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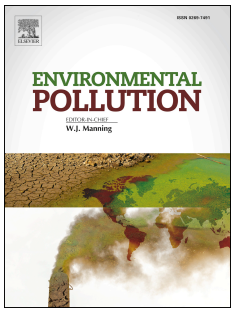

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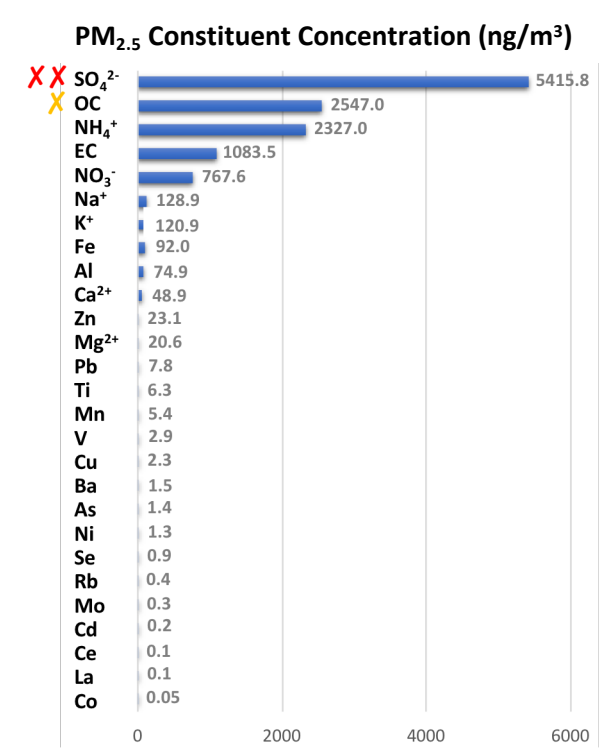
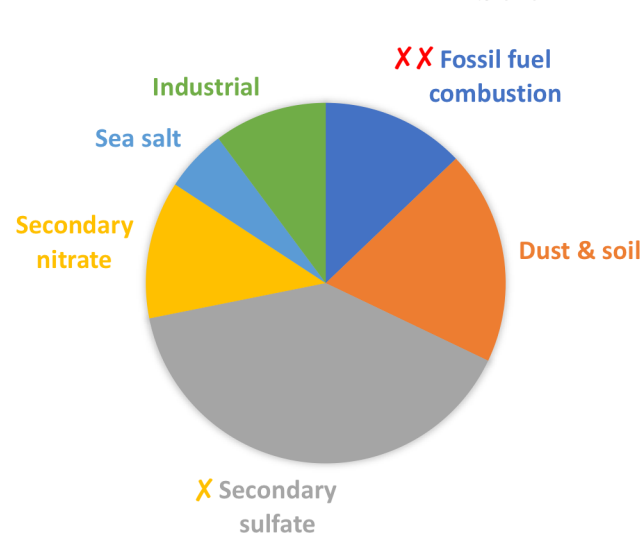


Daily average [SD]
$PM_{2.5}$ total mass:
18.5 [8.3] µg/m^3

Adult with severe asthma
active self-management



XX Associated with lower PEF (from personal monthly max), and robust in 2-pollutant model
X Higher odds of lung function decline (≥15% within 1-week), but not robust in 2-pollutant model

Associations of chemical composition and sources of $PM_{2.5}$ with lung function of severe asthmatic adults in a low air pollution environment of urban Nagasaki, Japan

