Environment International 112 (2018) 68–76

Contents lists available at ScienceDirect

Environment International

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

Air pollution and occurrence of type 2 diabetes in a large cohort study

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ARTICLE INFO

Keywords:
Air pollution
Cohort
Diabetes
Nitrogen oxides
Ozone
Particulate matter
Rome

ABSTRACT

The few cohort studies that have investigated the association between exposure to air pollution and occurrence of diabetes have reported conflicting results. We aimed to evaluate the association of long-term exposure to particulate matter (PM), nitrogen oxides (NO_x) and ozone (O_3), with baseline prevalence and incidence of type 2 diabetes in a large administrative cohort in Rome, Italy. A total of 1,425,580 subjects aged 35 + years (January 1st, 2008) were assessed and followed for six years. We estimated PM_{10}, $PM_{2.5-10}$, $PM_{2.5}$, NO_2, and NO_x exposures at residence using land use regression models, and summer O_3 exposure using dispersion modeling. To estimate the association between air pollutant exposures and prevalence and incidence of diabetes, we used logistic and Cox regression models, considering individual, environmental (noise and green areas), and contextual characteristics. We identified 106,387 prevalent cases at baseline and 65,955 incident cases during the follow-up period. We found positive associations between nitrogen oxides exposures and prevalence of diabetes with odds ratios (ORs) up to 1.010 (95% CI: 1.002, 1.017) and 1.015 (1.009, 1.021) for NO_2 and NOx, respectively, per fixed increases (per 10 μg/m^3 and 20 μg/m^3, respectively). We also found some evidence of an association between NOx and O_3 and incidence of diabetes, with hazard ratios (HRs) of 1.011 (95%CI: 1.003–1.019) and 1.015 (1.002–1.027) per 20 and 10 μg/m^3 increases, respectively. The association with O_3 with incident diabetes was stronger in women than in men and among those aged < 50 years. In sum, long-term exposure to nitrogen oxides was associated with prevalent diabetes while NOx and O_3 exposures were associated with incident diabetes.

1. Introduction

The link between long-term exposure to air pollution and several health outcomes, including natural and cause-specific (cardiovascular and respiratory) mortality (Beelen et al., 2014; Hoek et al., 2013; Pope et al., 2015) and incidence of various debilitating diseases (chronic obstructive pulmonary disease, cerebrovascular events, acute coronary events) (Brook et al., 2017; Cesaroni et al., 2014; Scheers et al., 2015; Schikowski et al., 2014; Stafoggia et al., 2014) has been widely studied during past years. In particular, the relationship between long-term air pollution exposure and health was investigated in Europe in the ESCAPE project (Beelen et al., 2014). Fine particles ($PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3) have been recognized as important risk factors for human health (World Health Organization, 2013a, 2013b).

Among the health outcomes investigated, diabetes has been suggested as positively associated with long-term exposure to air pollution (Eze et al., 2015). This relationship is supported by mechanistic hypotheses involving endothelial dysfunction and hyper-activity of the sympathetic nervous system (Rajagopalan and Brook, 2012). Recently, some animal studies evidenced a possible role of fine particle ($PM_{2.5}$) exposure and multiple-organ insulin resistance mediated by several biological pathways (such as Akt phosphorylation and insulin receptor substrate 1 [IRS-1] serine phosphorylation by NASH-like phenotype and CCR2 pathways) (Khafaie et al., 2013; Liu et al., 2014; Xu et al., 2011; Zheng et al., 2013).

The hypothesis that air pollution is related with diabetes is extremely relevant as the World Health Organization (WHO) estimated that this metabolic disorder afflicts > 9% of the global population (WHO, 2014) and entails several severe health consequences.

Several studies and systematic reviews have investigated the role of air pollution on the occurrence of the most common form of diabetes that involves adult subjects, type 2 diabetes, but the results remain controversial. Some of them supported the link between air pollution and risk of new onset of diabetes (Balti et al., 2014; Eze et al., 2015). However, other observational studies were negative (Coogan et al., 2016a, 2016b) or found a positive association only with distance from

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https://doi.org/10.1016/j.envint.2017.12.007
Received 12 July 2017; Received in revised form 5 December 2017; Accepted 5 December 2017

major traffic roads (Dijkema et al., 2011; Puett et al., 2011). A recent study conducted in North America reported a positive association between ozone exposure and both incidence of diabetes and diabetes related mortality (Jerrett et al., 2017).

The aim of our study is to evaluate the potential association between long-term exposure to particulate matter (PM_{10}, $PM_{2.5–10}$, $PM_{2.5}$), soot $PM_{2.5}$ absorbance, nitrogen oxides (NO_2, NO_x), and ozone (O_3) and adult diabetes in a large administrative cohort of Rome (Italy) residents, and to test for a possible effect modification by sociodemographic factors and preexisting health conditions.

2. Material and methods

2.1. Study population

The Rome Longitudinal Study has been described in detail elsewhere (Cesaroni et al., 2010, 2013). Briefly, it is the cohort of residents in Rome at the 2001 census, followed through various administrative databases, including mortality, hospitalization, and, since 2006, drug prescriptions. We included subjects aged 35 years or more on 1st January 2008 (or who reached age 35 during follow-up) and followed them until 2013, or migration, their 100th birthday, death or indications that they received a diagnosis of type 2 diabetes. Individual information, recorded at the 2001 census, included several socio-demographic characteristics such as educational level, occupation, place of birth, and marital status. Furthermore, to better characterize residential social deprivation, we used a small-area (census block, average population: 470 inhabitants) composite index of socioeconomic position (SEP) (Cesaroni et al., 2006).

