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Causality test of ambient fine particles and human influenza in Taiwan: Age group-specific disparity and geographic heterogeneity

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ABSTRACT

Influenza is a major global public health problem, with serious outcomes that can result in hospitalization or even death. We investigate the causal relationship between human influenza cases and air pollution, quantified by ambient fine particles < 2.5 μm in aerodynamic diameter ($PM_{2.5}$). A modified Granger causality test is proposed to ascertain age group-specific causal relationship between weekly influenza cases and weekly adjusted accumulative $PM_{2.5}$ from 2009 to 2015 in 11 cities and counties in Taiwan. We examine the causal relationship based on posterior probabilities of the log-linear integer-valued GARCH (generalized autoregressive conditional heteroscedastic) model with covariates, which enable us to handle characteristics of influenza data such as integer-value, lagged dependence, and over-dispersion. The resulting posterior probabilities show that the adult age group (25–64) and the elderly group in New Taipei in the north and cities in southwestern part of Taiwan are strongly affected by ambient fine particles. Moreover, the elderly group is clearly affected in all study sites. Globalization and economic growth have resulted in increased ambient air pollution (including $PM_{2.5}$) and subsequently substantial public health concerns in the West Pacific region. Minimizing exposure to air pollutants is particularly important for the elderly and susceptible individuals with respiratory diseases.

1. Introduction

Influenza is a contagious respiratory illness caused by the influenza virus, which infects the respiratory tract. It can cause mild to severe illness and could lead to serious illness and life-threatening complications, such as hospitalization and death.

It is widely known that air pollution is a leading cause of human morbidity and mortality throughout the world, particularly in individuals with existing lung disease. Of the most common air pollutants, fine particles < 2.5 μm in aerodynamic diameter ($PM_{2.5}$) can be accumulated in the lung parenchyma, inducing several respiratory diseases (Falcon-Rodriguez et al., 2016), and are associated with an increased risk of exacerbations and respiratory symptoms.

Exposure of fine particles causes reactive oxygen species (ROS), including hydroxyl radical, superoxide from alveolar macrophages and pulmonary epithelial cells. These reactive oxygen species induce ROS-mediated oxidative stress that changes the signal pathway in pulmonary epithelium cell. These signaling pathway is associated with activation of gene transcription, expression of inflammatory molecules such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) and DNA damage inside the lungs. Furthermore, altering the respiratory tract barrier function and antioxidant defenses can cause airway inflammation and significant change of pulmonary function, which may lead to health effects in human lungs including the respiratory effects that cause chronic obstructive pulmonary disease (COPD), asthma and pulmonary fibrosis, and physiological alterations such as decreased lung function, resulting in increased inflammation and exacerbations in patients with COPD (Falcon-Rodriguez et al., 2016). Moreover, long-term inflammation in airway causes cellular changes and epigenetic modifications. This study aims to investigate the association between $PM_{2.5}$ and human seasonal influenza in cities and counties in Taiwan, under the hypothesis that higher exposure concentration is associated with severe lung inflammation and epithelial damage; subsequently humans infected by the influenza virus are likely to have more exacerbating response.

Paulin and Hansel (2016) consider the effects of $PM_{2.5}$ exposure on objective measurements of lung function in both healthy individuals and those with existing lung disease. Chen et al. (2017) examine the relationship between ambient $PM_{2.5}$ and influenza incidences at the national level in China and explore the association under different

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temperatures. Many studies have shown association between changes in air pollution and subsequent changes in respiratory illness or deaths and in various age groups. For example, Chardon et al. (2007) use distributed lag models to determine a significant delayed heath effect of ambient particles ($PM_{2.5}$ and PM_{10}) on the number of doctors' house calls for asthma. Xu et al. (2013) find a significant interaction effect between PM_{10} and mean temperature on pediatric influenza. Schwartz et al. (2015) investigate a causal association between daily $PM_{2.5}$ and deaths in Boston, Massachusetts.

Human infections caused by the 2009 H1N1pmd09 virus were first reported in Mexico in April, which was followed by a global pandemic with many severe illnesses and deaths, many of which were caused by severe pneumonia (Ho et al., 2010). Feng et al. (2016) demonstrate a short-term delay effect with two days and $PM_{2.5}$ was strongly associated with influenza-like illness risk at flu season (from October to April) in Beijing, for all age-groups (p-value < 0.001) when $PM_{2.5}$ concentration is above 70 $\mu g/m^3$. This significant pattern is most pronounced for the middle age-group (age 25–59), closely followed by young adult (age 15–24), then the elderly (> 60 years old) and children (age 5–14). However, small children under 5 years of age had the least association.