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Abstract

Previous studies have linked ambient $PM_{2.5}$ to decreased pulmonary function, but the influence of specific chemical elements and emission sources on the severe asthmatic is not well understood. We examined the mass, chemical constituents, and sources of $PM_{2.5}$ for short-term associations with the pulmonary function of adults with severe asthma in a low air pollution environment in urban Nagasaki, Japan. We recruited 35 asthmatic adults and obtained the daily record of morning peak expiratory flow (PEF) in spring 2014-2016. $PM_{2.5}$ filters were extracted from an air quality monitoring station (178 days) and measured for 27 chemical elements. Source apportionment was performed using Positive Matrix Factorization (PMF). We fitted generalized linear model with generalized estimating equation (GEE) method to estimate changes in PEF (from personal monthly maximum) and odds of severe respiratory deterioration (first ≥ 15% PEF reduction within a 1-week interval) associated with mass, constituents, and sources of $PM_{2.5}$, with adjustment for temperature and relative humidity. Constituent sulfate (SO_4^{2-}) and $PM_{2.5}$ from oil combustion and traffic were associated with reduced PEF. An interquartile range (IQR) increase in SO_4^{2-} (3.7 μg/m^3, average lags 0-1) was associated with a decrease of 0.38% (95% confidence interval = -0.75% to -0.001%). An IQR increase in oil combustion and traffic-sourced $PM_{2.5}$ (2.64 μg/m^3, lag 1) was associated with a decrease of 0.33% (-0.62% to -0.002%). We found a larger PEF decrease associated with $PM_{2.5}$ from dust/soil on Asian Dust days. There was no evidence linking total mass and metals to reduced pulmonary function. The ventilatory capacity of adults with severe asthma is susceptible to specific constituents/sources of $PM_{2.5}$ such as sulfate and oil combustion and traffic despite active self-management of asthma and low air pollution levels in the study location.

Keywords: particulate matter; sulfate; oil combustion & traffic; dust; spirometry; asthma

Capsule: Sulfate aerosols and $PM_{2.5}$ from oil combustion and traffic negatively affect lung function of adults with severe asthma in low $PM_{2.5}$ area.

1. Introduction

Inverse association between ambient particulate matter with aerodynamic diameter of ≤ 2.5 μm ($PM_{2.5}$) and respiratory morbidity has been widely documented (Xu et al., 2016; Bell et al., 2009; Bell et al., 2014). Several studies have also documented a negative association between $PM_{2.5}$ and lung function, but the reported risk estimates varied geographically and seasonally (Lagorio et al., 2006; Ma et al., 2008; Wiwatanadate and Liwsrisakun, 2011; Strak et al., 2012; Wu et al., 2014a; Yamazaki et al., 2011). It has been suggested that this heterogeneity could be explained by the mixture of $PM_{2.5}$ chemical constituents, which varied depending on the type of emission sources and their temporal characteristic, thereby resulting in different toxicity across study locations and season (Bell et al., 2007; Hong et al., 2007). These observations highlight the importance to understand how specific chemical constituents and emission sources of $PM_{2.5}$ affect the lung functions of populations in different locations and time period. But research in this area remains limited, especially in low concentration environments such as Japan.

There is also a lack of understanding of how lung function of severe asthmatic individuals, a highly susceptible subgroup, can be influenced by certain chemical species or sources of $PM_{2.5}$. Evidence of association between the overall mass of $PM_{2.5}$/PM_{10} and lung function has been indicated previously in healthy individuals (Chang et al., 2012; Zwozdziak et al., 2016) and the asthmatic (Lagorio et al., 2006; Liu et al., 2009; Ma et al., 2008; Odajima et al., 2008; Wiwatanadate and Liwsrisakun 2011; Yamazaki et al., 2011). Specific chemical constituents of $PM_{2.5}$ and their emission sources have been linked to reduced pulmonary functions in healthy adults (Wu et al., 2013; Cakmak et al., 2014; Wu et al., 2014b). In addition, a study has demonstrated that children without the use of inhaled corticosteroids recorded larger risk estimates associated with exposure to $PM_{2.5}$ total mass, implying potential effect modification by treatment (Liu et al., 2009). Research is therefore pertinent to provide a comprehensive chemical and source-specific characterization of $PM_{2.5}$ exposure among the severe asthmatic.

