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Does consideration of larger study areas yield more accurate estimates of air pollution health effects? An illustration of the bias-variance trade-off in air pollution epidemiology

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ABSTRACT

Background: Spatially-resolved air pollution models can be developed in large areas. The resulting increased exposure contrasts and population size offer opportunities to better characterize the effect of atmospheric pollutants on respiratory health. However the heterogeneity of these areas may also enhance the potential for confounding. We aimed to discuss some analytical approaches to handle this trade-off.
Methods: We modeled NO_2 and PM_{10} concentrations at the home addresses of 1082 pregnant mothers from EDEN cohort living in and around urban areas, using ADMS dispersion model. Simulations were performed to identify the best strategy to limit confounding by unmeasured factors varying with area type. We examined the relation between modeled concentrations and respiratory health in infants using regression models with and without adjustment or interaction terms with area type.
Results: Simulations indicated that adjustment for area limited the bias due to unmeasured confounders varying with area at the costs of a slight decrease in statistical power. In our cohort, rural and urban areas differed for air pollution levels and for many factors associated with respiratory health and exposure. Area tended to modify effect measures of air pollution on respiratory health.
Conclusions: Increasing the size of the study area also increases the potential for residual confounding. Our simulations suggest that adjusting for type of area is a good option to limit residual confounding due to area-associated factors without restricting the area size. Other statistical approaches developed in the field of spatial epidemiology are an alternative to control for poorly-measured spatially-varying confounders.

1. Introduction

The respiratory system is vulnerable to exposure to airborne toxicants during development (Baïz et al., 2011; Bateson and Schwartz, 2008; Bråbäck and Forsberg, 2009; Clark et al., 2010; Latzin et al., 2009, 2011; Mauad et al., 2008; Pinkerton and Joad, 2000; Pope, 1989; Sram et al., 2005; Woodruff et al., 2008; Wu et al., 2009). Early life exposure to ambient air pollution has been associated with cord blood

Abbreviations: ADMS, atmospheric dispersion modeling system; BMI, body mass index; CI, confidence interval; ETS, environmental tobacco smoke; ISAAC, international study of asthma and allergies; LUR, land-use regression; NO_2, nitrogen dioxide; OR, odds ratio; O_3, ozone; PM_{10}, particulate matter with an aerodynamic diameter below 10 μm.

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immunologic parameters (Baïz et al., 2011; Latzin et al., 2011), decreased lung function in newborns (Latzin et al., 2009), asthma and asthma-related symptoms in the first year of life (Aguilera et al., 2013; Andersen et al., 2008; Bateson and Schwartz, 2008; Bråbäck and Forsberg, 2009; Brauer et al., 2002; Clark et al., 2010; Ebisu et al., 2011; Esplugues et al., 2011; Gehring et al., 2002; Gouveia and Fletcher, 2000; Karr et al., 2009; Morgenstern et al., 2007; Nordling et al., 2008; Orazzo et al., 2009; Pino et al., 2004; Pope, 1989; Ryan et al., 2005). Early studies relied on permanent monitoring stations to assess exposure (Andersen et al., 2008; Bateson and Schwartz, 2008; Bråbäck and Forsberg, 2009; Gouveia and Fletcher, 2000; Latzin et al., 2009, 2011; Orazzo et al., 2009; Pino et al., 2004; Pope, 1989; Sram et al., 2005), an approach with a limited spatial resolution. Over the last decade, models with improved spatial resolution such as dispersion or land-use regression (LUR) models (Hoek et al., 2008) have been increasingly applied (Aguilera et al., 2013; Bråbäck and Forsberg, 2009; Brauer et al., 2002; Clark et al., 2010; Ebisu et al., 2011; Esplugues et al., 2011; Gehring et al., 2002; Karr et al., 2009; Morgenstern et al., 2007; Nordling et al., 2008; Ryan et al., 2005). Such approaches allow consideration of large study areas as a whole, including city centers, surrounding suburban and sometimes rural areas. Considering such large areas entails a potential increase in exposure contrasts and study size, which is a priori desirable in terms of statistical power.

However, the greater population heterogeneity may also increase the potential for confounding, in particular due to spatially-varying factors.

Indeed, not only do ambient air pollution levels vary largely over space, but also possibly other parameters such as exposure to infectious factors, to sources of allergens (e.g. pet ownership, dairy farms, pollen), health-care access and distribution of personal characteristics such as socioeconomic status, smoking and diet (Wright and Subramanian, 2007). Residual confounding may occur if these asthma risk factors are unevenly distributed across types of areas (rural and urbanized areas) and are not assessed, or are assessed with measured error or poorly taken into account in regression models. The alternative between studying small homogeneous areas with fewer subjects and expanding area size together with population heterogeneity and possibly resulting bias can be seen as an illustration of the classical epidemiological trade-off between bias and variance.