Each subject included in the Rome Longitudinal Study was linked, using an anonymous identifier, with the Regional Health Information System (HIS), which include the Drug Prescriptions Registry, the Exempt from Copays Registry, and the Hospital Discharges Registry. The Drug Prescriptions Registry database contains individual records for each medical prescription by general practitioners of the National Health Service, dispensed in public and private pharmacies, and the date of dispensing. The registry is limited to drugs dispensed to outpatients, and reimbursed by the healthcare system. The Exempt from Copays Registry includes data on all residents who qualify for free healthcare services for particular conditions, i.e. disability, and chronic diseases including diabetes. The Hospital Information System (HIS) routinely collects data from all regional hospitals, including patient demographic data, admission referral source, discharge status, discharge diagnoses, procedures (according to the International Classification of Disease, Ninth Revision, Clinical Modification [ICD-9-CM]), and the regional code of the facility.

Record linkage procedures were anonymous and were allowed since the Rome Longitudinal Study is part of the National Statistical Program for the years 2011–2016, and was approved by the Italian Data Protection Authority.

2.2. Outcome definition

Subjects were defined as diabetic if they qualified for free healthcare for diabetes (code: 013.250) in the Exempt from Copays Registry, or were admitted to hospital with a diagnosis of diabetes (ICD-9-CM code: 250.0) during the period 2002–2013 (principal or secondary diagnosis), or were prescribed hypoglycemic drugs (Anatomical Therapeutic Chemical classification system [ATC] code: A10) at least two times in one year during 2006–2013. All subjects who met our criteria as diabetic at baseline (January 1st, 2008) were considered as prevalent cases and excluded from the study on incidence. The algorithm was developed in the context of a previous study (Fano et al., 2013) and validated using two random population samples in the area of Rome (1172 subjects aged 35–69 years and 442 subjects aged 35–100, respectively). In the two samples measured glycated hemoglobin (cut-off 5.7%) in fasting blood was available, and was considered as a marker of diabetes. When we applied to these populations the our algorithm to identify cases of diabetes the overall sensitivity was 0.86 and the specificity was 0.97.

2.3. Exposure assessment

We estimated average annual exposure to air pollutants (PM_{10}, $PM_{2.5–10}$, $PM_{2.5}$, $PM_{2.5}$ absorbance, NO_2, and NO_x) at baseline (January 1st, 2008) residential address for each individual by land-use regression (LUR) models, developed using measures taken in 2010 within the ESCAPE project. The measurement campaign and the development of LUR models are described elsewhere (Beelen et al., 2013; Cyrys et al., 2012; Eeftens et al., 2012a; Eeftens et al., 2012b). Briefly, a monitoring campaign was conducted in Rome in 2010 to measure PM at 20 sampling sites, and nitrogen oxides at 40 sampling sites. Each site was chosen to represent the spatial distribution of residential addresses, and pollutants were measured there for 14 days in the cold, warm, and intermediate seasons. A temporal correction was calculated to obtain the annual average using a background reference site that operated for the entire year (Cyrys et al., 2012; Eeftens et al., 2012b). Several variables such as land use, traffic load on major and minor roads, population and household density, urban green, etc. were used to predict the pollutants listed above. These models displayed a R^2 ranging from 87% (NO_2) to 71% ($PM_{2.5}$) and an R^2 cross-validated from 76% (NO_2) to 59% (PM_{10}) in Rome.

Residential exposure to summer (May–September) daily (8 h) and seasonal O_3 (2005) was estimated using a 1 km–grid dispersion model [the Flexible Air quality Regional Model (FARM)], a three-dimensional Eulerian model of the transport and multiphase chemistry of pollutants in the atmosphere (Gariazzo et al., 2007). The FARM model used data obtained by a monitoring campaign in summer of 2005, characterized by classic high levels of ozone in the Mediterranean area. The model required a few predictor variables such as industrial emissions, meteorology factors etc. to predict the spatial distribution of O_3 in Rome.

In our analysis, we used air pollutants as continuous variables. For each subject we used an indicator of urban green exposure as possible confounder of the relationship between air pollution and diabetes. We used Normalized Difference Vegetation Index (NDVI) calculated by Landsat 5 Thematic Mapper (TM) satellite images (http://earthexplorer.usgs.gov/). NDVI is a common indicator of green vegetation and was developed using the analysis of surface reflectance measurements. The NDVI values range from -1 to $+1$, with $+1$ indicating a high density of green leaves, -1 representing water features and values close to zero referring to barren areas of rock, sand or snow (Weier and Herring, 2000). We overlapped a grid map of 30x30m cells over the city of Rome. For each cell, we estimated a value of NDVI. For each subject we derived a single NDVI value by averaging values of each cell in a 300 m buffer around the residence addresses.

Residential noise exposure was assessed using annual day-evening-night A-weighted equivalent continuous noise levels (Lden) indicator, defined by the European Environmental Agency (EEA, 2010) as average sound pressure level over all days, evenings and nights in a year. This is the general purpose indicator defined in EU-directive 2002/49 (EEA, 2010; European Parliament and Council of the European Union, 2002). Lden was estimated using an approach described in details elsewhere (Licitra et al., 2016; Licitra and Ascari, 2012). Briefly, traffic noise levels were estimated for each residential address through the acoustic model Sound Plan 7.4, using several information including 2009 traffic flow data and buildings geometry. We estimated Lden at receivers (one receiver every 4 m) along the façades of buildings. In order to relate a unique noise value to each subject, we calculated the energetic mean of all façade receivers around the building where the subjects lived (Ascari et al., 2017).