The current study examines the associations of $PM_{2.5}$ total mass, its chemical constituents, and sources with the lung function of adults diagnosed with severe asthma with ongoing self-management in an urban area in Nagasaki prefecture, Japan. The study focuses on the spring season in consideration of the susceptibility of the region to transported air pollutants including Asian Dust (AD) facilitated by the predominantly westerly winds from the Asia

continent during this period (Guo et al., 2017). Furthermore, the relatively low concentration of $PM_{2.5}$ (daily mean [SD] during the study period = 18.5 [8.3] $\mu g/m^3$; daily mean of 35 $\mu g/m^3$ is the air quality standard in Japan) provides a unique opportunity to study the sensitivity of severe asthmatic adults exposed to a low ambient level.

2. Materials and Methods

2.1. Study participants and health measurements

A panel study was conducted to investigate the short-term association of the chemical constituents and sources of $PM_{2.5}$ with the lung function of adults clinically diagnosed with severe asthma. We recruited patients from Nagasaki University Hospital and Isahaya General Hospital (Fig. S1). Patients diagnosed with chronic obstructive pulmonary disease or enrolled in clinical trials at the time of recruitment were deemed ineligible and excluded. We administered questionnaires to elicit background information such as age, sex, smoking status, disease condition, and existing cardiovascular or respiratory comorbidities. Lung function data were collected prospectively between the year 2014 and 2016, during which participants were instructed to measure their peak expiratory flow rate (PEF, L/min) using a portable peak flow meter (Mini-Wright^{TM}, Clement Clarke, Edinburgh, UK) twice a day – morning and evening – and record the data in a personal diary. We extracted the lung function data for spring season (March to May), a period coinciding with occasional AD events that affect air quality in the region. For data analysis, the following exclusion criteria were applied: participant with home address outside Nagasaki city or Isahaya city (n=1), smokers (n=5), elderly subjects over 65 years of age (n = 25), and subjects with excessive missing data (n = 8), leaving a total of 35 adults (30 from Nagasaki city and 5 from Isahaya city) for the final analysis.

We collected written informed consent from all participants before the study, the protocol for which was approved by the clinical research ethics committee of Nagasaki University Hospital (No. 13062413).

2.2. Environmental data

We obtained daily data on $PM_{2.5}$ and its chemical constituents from the Nagasaki Prefectural Institute of Environment and Public Health. Measurements of outdoor $PM_{2.5}$ ($\mu g/m^3$) were provided by two continuous monitoring stations located near the hospitals in Nagasaki city

and Isahaya city (Fig. S1). Readings from the two stations were highly correlated (r = 0.96). To obtain the chemical elements of $PM_{2.5}$, we extracted the polytetrafluoroethylene (PTFE) and quartz filters from the monitoring station at Isahaya city (Whatman $PM_{2.5}$ PTFE membrane filters and Pallflex Air Monitoring 2500 QAT-UP filters). The filters were automatically replaced at noon every day and collected once a week for analysis. To prevent contamination and improve quantification, field blank filters subject to the same condition of sample collection were deployed, and blank concentrations were used to revise all daily measurements. Filter samples were available on 178 days (March 1 to March 30 in 2014, March 2 to May 31 in 2015, and March 1 to April 26 in 2016 for a total of approximately 6 months). The carbonaceous fractions in the dust particles, organic carbon (OC) and elemental carbon (EC), were measured using the thermal optical reflectance method (Lab OC-EC Aerosol Analyzer, Sunset Laboratory Inc., OR, USA). The ionic components of $PM_{2.5}$ such as sulfate (SO_4^{2-}), nitrate (NO_3^-), ammonium (NH_4^+), sodium ion (Na^+), potassium ion (K^+), magnesium ion (Mg^{2+}), and calcium ion (Ca^{2+}) were determined using ion chromatography; metal components such as aluminium (Al), arsenic (As), barium (Ba), cadmium (Cd), cerium (Ce), cobalt (Co), copper (Cu), iron (Fe), lanthanum (La), manganese (Mn), molybdenum (Mo), nickel (Ni), lead (Pb), rubidium (Rb), selenium (Se), titanium (Ti), vanadium (V), zinc (Zn) were determined using inductively coupled plasma mass spectrometry (ICP-MS). For concentrations below the limit of detection, we substituted the data with values equivalent to half the corresponding detection limit (DL). Chemical species with over 80% of values below DL were excluded from further analysis.

