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Hydrogen sulfide and particle matter levels associated with increased dispensing of anti-asthma drugs in Iceland's capital

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ABSTRACT

Background: Air pollutants in Iceland's capital area include hydrogen sulfide (H_2S) emissions from geothermal power plants, particle pollution (PM_{10}) and traffic-related pollutants. Respiratory health effects of exposure to PM and traffic pollutants are well documented, yet this is one of the first studies to investigate short-term health effects of ambient H_2S exposure.

Objectives: The aim of this study was to investigate the associations between daily ambient levels of H_2S, PM_{10}, nitrogen dioxide (NO_2) and ozone (O_3), and the use of drugs for obstructive pulmonary diseases in adults in Iceland's capital area.

Methods: The study period was 8 March 2006 to 31 December 2009. We used log-linear Poisson generalized additive regression models with cubic splines to estimate relative risks of individually dispensed drugs by air pollution levels. A three-day moving average of the exposure variables gave the best fit to the data. Final models included significant covariates adjusting for climate and influenza epidemics, as well as time-dependent variables.

Results: The three-day moving average of H_2S and PM_{10} levels were positively associated with the number of individuals who were dispensed drugs at lag 3–5, corresponding to a 2.0% (95% confidence interval [CI] 0.4, 3.6) and 0.9% (95% CI 0.1, 1.8) per 10 $\mu g/m^3$ pollutant concentration increase, respectively.

Conclusion: Our findings indicated that intermittent increases in levels of particle matter from traffic and natural sources and ambient H_2S levels were weakly associated with increased dispensing of drugs for obstructive pulmonary disease in Iceland's capital area. These weak associations could be confounded by unevaluated variables hence further studies are needed.

1. Introduction

Short-term changes in levels of several air pollutants have been shown to be positively associated with immediate measures of respiratory effects such as hospital admissions for asthma (Villeneuve et al., 2007) and chronic obstructive pulmonary disease (COPD) (Sunyer et al., 2000). The toxic effects of hydrogen sulfide (H_2S) in occupational settings are well known (WHO, 2000) and some studies of background exposure due to H_2S from geothermal sources in Hawaii, New Zealand and the Azores have indicated that H_2S may have negative effects on respiratory health (Durand and Wilson, 2006; Longo, 2009; Amaral and Rodrigues, 2007). These studies focused on long-term effects of chronic exposure. We are not aware of any studies on intermittent exposure to ambient H_2S and effects on respiratory health.

Iceland's capital area, which includes Reykjavik and its surrounding municipalities, has a reputation for being among the cleanest metropolitan areas in the world since there is little industrial pollution and geothermal energy has replaced the use of fossil fuels for house heating. However, when weather conditions in Reykjavik are dry and windy, often in winter and spring, particulate matter with a diameter less than 10 μm (PM_{10}) levels in Reykjavik may increase sharply and even surpass those of much larger European capitals (Jóhannsson, 2007). The main source of PM in Iceland's capital area is traffic related (UHR, 2007), though the contribution from naturally occurring sandstorms is substantial (Arnalds, 2010). In Iceland, many cars are driven with studded tires, thus eroding the asphalted streets during winter, and per capita car ownership is among the highest

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in the world (Economist, 2008). Moreover, H_2S is emitted from the geothermal harnessing sites outside the city and the distinct 'rotten egg' odor is sometimes detectable in the city. Potential effects on population health remain to be investigated.

In small populations, such as Iceland, hospital admission and mortality rates are likely to be too low to provide sufficient statistical power to study the association between air pollution and health effects. Medication to relieve the symptoms of obstructive respiratory diseases, such as asthma and COPD is dispensed by prescription and is used both incidentally and regularly (Hallas, 2005). The use of these drugs, hereafter referred to as anti-asthma drugs, has been suggested as a more sensitive marker for respiratory morbidity than hospital emergency room visits and hospital admissions (Menichini and Mudu, 2010). Furthermore, significant correlation has been reported between individual emergency room visits for asthma and subsequent prescription fills for instant asthma symptom-relieving drugs (Naureckas et al., 2005).

Previous panel studies have indicated associations between air pollution levels and symptom severity or use of anti-asthma drugs (von Klot et al., 2002) and COPD (Trenga et al., 2006; Lagorio et al., 2006). Ecological studies of anti-asthma drug dispensing within a geographically confined area have shown similar associations (Laurent et al., 2009; Vegni et al., 2005; Pitard et al., 2004; Zeghnoun et al., 1999).

The Icelandic health service is primarily financed by the central government. Patients pay a small part of the cost for prescribed drugs and out-patient visits (Halldórsson, 2003). One Icelandic questionnaire study showed anti-asthma drug usage to be most common among young children and the elderly; 28% of users were 65 years or older (Gíslason et al., 1997).

With almost 100% complete national registration of prescription drug utilization and constant surveillance of air pollution levels in the capital area, Iceland offers a unique setting to study Reykjavik's potential respiratory effects of ambient air pollution. In this study, we examined whether increases in air pollution levels – particularly H_2S – were associated with subsequent increases in dispensing of anti-asthma drugs in the capital area of Iceland. Furthermore, we tested whether the associations were dependent upon pollutants being measured as daily peak levels or 24-h mean levels.

2. Material and methods

The present study was designed as a register-based, time-series study in which the daily number of individuals who were dispensed anti-asthma drugs was modeled as a function of daily air pollution levels and covariates using methods based on Poisson regression models. The source population included adult individuals (eighteen years or older) living in the capital area of Iceland at the time of the study according to Statistics Iceland (2009). Permission for studying and extracting data was obtained from the National Bioethics Committee (ref. no.: VSNb2008050023/03-15) and the Data Protection Authority (ref. no.: 2008080569). No person-identifiable information was involved in the study data.