The present study aimed to document this bias-variance trade-off related to confounding, size and heterogeneity of study area that may occur in studies of air pollution health effects relying on exposure models that are applied to a large study area. We did not consider the impact on exposure misclassification of using models with a fine spatial resolution, compared e.g., to approaches resting on permanent air quality monitoring stations (Gulliver et al., 2011; Lepeule et al., 2010; Marshall, 2008). We illustrated this trade-off in a study of ambient air pollution effects on respiratory health in the first year of life using simulations and real data. First, we conducted a simulation study to estimate the bias and statistical power in studies with area-dependent unmeasured confounders, to illustrate the efficiency of various analytical approaches. Secondly, we assessed the association between air pollution levels and infant respiratory health in a mother–child cohort study using several analytical approaches to limit residual confounding.

2. Material and methods

2.1. Study population

This study relies on mother–child pairs from the EDEN mother–child cohort. The EDEN mother–child cohort study is a population-based prospective study on pre- and early postnatal nutritional, environmental and social determinants of the children's development and health (Baïz et al., 2011; Drouillet et al., 2009; Hampel et al., 2011; Slama et al., 2009). Between 2003 and 2006, pregnant women expecting singletons at the University Hospitals in Poitiers and Nancy, two middle-sized cities in West and East France, were invited to participate. Criteria of exclusion were inability to speak and read French, multiple pregnancies, known diabetes before pregnancy and intention to give birth or to move outside the study regions within the next three years. The study was reviewed and approved by the relevant ethical committees (Comité Consultatif pour la Protection des Personnes dans la Recherche Biomédicale, Le Kremlin-Bicêtre University hospital, and Commission Nationale de l'Informatique et des Libertés), and all participating women gave informed written consent for themselves and their child.

Personal characteristics of the parents were obtained during pregnancy using self-administrated questionnaires and interviews. At 4 and 8 months of age, self-administrated parental questionnaires were used to follow-up the health of children and the personal characteristics of the family. At 12 months of age, the children were offered a clinical examination, and, if needed, trained nurses supported the completion of the questionnaire. We restricted the population to the 1082 mother–child pairs with estimated air pollution exposure and information from follow-up at least once during the first year after the index birth (Fig. 1).

2.2. Air pollution exposure assessment

Outdoor air pollution levels of nitrogen dioxide (NO_2) and particulate matter with an aerodynamic diameter below 10 μm (PM_{10}) were estimated at the maternal home addresses with a dispersion model implemented with ADMS-Urban software (CERC, Cambridge, UK) and averaged for the whole pregnancy (Carruthers et al., 2000; CERC, 2001; Hampel et al., 2011; Righi et al., 2009). This dispersion model took into account temporal variations in background air pollution levels, emission from traffic and industries and hourly meteorological conditions. All pregnancy home addresses were geocoded in ArcGIS 9.3 (ESRI, Redlands, CA, USA). The study areas covered surfaces of 739 km^2 and 900 km^2, respectively, around Poitiers and Nancy (Fig. 2 and Supplementary materials).

Changes of home address between inclusion and delivery ($n = 249$) were taken into account by calculating time-weighted means of exposure at each address over the relevant periods. We restricted our study population to those for whom there were less than 10% missing values in the daily air pollution values over the whole pregnancy. The study area was divided into city-centers, urban, or rural areas. The city-center areas were defined as the two cities of Poitiers and Nancy; the urban area corresponded to the metropolitan areas around the two cities, using the smallest French administrative subdivision of the two 'communauté de communes' (federation of municipalities having a joint urban development project) of "Communauté urbaine du Grand Nancy" and "Grand Poitiers". Rural areas corresponded to the remaining areas.

2.3. Respiratory outcomes

The questionnaire was derived from the International Study of Asthma and Allergies (ISAAC) questionnaire and adapted to derive asthma phenotypes in the first year of life (Hederos et al., 2007). Parents were asked: "Did your child have diagnosed asthma since birth?" when the child was 8 and 12 months, and "Did your child have diagnosed asthma during the previous 4 months?" at 12 months of age. Likewise parents

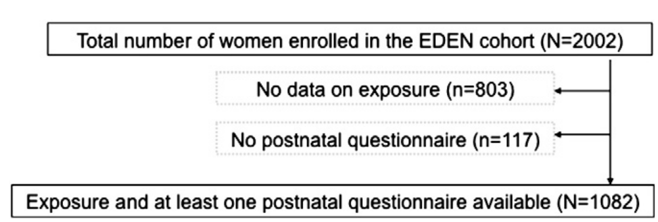

Fig. 1. Study population.