We obtained daily 24-h averages of air temperature (°C) and relative humidity (%) from the Japan Meteorological Agency (JMA). Temperatures were measured at two stations (r = 0.99), while relative humidity at one station in Nagasaki city (Fig. S1).

2.3. Statistical Analyses

We examined PEF measured in the morning because $PM_{2.5}$ chemical constituents were measured from noon to noon. To account for the heterogeneity of lung function across participants, daily individual PEF readings were converted into percent deviations from the personal monthly maximum PEF given as $[(x_t - \max\{x_{m1},\ldots, x_{mn}\})*100/x_t]$, where x_t represents the PEF value on day t in a given year, m represents the corresponding month for day t, and n is the number of days in month m. In addition, to indicate a sign of possible

asthma, we created a binary outcome variable to represent significant respiratory deterioration, computed as 15% or larger reduction in PEF from the personal monthly maximum. The cut-off value was recommended based on expert opinion with consideration to the ongoing self-management of asthma by patients to prevent development of an exacerbation during the study. To exclude repeated deteriorations that might be correlated, we considered only the first incidence (morning or evening) within a rolling 1-week period.

Positive matrix factorization (PMF) receptor model was applied to determine the major sources of $PM_{2.5}$ and their daily contributions to chemical constituents at the study location. Analyses were performed using the US EPA PMF 5.0 (United States Environmental Protection Agency). A total of 27 chemical species were included in the PMF analysis. We down-weighted chemical species with weak correlation between the observed and predicted values (Table S1). For each species, measurements below the DL were replaced with values half the corresponding DL and given an uncertainty of DL*5/6. Missing measurements were replaced with year-specific median and given an uncertainty four times the replacement value. For all other measurements, uncertainty was computed as $0.05*x_i + DL_i$ on sample *i* of a particular species for *n*=178 samples collected (Ito et al., 2004). We selected 6 to 9 factors initially and produced multiple PMF solutions for comparison with existing results from related studies (Suzuki et al., 2014; personal communication with Nagasaki Prefectural Institute of Environment and Public Health). A total of 6 sources were identified after multiple base and bootstrap runs. To minimize rotational ambiguity, we performed factor rotation and the final model has an FPEAK value of -0.1 with a small increase (0.07%) in the *Q*-value (robust). To evaluate the variability of PMF solutions, we performed 500 bootstrap runs and computed interval ratio for each species in a factor (Brown et al, 2015). The final model was then used to estimate the daily levels of $PM_{2.5}$ sources and chemical constituents.

We fitted generalized linear model (GLM) with generalized estimating equation (GEE) method to handle the within-subject correlation using a first-order autoregressive correlation structure (AR1) to investigate the short-term associations of $PM_{2.5}$, its chemical constituents and sources with the decline of PEF (using an identity link function), or the events of severe respiratory deterioration (using a logit link function). Chemical constituents that were potentially harmful based on previous studies were included (Bell et al., 2014; Hong et al., 2010; Lagorio et al., 2006; Wu et al., 2014b) – OC, EC, SO_4^{2-}, NH_4^+, NO_3^-, Al, As, Cd, Cu, Fe, K, Mn, Ni, Pb, Ti, V, and Zn. For each chemical constituent and source, we examined the

single- and multi-day average exposure from lag 0 to 2. Temporal trend in the time series (nearly 6 months) was accounted for using a natural cubic spline of calendar time with 7 degrees of freedom. We included the day of the week, daily mean temperature and relative humidity (both at lag 1), age and sex for adjustment. For constituents or sources that showed evidence of associations in a single-pollutant model (p-value < 0.10), we checked their sensitivity to the other particles or sources by including an adjustment term representing the concentration of total mass. We also checked the sensitivity of the estimates to existing cardiovascular and respiratory diseases. To examine possible effect modification by AD, we extracted the information of AD events reported by JMA (visibility-based) and using an interaction term, we estimated the changes of PEF associated with $PM_{2.5}$ total mass and PMF-resolved sources on the AD and Non-AD days.