The above cited studies reveal a potential pattern of age group-specific disparity and geographic heterogeneity relating to the association that has been established between $PM_{2.5}$ concentration and influenza illness. Therefore, in the present study we focus on whether there is a significant causal relationship between $PM_{2.5}$ and clinical influenza cases in different age groups, as well as any geographical heterogeneity that might exist due to dissimilarity in $PM_{2.5}$ levels.

Granger causality is a method for establishing, via a hypothesis testing paradigm, whether movements in one time series causally correlate to movements in another. We propose modified Granger causality test approaches for five age groups and 11 administrative districts (cities and counties) in Taiwan from 2009 to 2015, during the pandemic and post-pandemic years (see, e.g., Hsieh et al., 2016).

Causality studies have been widely used in environmental health, notably in investigating the associations between exposures to air pollution, weather variables, pollen, etc., and health outcomes such as mortality, myocardial infarction, or disease-specific hospital admissions. Various studies in the literature consider the causal relationship between multivariate time series based on multiple linear regression analysis with the Gaussian assumption.

Bhaskaran et al. (2013) investigate the associations between exposure and outcome based on time series regression, which does not take integer-valued time series into consideration, but instead relies on the Gaussian assumption. The outcome variable in this study is weekly counts (the number of influenza cases). Chen et al. (2017) use a Poisson regression model to estimate the $PM_{2.5}$-influenza association, after controlling for potential confounders. However, Brandt et al. (2000, pp. 824–825) point out that since a regression model for event count includes a lagged dependent variable, the exponentiated coefficient on the lagged variable is no longer an autocorrelation coefficient (as it would be in the Gaussian model). We aim to fill the gap in the literature by developing suitably extensions of the Granger causality test on integer-valued time series.

2. Materials and methods

2.1. Data collection

We access the numbers of weekly influenza cases from Real-time Outbreak and Disease Surveillance System (RODS) on the website of Centers for Disease Control, Ministry of Health and Welfare, R.O.C. (Taiwan CDC, 2017). This surveillance system records the case number of clinical visits in outpatient department of contracted hospitals in Taiwan, defined as “influenza and its associated pneumonia”, from Taiwan National Health Insurance System which provides universal health insurance for all persons living in Taiwan (NHI, 2017).

Fig. 1. Geographical locations of the 11 study sites (in color) in Taiwan.

We consider the numbers of clinical visits since week 1, 2009 to week 52, 2015 at 11 study sites, including Keelung, New Taipei, Taipei, Taichung, Changhua, Nantou, Yunlin, Chiayi, Tainan, Pingtung, and Kaohsiung. We provide the 11 administrative districts in order of their geographical locations, shown in Fig. 1. Moreover, we classify the weekly incident cases from each consultation into five age groups: small children (age 0–4 years), children (age 5–14), adolescent (age 15–24), adults (age 25–64), elderly (age ≥ 65), and the all age-group, in order to estimate age-related pollution effects.

For our clinic-based data, we define the population at risk in a selected study site as the people who live in the study site and making a clinic visit if needed. The weekly number of clinical influenza cases is used to calculate the weekly incidence of each age group in each city from 2009 to 2015.

We retrieve the hourly data of $PM_{2.5}$ from the Environmental Protection Administration, Executive Yuan, R.O.C. (Taiwan, EPA) (EPA, 2017) from January 1, 2009 to December 31, 2015. The hourly data are recorded by an automatic monitoring device from each monitoring station in the 11 cities or counties in western Taiwan that we have selected. We then convert the hourly data into weekly cumulative $PM_{2.5}$ data as follows.

First, we aggregate the original hourly data into cumulative data on the basis of counting valid hours numbering > 17 h in a day, since a valid daily $PM_{2.5}$ is commonly defined as at least 75% of the scheduled sampling days according to United States Environmental Protection Agency (US EPA, 1999). Next, we divide the cumulative data by the valid hours to obtain the hourly average data, which is then multiplied by 24 h to yield the daily $PM_{2.5}$ data. We proceed similarly to define the valid weekly $PM_{2.5}$ data, by requiring the valid number of daily data to be more than four days during a week. We subsequently divide the cumulative data in a valid week by the valid days to obtain the weekly average $PM_{2.5}$ data. The weekly cumulative data is then generated from weekly average data multiplied by 7 days. Finally, adding up the weekly cumulative data of each monitoring station in a study site yields the weekly $PM_{2.5}$ data of each city/county. Our aim in using the cumulative $PM_{2.5}$ data is to preserve the spatial variance of each study site, since each study site has different numbers of monitoring stations, and more importantly, different types of monitoring stations due to heterogeneity in the urban/rural makeup of each city/county.