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Particulate matter modifies the association between airborne pollen and daily medical consultations for pollinosis in Tokyo

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HIGHLIGHTS

- Ambient $PM_{2.5}$ and SPM modify the effect of pollen on daily new cases of pollinosis.
- The cumulative effect of pollen was larger with higher levels of $PM_{2.5}$ and SPM.
- Particulate pollutants may act as an adjuvant to promote pollinosis symptoms.

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ABSTRACT

Pollen from Japanese cedar (*sugi*) and cypress (*hinoki*) trees is responsible for the growing prevalence of allergic rhinitis, especially pollinosis in Japan. Previous studies have suggested that air pollutants enhance the allergic response to pollen in susceptible individuals. We conducted a time-stratified case-crossover study to examine the potential modifying effects of $PM_{2.5}$ and suspended particulate matter (SPM) on the association between pollen concentration and daily consultations for pollinosis. A total of 11,713 daily pollinosis cases (International Classification of Diseases, ICD-10, J30.1) from January to May, 2001–2011, were obtained from a clinic in Chiyoda, Tokyo. Daily pollen counts and the daily mean values of air pollutants ($PM_{2.5}$, SPM, SO_2, NO_2, CO, and O_3) were collected from monitoring stations across Tokyo. The effects of pollen were stratified by the level of $PM_{2.5}$ and SPM to examine the interaction effect of pollen and particulate pollutants. We found a statistically significant interaction between pollen concentration and $PM_{2.5}$/SPM. On days with a high level of $PM_{2.5}$ (>95th percentile), an interquartile increase in the mean cumulative pollen count (an average of 28 pollen grains per cm^2 during lag-days 0 to 5) corresponded to a 10.30% (95%CI: 8.48%–12.16%) increase in daily new pollinosis cases, compared to 8.04% (95%CI: 7.28%–8.81%) on days with a moderate level of $PM_{2.5}$ (5th–95th percentile). This interaction persisted when different percentile cut-offs were used and was robust to the inclusion of other air pollutants. A similar interaction pattern was observed between SPM and pollen when a less extreme cut-off for SPM was used to stratify the effect of pollen. Our study showed the acute effect of pollen was greater when the concentration of air particulate pollutant, specifically $PM_{2.5}$ and SPM, was higher. These findings are consistent with the notion that particulate air pollution may act as an adjuvant that promotes allergic disease (i.e. pollinosis).

1. Introduction

Japanese cedar (*Cryptomeria japonica*) pollen is the most common and potent seasonal allergen causing seasonal allergic rhinitis in Japan (Okubo et al., 2005). A sharp growth in the number of cases of Japanese cedar pollinosis (hereafter termed pollinosis) during the last two decades has led to it being recently described as a 'national affliction' (Yamada et al., 2014). A recent study has documented for instance, how the overall prevalence of pollinosis in Japan rose from 17.4% in 1998 to 26.5% in 2008 (Nakae and Baba, 2010), while other authors have suggested that more than one-third of the population may be currently suffering from pollinosis (Yamada et al., 2014). All age groups are being affected by the occurrence of pollinosis (Okuda, 2003; Ozasa

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et al., 2002), with its associated symptoms of sneezing, rhinorrhea, nasal itching, obstruction, and eye irritation (Tanaka et al., 2012) interfering severely with the daily activities of almost one-third of sufferers during the pollen season (Okuda, 2003) (which usually stretches from February to April each year). Given the extent of its occurrence and the potential severity of its symptoms, pollinosis now constitutes a major public health problem in Japan (Okuda, 2003) with the annual economic losses that result from it estimated to be in excess of 280 billion yen (Yamamoto et al., 2010).

The sharp growth in the prevalence of pollinosis in Japan in recent years may be due to the higher exposure of the population to Japanese cedar pollen antigens, i.e. Cry j 1 and Cry j 2 (Nakae and Baba, 2010; Nakamura et al., 2004), cypress pollen antigens (Ganbo et al., 1995), and to the high cross-antigenecity between these two pollen species. This was highlighted in an earlier Japanese study which showed that 69% of patients who tested positive for cedar antigens were also positive for cypress antigens (Ganbo et al., 1995). The precursor for the current situation lies in the period that followed in the wake of World War II when Japanese cedar and cypress trees were cultivated as a source of cheap building material. Cheaper wood imports from the mid-1960s onward however, meant that most foresters eventually abandoned the industry, leaving these trees – which cover 19% of the land area of Japan – to continue growing unattended (Yamada et al., 2014). This situation may have been further exacerbated by the effect of climate change which has been linked to a possible increase in the amount of pollen aeroallergen (Beggs, 2004). In Japan specifically, the average temperature has increased by 1.15 °C in the past century (Yamada et al., 2014), with researchers linking higher temperatures to the earlier occurrence of the pollen season (Teranashi et al., 2006).