Results were reported as percentage changes of PEF from the personal monthly maximum or as odds ratios (OR) of the first severe respiratory deterioration within a rolling 1-week interval and the corresponding 95% confidence intervals for an interquartile (IQR) increase in the level of $PM_{2.5}$ chemical constituents or sources (Table 2). The GLM modeling with GEE method was performed in R version 3.3.3 (R Core Team, 2017) using the *geepack* package (Højsgaard et al., 2006).

3. Results

Thirty five asthmatic adults aged 20 to 65 years were analyzed, providing an average of 208 days of lung function measurements. The average PEF for males and females was 499 L/min and 329 L/min, respectively (Table 1). The largest PEF decrease from the personal monthly maximum was approximately 46% and 52% for males and females, respectively. The frequency of severe respiratory deterioration within a 1-week rolling period ranged from 0-10 times at an average of 3 events per person.

Table 2 summarizes the daily level of $PM_{2.5}$ total mass, composition by carbon, ion, metal, contribution by sources and weather variables. Daily $PM_{2.5}$ averaged 18.5 $\mu g/m^3$ and was composed of mainly SO_4^{2-} (29.4%), OC (15.2%), NH_4^+ (12.8%), EC (6.3%), and NO_3^- (5.1%). PMF analysis resolved 6 profiles to describe the possible sources of $PM_{2.5}$ (Fig. S2). Bootstrap resamples reproduced 100% of all base profiles, except the oil combustion and traffic profile at 89.6%. Interval ratios for the key species in each source profile were generally low, except for those in the dust and soil profile (Fig. S3). The largest contribution

was from secondary sulfate (38.3%), followed by dust and soil (18.5%), oil combustion and traffic (12.4%), and secondary nitrate (11.9%). The concentrations and proportions of chemical species by source profile are described in Table S1 and Fig. S2.

Fig. 1 shows the estimated effects of $PM_{2.5}$ total mass and chemical constituents on PEF or the occurrence of severe respiratory deterioration. There was weak evidence linking SO_4^{2-} and NH_4^+ to a decrease of PEF at lag 1. When averaged across lags 0-1, an increase in SO_4^{2-} was associated with 0.38% reduction in PEF (95% CI: -0.75%, -0.001% for an IQR increase of 3.7 $\mu g/m^3$, Table S2). We observed weak evidence suggesting increased odds of severe respiratory decline for increases in $PM_{2.5}$ and NO_3^- at lag 0. For OC, an increase in the 2-day average level was associated with higher odds of severe respiratory decline (OR: 1.58; 95% CI: 1.002, 2.51 for an IQR increase of 1.8 $\mu g/m^3$, Table S3).

Fig. 2 shows the estimated effects of PMF-resolved sources of $PM_{2.5}$ on lung functions. An increase in oil combustion and traffic source-specific $PM_{2.5}$ level was associated with 0.33% reduction in PEF at lag 1 (95% CI: -0.62%, -0.002% for an IQR increase of 2.64 $\mu g/m^3$, Table S2). A weak negative association with PEF was observed for the secondary sulfate source-apportioned $PM_{2.5}$ averaged across lags 0-1. This source was also associated with higher odds of severe respiratory deterioration at lag 1 (OR: 1.59; 95% CI: 1.18, 2.13 for an IQR increase of 6.65 $\mu g/m^3$), with larger odds estimated for multi-day exposure, i.e. average lag 0-1 (Table S3).