2.1. Data

The Directorate of Health registers all prescription drugs dispensed to the total outpatient population in Iceland in the Medicines Registry and stores the individual level data under unique, encrypted personal identity numbers given to each resident at birth or immigration. Drug data are registered according to the World Health Organization Anatomical Therapeutical Chemical drug classification (WHO, 2003). In this study, we measured the daily number of individuals aged 18 years and older who filled one or more prescriptions for anti-asthma drugs (Anatomical Therapeutical Chemical group R03) between 8 March 2006 and 31 December 2009. The data were stratified into the following drug categories: adrenergic inhalants (R03A), other inhalants (R03B), adrenergic drugs for systemic use (R03C) and other drugs (R03D).

The Reykjavik Municipality Department of the Environment and The Environment Agency of Iceland continuously measure air pollution levels and weather factors at a measuring station located at a large intersection of two main roads in Reykjavik. Approximately 70,000 cars pass this intersection daily (UHR, 2008). Based on existing literature, available data and inter-correlational factors, we chose four pollutants for our model: PM_{10}, NO_2, O_3 and H_2S. PM_{10} is measured with an Andersen EMS IR Thermo. NO_2 is measured with Horiba APNA, O_3 with Horiba APOA, and H_2S with Horiba APSA 360. The concentration of finer particles, $PM_{2.5}$, is measured at the same site, but the data were unfortunately not of sufficient quality to use in this study.

The air pollution data were provided to us as 30 min or 60 min means by the City of Reykjavik Department of the Environment. Data were available for all four pollutants from 8 March 2006 to 31 December 2009. Additionally, the following background variables were included in the analyses: the 24-h mean relative humidity (%) and temperature (°C) measured at the same site as the pollutants; daily pollen counts during summer (provided by the Icelandic Institute of Natural History); and the monthly number of influenza cases reported from primary health care units and hospitals to the Directorate of Health.

2.2. Measures

For days with at least 75% complete measurements of the relevant pollutants, we calculated the daily (midnight to midnight) 1-h peak pollution (the maximum daily 1-h mean) and the daily 24-h mean concentrations (8-h for O^3). For days with at least 75% complete measurements of temperature and relative humidity we calculated the daily 24-h mean concentrations. For each day, we calculated the three-day moving average from the daily mean and peak values of the same day, the day before and two days before (lag 0–2), 3 to 5 day before (lag 3–5), 6 to 8 day before (lag 6–8), 9–11 day before (lag 9–11) and 12–14 day before (lag 12–14).

The monthly number of influenza cases was recalculated into a binary variable to indicate whether there was an influenza epidemic. The cut-off value of 300 registered cases per month was chosen after inspecting the data and also because it is approximately 1% of the population of Iceland. Binary variables were introduced to adjust for day-of-week effects and public holidays as pharmacy opening hours, and subsequently the availability of drugs, were very different on non-weekdays. To adjust for temporary changes in dispensing patterns in relation to a new reimbursement regulation (Act no. 236/2009) effective from January 1 2009, we introduced binary variables.

2.3. Data analysis

We calculated descriptive statistics for pollution variables and the daily number of individuals who filled a prescription for the relevant drugs and calculated the correlations (Pearson's correlation coefficient) between pollutants and weather variables. The associations between the daily count of individuals who were dispensed drugs, (the outcome variable) and air pollution levels (the exposure variable) were modeled with a log-linear Poisson model with time indicator variables (Dominici et al., 2003; Whitaker et al., 2007; Peng and Dominici, 2008).

The data were fitted to a generalized additive model (GAM), assuming a Poisson distribution for the outcome variable. The model included the following variables H_2S, PM_{10}, NO_2, O_3, (exposure variables), temperature, relative humidity, total pollen count, influenza season (background variables), day-of week and holiday binary variables, time trend and seasonal trend (time-dependent variables). For exposure and background variables we included lags up to 14 day (Menichini and Mudu, 2010). We transformed the pollution and weather variables into three-day distributed lag variables; the three-day structure was chosen in an effort to decrease the number of parameters without smoothing the exposure variables too much.

The daily number of individuals who were dispensed a drug was first modeled with single-pollutant models including all other covariates. Effect modification and inter-correlation effects were explored in pairwise two-pollutant models with all other covariates. Finally, all pollutants were introduced into multi-pollutant models. Insignificant background variables were removed (exclusion criteria: $p > 0.05$).

Two versions of the outcome variable, either the number of individuals dispensed any anti-asthma drug or as those dispensed adrenergic inhalants, were modeled with two versions of the exposure variables, either the three-day averages of 24 h mean pollution or the three-day averages of 1 h peak pollution.

Seasonal trends were adjusted for with cubic, cyclical, penalized smoothing splines, as suggested by Gasparrini and Armstrong (2010), with 12 degrees of freedom for the annual cycle with penalty based on second derivatives. Time trend was adjusted for with fixed, cubic smoothing splines with 5 degrees of freedom (approximately 1.5 degrees of freedom per year) without penalization. The number of degrees of freedom was selected based on the existing literature, Akaike's Information Criterion and visual inspection of the splines for signs of overfitting. The final models were inspected with respect to their residuals. The residuals were in accordance with the Poisson and independence assumptions; their over-dispersion was non-significant and their autocorrelation was non-significant. Though we acknowledge that recurring individuals can induce some dependence, we assumed independence between the daily counts. This assumption is supported by the non-significant autocorrelation of the residuals.