Despite some evidence that cedar pollen counts in Japan *were* significantly higher in the period 1995 to 2013 compared with 1965 to 1994 (Yamada et al., 2014), and that there is a correlation between regional pollen counts and the occurrence of cedar pollinosis (Okuda, 2003), it is also possible that other factors may be affecting the pollen-pollinosis relation. In particular, an early study showed that in areas in Japan where pollen counts were nearly identical, the incidence of pollinosis was higher among residents living along main roads (Ishizaki et al., 1987). Together with this, the fact that more recent research has highlighted that the pollen sensitization rate (and therefore possibly the prevalence of pollinosis) may be higher in urban rather than in rural areas in Japan (Kaneko et al., 2005), even though pollen dispersion might actually be lower in urban areas (Ishibashi et al., 2008), has led to the suggestion that the effects of air pollutants may be important when it comes to understanding the impact of pollen aeroallergens on the occurrence of allergic disease in this setting (Ishibashi et al., 2008; Nakae and Baba, 2010; Williams, 2005). Some support for this notion comes from earlier epidemiological studies which showed that long-term exposure to fine particulate matter ($PM_{2.5}$) was associated with an increased prevalence of hay fever among children in the US (Parker et al., 2009) and in Germany (Morgenstern et al., 2008). However, a follow-up study of these latter children did not support positive associations consistently at older ages (Fuertes et al., 2013), while a recent meta-analysis of several European birth cohorts also failed to find any link between air pollution and allergic sensitization (Gruzieva et al., 2014). Similarly, an earlier study that targeted adults in Germany also found no significant association between the regional concentration of $PM_{2.5}$ and allergic sensitization in urban areas (Bedada et al., 2007).

The idea that air pollutants may have the potential to affect the allegenicity of pollen has been raised by a number of authors previously (D'Amato, 2000, 2002; D'Amato et al., 2010). It has been suggested for example, that air pollution might be interacting with pollen grains to increase the bioavailability of pollen allergens of a different allergenicity (Ghiani et al., 2012; Knox et al., 1997; Motta et al., 2006; Wang et al., 2012). It is also possible that air pollutants might facilitate pollen grains' penetration into the respiratory system (D'Amato et al., 2005). In particular, some evidence indicates that particulate matter has an inflammatory effect on the airways and thus enhances the allergic response in individuals susceptible to pollen allergens (D'Amato et al., 2007).

Gaining a better understanding of the association between air pollution and pollen in terms of subsequent health outcomes may therefore be an important research task. Despite this, to the best of our knowledge, no previous study has examined whether there might be an interaction effect between airborne pollen and air pollution, e.g., if the effect of pollen on allergic disease is greater when there is a higher concentration of particulate matter. This is an important research gap, especially given the fact that Makra et al. (2013) found that in Hungary, the strongest correlations between patient numbers and pollutants were during the *Ambrosia* pollen season compared to the non-pollen season. This may be indicative of an interactive relation between pollen and air pollutants as reflected in poorer health outcomes.

Against this background and building on earlier research which has shown that both airborne pollen (Annesi-Maesano et al., 2012; Ross et al., 1996; Zhang et al., 2012) and air pollutants (Makra et al., 2013; Zhang et al., 2011) are independently associated with medical consultations for allergic respiratory disease, the aim of the current study was to examine both exposures simultaneously to see whether there is a significant interaction between airborne pollen and particulate matter concentration on daily doctor consultations for pollinosis in Japan.

2. Materials and methods

2.1. Clinic visit data

The current study was undertaken in Tokyo, Japan. Like other areas in Japan, the city has experienced a sharp growth in the number of cases of pollinosis in recent years, with its prevalence among the population rising from 18.2% to 28.2% in the period between 1996 and 2006 (Nishihata et al., 2010). We obtained the daily number of consultations for pollinosis (ICD-10, J30.1) from January to May, 2001–2011, from a general practice in the Chiyoda ward of Tokyo (Fig. 1). The medical data were compiled by the same physician using the same criteria throughout the study period for consistency. The study included only the initial consultations with clinical symptoms of pollinosis in a given year, to capture the onset of allergic symptoms during the pollen season. Revisits which were mainly for prescription refills were excluded. Based on interviews and intranasal observation, pollinosis was diagnosed if a patient met two conditions: (1) if they had a prior diagnosis of pollinosis or exhibited nasal symptoms every year during the Japanese cedar pollinosis season; and (2) during the clinic visit they were sneezing, had a running or blocked nose, without signs of other diseases such as the common cold, i.e. fever, sore throat, headache, being present (Nishihata and Saito, 2012). When required specific IgE tests were conducted, otherwise the specific variety of pollinosis (i.e. as being due to Japanese cedar or Japanese cypress pollen) was not differentiated, which was the case for most of the patients. Visits for prophylactic treatment without presentation of pollinosis-related symptoms and revisits for pollinosis treatment were excluded (Nishihata and Saito, 2012). Ethical approval for the study was obtained from the Ethics Committee of the Graduate School of Medicine, the University of Tokyo.

2.2. Pollen data

Daily measurements of the concentration of pollen were available from the Tokyo Metropolitan Institute of Public Health at 9 monitoring locations (Fig. 1) selected to represent the exposure level of patients living in, and commuting to Tokyo from the surrounding areas. The density of pollen from *Cryptomeria japonica* and *Chamaecyparis obtusa* (respectively known as the Japanese cedar and Japanese cypress, or *sugi* and *hinoki* in Japanese) was measured using the Durham method, which involves counting the number of pollen grains that become attached each day (24 h) to a vaseline coated glass slide, fixed inside a