The results of multi-pollutant models are shown in Tables S4 and S5. The significant reductions in PEF associated with sulfate component and the oil combustion and traffic source were fairly insensitive to adjustment for other constituents (Table S4). The significant odds of severe respiratory deterioration associated with OC and the secondary sulfate source were sensitive to adjustment (Table S5). Additional adjustment for existing cardiovascular and/or respiratory diseases had negligible effect on the risk estimates (Table S6 and S7).

Table S8 summarizes the total mass and PMF-resolved sources of $PM_{2.5}$ by the occurrence of AD. Except for the secondary sulfate source, all other air pollutants showed higher concentrations on AD days. There was evidence of effect modification by AD; the estimated effect of $PM_{2.5}$ from dust and soil was larger on AD days (Table S9).

4. Discussion

This study examined the associations of ambient $PM_{2.5}$, its chemical constituents and sources with the lung function of severe asthmatic adults during the spring season in Nagasaki and Isahaya city located on Kyushu island in southern Japan. We found that SO_4^{2-} and $PM_{2.5}$ from oil combustion & traffic source were associated with reduced PEF in adults diagnosed with severe asthma. The associations were observed on the preceding day (lag 1) and remained significant in multi-pollutant models. We also found increased odds of severe respiratory deterioration attributable to increases in OC and $PM_{2.5}$ apportioned to secondary sulfate source, but these associations were attenuated in a multi-pollutant setting. There was weak evidence linking $PM_{2.5}$ total mass to the higher odds of severe respiratory deterioration. None of the metals selected for analysis significantly influenced the lung function of study subjects. We also did not find evidence of effect modification by AD events during the study period.

Results of our study suggest that certain chemical constituents of $PM_{2.5}$ are likely more harmful than others in adults with severe asthma. In the current study, the ambient level of $PM_{2.5}$ was low (mean [SD] of 18.5 [8.3] $\mu g/m^3$), well within the air quality standard in Japan (daily mean of 35 $\mu g/m^3$ or less). We did not find significant evidence of reduced lung function attributable to $PM_{2.5}$ total mass. But the two dominant species, SO_4^{2-} and OC, demonstrated inverse associations. We estimated a very small change in PEF associated with SO_4^{2-}, and the association was robust to the adjustment for other species. In contrast, the estimated effect of OC was sensitive to the same adjustment likely because of collinearity with species originating from the same source (Fig. S2). A panel study of 21 healthy college students in Beijing, China, reported comparable findings, but at higher exposure levels (medians [IQR] of $PM_{2.5}$ mass and sulfate were 57.3 [63.4] $\mu g/m^3$ and 6.6 [15.3] $\mu g/m^3$, respectively) (Wu et al., 2013). The study found an inverse association between sulfate and PEF with an estimated reduction of 0.99% (95% CI: -1.67%, -0.32%) in evening PEF per IQR increase in the 3-day average concentration of the pollutant (15.3 $\mu g/m^3$). The study also reported an association of $PM_{2.5}$ total mass with FEV_1, but not with PEF. The inconsistency has been noted elsewhere (Strak et al., 2012), and might be related to the lower sensitivity of PEF in detecting a small change in the ventilatory function (Giannini et al., 1997). It has also been suggested that PEF measurement requires more effort from subjects (Thiadens et al., 1999), and is more error-prone and less reliable (Wu et al., 2013). The underlying mechanism linking sulfate to lung function at low concentration is not well understood. Exposure may impact pulmonary mechanical function including airway responsiveness, but the reported

effects on asthmatics so far have been inconsistent especially at low air pollutant concentrations (Schlesinger and Cassee, 2003). Sulfate has been implicated to influence the bioavailability of certain metallic species, which contribute to the cytotoxicity of PM (Reiss et al., 2007), but further investigation is necessary to address the association at lower exposure level.

