidence interval (CI): 1.11; 1.02–1.21 per 10 μg/m^3), while Park et al. (2015) (1.02; 0.95–1.10 per 2.4 μg/m^3), Puett et al. (2011) (1.03; 0.96–1.10 per 4 μg/m^3), and Weinmayr et al. (2015) (1.08; 0.89–1.29 per 2.3 μg/m^3) did not detect significant associations, and Coogan et al. (2012) detected strong positive, but non-significant association (1.63; 0.78–3.44 per 10 μg/m^3). Finally, it is uncertain which pollutant is most relevant for diabetes development, as few cohorts have data on multiple pollutants (Krämer et al., 2012; Puett et al., 2011; Coogan et al., 2012; Weinmayr et al., 2015) and only two present two-pollutant models, both showing weak associations with $PM_{2.5}$ (Puett et al., 2011; Coogan et al., 2012). Coogan et al. (Coogan et al., 2012) reported stronger association with NO_x than with $PM_{2.5}$, while Puett et al. (Puett et al., 2011) found stronger effects with coarse particles $PM_{2.5–10}$ than with $PM_{2.5}$, contrary to the evidence from experimental studies in mice (Sun et al., 2009) which found $PM_{2.5}$ to contribute to the development of diabetes.

Here we examined the association between long-term exposure to $PM_{2.5}$, PM_{10}, NO_2 and NO_x, estimated at the residence by a high-resolution dispersion model, and incidence of diabetes in Danish female nurses aged over 44 years, in single and two-pollutant models, and tested for effect modification by relevant lifestyle, co-morbidities, and level of urbanization.

2. Methods

2.1. The Danish Nurse Cohort

The Danish Nurse Cohort (Hundrup et al., 2012) was inspired by the American Nurses' Health Study to initially investigate the health effects of hormone replacement therapy (HRT) in a European population. The cohort was initiated in 1993 by sending a questionnaire to 23,170 female members of the Danish Nursing Organization who were older than 44 years at the time. The Danish Nursing Organization includes 95% of all nurses in Denmark. In total, 19,898 (86%) nurses replied, and the cohort was reinvestigated in 1999 when additionally 10,534 nurses (who had had reached the age of 44 years in the period 1993–99) were included, and in 2009, but without inclusion of new nurses. The questionnaire included questions on socio-economic and working conditions, parents' occupation, weight and height including birth-weight, lifestyle (diet, smoking, alcohol consumption and leisure time physical activity), self-reported health, family history of cardiovascular disease and cancer, parity, age at first birth, age of menarche and menopause, use of oral contraceptives and hormone therapy (HT), removal of uterus and ovaries. In this study we used the earliest baseline information from 1993 (19,898) or 1999 (8833) for 28,731 female nurses.

The cohort was linked to the Central Population Register (Pedersen, 2011) to obtain the nurses' residential address information since 1971 until 2013, and vital status information at 31st December 2013 (active, date of death or emigration), and to the Danish Address Database to obtain the geographical coordinates.

2.2. Danish National Diabetes Register

The Danish National Diabetes Register (NDR) (Carstensen et al., 2011) was established to describe and monitor the prevalence and incidence of diabetes in Denmark since 1995, by linking four existing Danish registries: the National Patient Register (NPR) (Lynge et al., 2011), containing hospital discharge diagnosis since 1973, the National Health Service Register (NHSR) (Andersen et al., 2011), with information on all services provided by general and specialist practitioners since 1990, and the Danish National Prescription Registry (DNPR) (Kildemoes et al., 2011), containing all prescriptions dispensed at Danish pharmacies since 1993. NDR classifies people as diabetic if they fulfill a minimum of one of the following criteria: 1) diabetes hospital discharge diagnosis since 1995 (ICD-10 code E10-14, DH36.0, DO24) in the NPR; 2) chiropody as a diabetic patient, 3) five blood-glucose measures within one year, or 4) two blood glucose measures per year in five coherent years in the NHSR; or 5) second purchase of insulin or oral anti-diabetic drugs within 6 months registered in DNPR (Carstensen et al., 2011). Date of the first fulfilled criterion is considered the date of the onset of diabetes, and the majority of diabetic have several criteria fulfilled. Since the results of blood glucose measurements (criteria 3 and 4) are not available in the NHSR, the nurses who had either criteria 3 or 4 as the single inclusion criteria in NDR were not considered diabetic in this study. NDR does not distinguish between type 1, type 2 or gestational diabetes. Because of the different dates of initiation of the underlying registers and accumulation of prevalent cases, only incidence information after 1st January 1995 is reliable (Carstensen et al., 2011). Thus, the incidence of diabetes in this study was defined as the earliest record in the NDR occurring between 1st January 1995 and 31st December 2012.

2.3. Air pollution exposure data

We used the newly updated, high-resolution Danish air pollution dispersion modeling system (AirGIS) to estimate exposure to outdoor air pollution (Jensen et al., 2001) (more detail in the ESM). The necessary input data for carrying out the exposure modeling has been established for the first time in Denmark for particulate matter ($PM_{2.5}$ and PM_{10}) starting in 1990, whereas for the gaseous nitrogen oxide pollutants (NO_2 and NO_x) input data have been established since 1971. Since focus of this paper is $PM_{2.5}$, we have calculated annual mean concentrations of $PM_{2.5}$, PM_{10}, NO_2, and NO_x since 1990 at the residential addresses for nurses who had complete information on residential address history for at least 80% of the time since 1990 until 2013. Five-year running mean of available annual concentrations of $PM_{2.5}$, PM_{10}, NO_2, and NO_x was the main exposure proxy, as this was the longest possible exposure window between 1990, when modeling of $PM_{2.5}$ begun, and the beginning of the study follow-up in 1995. Additionally, 24-year running mean of NO_2 and NO_x, as the longest possible exposure window, was used in sensitivity analyses.