Environmental Research 154 (2017) 304–310

Contents lists available at ScienceDirect

Environmental Research

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

Interactions between cigarette smoking and ambient $PM_{2.5}$ for cardiovascular mortality

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ARTICLE INFO

Keywords:
Additive interaction
Air pollution
Cigarette smoking
Cardiovascular mortality
Particulate matter

ABSTRACT

Associations between long-term exposure to ambient fine particulate matter ($PM_{2.5}$) and all-cause and cardiovascular mortality are well documented however less is known regarding possible interactions with cigarette smoking. We previously reported a supra-additive synergistic relationship between $PM_{2.5}$ and cigarette smoking for lung cancer mortality. Here we examine interactions for all-cause and cardiovascular mortality among 429,406 current or never smoking participants in the prospective American Cancer Society Cancer Prevention Study-II with modeled $PM_{2.5}$ concentrations. Cox proportional and additive hazards models were used to estimate mortality associations and interactions on the multiplicative and additive scales. A total of 146,495 all-cause and 64,339 cardiovascular (plus diabetes) deaths were observed. The hazard ratio (HR) (95% confidence interval (CI)) for cardiovascular mortality for high vs. low $PM_{2.5}$ exposure (> 14.44 $\mu g/m^3$ vs ≤10.59 $\mu g/m^3$, 75th vs 25th percentile) was 1.09 (95% CI 1.05, 1.12) in never smokers. The HR for cigarette smoking was 1.89 (95% CI 1.82, 1.96) in those with low $PM_{2.5}$. The HR for both high $PM_{2.5}$ and cigarette smoking was 2.08 (95% CI 2.00, 2.17). A small significant excess relative risk due to interaction (0.10; 95% CI 0.02, 0.19) was observed. Quantification of the public health burden attributed to the interaction between $PM_{2.5}$ and cigarette smoking indicated a total of 32 (95% CI −6, 71) additional cardiovascular deaths per 100,000 person-years due to this interaction. In conclusion, $PM_{2.5}$ was associated with all-cause and cardiovascular mortality in both smokers and never smokers, with some evidence for a small additive interaction with cigarette smoking. Reductions in cigarette smoking will result in the greatest impact on reducing all-cause and cardiovascular death at the levels of $PM_{2.5}$ observed in this study. However, reductions in $PM_{2.5}$ will also contribute to preventing a proportion of mortality attributed to cigarette smoking.

1. Introduction

Associations between long-term exposure to ambient fine particulate matter ($PM_{2.5}$) and all-cause and cardiovascular mortality are well documented in cohorts conducted in diverse geographic locations across a range of $PM_{2.5}$ concentrations (Beelen et al., 2014a, 2014b; Cesaroni et al., 2013; Crouse et al., 2015; Newby et al., 2015; Pope et al., 2004, 2015). From a quantitative perspective, a recent meta-analysis of 10 studies reported a 6% (95% confidence interval (CI) 4, 8%) increase for all-cause mortality and a 15% (95% confidence interval (CI) 4, 27%) increase for cardiovascular mortality associated with each 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations (Hoek et al., 2013).

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http://dx.doi.org/10.1016/j.envres.2017.01.024
Received 25 October 2016; Received in revised form 18 January 2017; Accepted 20 January 2017
Available online 28 January 2017
0013-9351/

Some studies have assessed whether the excess relative risk (RR) between $PM_{2.5}$ and cardiovascular mortality is modified by cigarette smoking status, given that cigarette smoking is an established risk factor for cardiovascular disease, acting through multiple mechanisms including systemic inflammation (Hoek et al., 2013; U.S. Department of Health and Human Services, 2010). Pope et al., (2004, 2015) in the American Cancer Society Cancer Prevention Study-II (CPS-II) reported similar RRs for $PM_{2.5}$ and cardiovascular mortality across categories of cigarette smoking status. The Harvard Six Cities Study reported no interaction between $PM_{2.5}$ and cigarette smoking for cardiovascular mortality, although there were some larger $PM_{2.5}$ RRs in current smokers (Lepeule et al., 2012). In a study of health professionals, the excess RR between $PM_{2.5}$ and fatal coronary heart disease was larger among smokers, although the number of deaths among current smokers was small (n =47) (Puett et al., 2011). Conversely in the Nurses' Health Study, larger $PM_{2.5}$ RRs were observed in never smokers (Puett et al., 2008). However, to our knowledge, the possible interaction between $PM_{2.5}$ and cigarette smoking for cardiovascular mortality has not been assessed on the additive scale, which is most relevant for understanding biological significance and disease pathways, as well as public health decision-making, than the multiplicative scale (Ahlbom and Alfredsson, 2005; Brook et al., 2010; Greenland et al., 2008). Other recent studies examining associations between $PM_{2.5}$ and cardiovascular mortality did not address cigarette smoking status (Crouse et al., 2015; Cesaroni et al., 2013; Fischer et al., 2015; Naess et al., 2007).

We recently evaluated the interaction between $PM_{2.5}$ and cigarette smoking status on the additive scale for lung cancer mortality in the CPS-II (Turner et al., 2014). There was a relative excess risk due to interaction (RERI) of 2.19 (95% CI −0.10, 4.83) indicating a small increase in lung cancer risk among persons with both exposures, beyond what was expected from the sum of the individual effects. Though potential biological mechanisms are unclear, they may relate to differences in levels or timing of exposure, dose, or toxicity (IARC, 2004; Turner et al., 2014; U.S. Department of Health and Human Services, 2010). Further results on interactions between $PM_{2.5}$ and cigarette smoking could provide valuable insights into whether smokers should be considered as more susceptible to particulate matter air pollution than non-smokers, address an important data gap for air pollution burden of disease assessments, and inform knowledge on mechanisms.

This paper examines possible interactions on the additive scale between cigarette smoking and $PM_{2.5}$ in relation to all-cause and cardiovascular mortality in the CPS-II. We also consider absolute indicators of additive interaction by estimating the number of additional deaths attributable to interaction using additive hazard models.

2. Materials and methods

2.1. Study population

The CPS-II is a prospective cohort study of nearly 1.2 million participants enrolled by over 77,000 volunteers in 1982. Ethics approval for the CPS-II was obtained from the Emory University School of Medicine Human Investigations Committee. Participants were recruited in all 50 US states as well as the District of Columbia and Puerto Rico. Participants were largely friends and family members of the volunteers and had to be at least 30 years of age and have at least one family member aged 45 years or older. A four-page self-administered questionnaire completed at enrollment collected data on a range of demographic, lifestyle, medical, and other factors, including place of residence.

Follow-up for vital status has been conducted every two years. In 1984, 1986, and 1988, vital status was determined by the study volunteers, and confirmed by obtaining the corresponding death certificate. Since 1989, computerized linkage to the National Death Index has been used for follow-up (Calle and Terrell, 1993). Deaths were classified according to the underlying cause using the International Classification of Disease (ICD) 9 and 10 coding systems for mortality from all causes, as well as all cardiovascular diseases (plus diabetes) (ICD 9;10 390–459, 250; I00-I99, E10-E14), ischemic heart disease (ICD 9;10 410–414; I20-I25), heart failure, dysrhythmias, cardiac arrest (ICD 9;10 420–429; I30-I51), and cerebrovascular disease (ICD 9;10 430–438; I60-I69) (WHO, 1977, 1992). Over 99% of known deaths have been assigned an underlying cause.

Participants were excluded if they had invalid address information for geocoding place of residence (n=385,422) or had missing covariate data (n=130,119) (Jerrett et al., 2016; Pope et al., 2015; Turner et al., 2016). Excluded participants were similar to included participants in terms of age and sex, though there was a somewhat greater proportion of excluded participants with a < high school education (~19%) (Jerrett et al., 2016). Former smokers (n =172,689) and ever pipe or cigar smokers (n =66,951) were also excluded from the main analysis. A total of 429,406 never or current smoking participants were included here in which there were 146,495 all-cause and 64,339 cardiovascular (plus diabetes) deaths observed in 8,201,742 person-years of follow-up from 1982 through 2004.

2.2. $PM_{2.5}$ concentrations

$PM_{2.5}$ concentrations were assigned to each participant residence in 1982 using a national-level hybrid land use regression (LUR) and Bayesian Maximum Entropy (BME) interpolation model (Beckerman et al., 2013) also used in other analyses of the CPS-II cohort (Jerrett et al., 2016; Pope et al., 2015; Turner et al., 2014, 2016). Monthly $PM_{2.5}$ monitoring data were collected from 1,464 sites from 1999 through 2008, with approximately 10% of the sites reserved for cross validation. The base LUR model that predicted $PM_{2.5}$ concentrations included traffic within 1 km and green space in 100 m^3. Residual spatiotemporal variation in $PM_{2.5}$ concentrations was interpolated with a BME interpolation model. The two estimates were then combined. The LURBME model demonstrated strong agreement between estimated and observed $PM_{2.5}$ concentrations (R^2 =0.79) with little evidence for bias or influential outliers. $PM_{2.5}$ concentrations were averaged over the years 1999–2004 to coincide with the cohort follow-up period. $PM_{2.5}$ concentrations ranged from 1.38 to 27.94 μg/m^3 with a mean (SD) of 12.61 (2.85) μg/m^3.

2.3. Statistical analysis

Age-standardized all-cause and cardiovascular mortality rates and risk differences were calculated according to categories of cigarette smoking status at enrollment (current vs never smoker) and $PM_{2.5}$ concentrations (> 75th vs ≤25th percentile) (> 14.44 μg/m^3 vs ≤10.59 μg/m^3). Cox proportional hazards models were used to obtain adjusted hazard ratios (HRs) and 95% CIs for all-cause and cardiovascular mortality in relation to categories of cigarette smoking and $PM_{2.5}$ with follow-up through 2004 according to a common reference category of never smokers and low $PM_{2.5}$. Models were stratified by one-year age categories, sex, and race. Follow-up time since enrollment (1982) was used as the time axis. Models were adjusted for individual-level risk factors including education, marital status, body mass index (BMI), BMI squared, passive smoking (hours), quintiles of vegetable/fruit/fiber and fat intake, alcohol consumption (beer, liquor, wine), occupational exposures (asbestos, chemicals/acids/solvents, coal or stone dusts, coal tar/pitch/asphalt, formaldehyde, and diesel engine exhaust), an 'occupational dirtiness index', and sociodemographic ecological covariates (median household income; and percentage of African American residents, Hispanic residents, adults with post-secondary education, unemployment, and poverty) at both the ZIP code and ZIP code minus the county level mean from the 1990 U.S. Census (Jerrett et al., 2016; Pope et al., 2015; Turner et al., 2014,