Secondary sulfate emission source was associated with higher odds of severe lung function deterioration in single-pollutant model. The source was marked by high loadings of SO_4^{2-}, NH_4^+, OC, and EC (Table S1 and Fig. S2) and was the largest contributor to ambient $PM_{2.5}$ (38.3%) at the study location. The estimated effect for this source was likely driven by OC for which an association was observed independently (Table S3). Relatively similar source profile has been documented in Seoul (Heo et al., 2009) and Taiwan (Gugamsetty et al., 2012). Studies that reported this source described it as common near industrialized areas where there were high concentrations of sulfur dioxide (SO_2), an important precursor for the formation of secondary sulfates through photochemical or chemical processes (Heo et al., 2009; Gugamsetty et al., 2012; Oguilei et al., 2006; Wu et al., 2014b). In Beijing for example, coal-burning industrial facilities have been implicated as a major source of SO_2 contributing to sulfate level in the city (Wu et al., 2014b). In Baltimore, Maryland, USA, coal-fired power plants have been linked to high sulfate loading through the analysis of wind direction, which demonstrates the possibility of long-range transport (Oguilei et al., 2006). The mixing of local and transported secondary sulfate was also observed in a study in Detroit, Michigan, USA (Morishita et al., 2006), where high sulfur concentration exceeding the capacity of local sources was recorded, indicating the possibility of transported secondary sulfate particles from distant industrial sources and power plants. In Seoul, Korea, a multi-year source-apportionment study has suggested two possible sources of transported sulfate aerosols that affected the city – the industrial areas on eastern coastal China and emissions from the ships on Yellow Sea (Heo at al., 2009). Indeed, findings from a study conducted at Fukuoka city and Fukue island in Japan supported the supposition of long-range transport (Suzuki et al., 2014). The study showed that aerosol concentrations at the two study sites were affected by coal combustion emissions originating from continental Asia, as well as by emissions from marine ships. These findings imply susceptibility of the study location to both local and transported sulfate aerosols in the region given the proximity and the downwind travel of continental air masses.

Oil combustion and traffic source showed a consistent association with reduced ventilatory capacity in adults with severe asthma. This source was characterized by high loadings of V, Ni, Se, and Mo (Fig. S2). Previous studies conducted in Beijing (Yu et al., 2013) and Taiwan (Gugamsetty et al., 2012) have reported comparable source profile with the exception of Mo. V and Ni are known tracers for oil combustion and traffic emissions, respectively. Some known examples of oil combustion sources are oil-fired power plants, ships, and heating oil (Lee et al., 2011; Bove et al., 2016), while for traffic emission, gasoline and diesel engines are commonly reported (Lin et al., 2015; Shafer et al., 2011). Mo was not commonly observed in this source profile but when highly correlated with Cu, might indicate wear debris from road traffic as suggested in a study of traffic-derived particles (Lin et al., 2015). In the current study, the correlation between the two was high (Spearman's $\rho = 0.85$) implying road traffic related contributions. Se has been attributed to coal combustion (Morishita et al., 2006), but in the current study a large proportion of the element was also found in another PMF-resolved source profile labeled as industrial emission source (Fig. S2), which did not exhibit a relationship with lung function.

Whereas a negative association was observed with the oil combustion and traffic source, we did not detect similar association with the individual trace elements, i.e. V and Ni. A possible explanation is the variety of sources producing these elements. For example, it was noted previously that besides traffic/oil combustion, V and Ni could also be emitted by marine vessels and industrial sources (de Foy et al., 2012). Consequently, PMF-resolved source-specific particles might show an association when the individual element aggregated from multiple sources does not, or vice-versa (Bell et al. 2014). Other possible explanations include inconsistency in measurement quality and uncertainties in the source-apportionment method and the measures of constituents. Notwithstanding, V and Ni have been previously linked to negative respiratory health outcomes. A study based on a birth cohort recruited in New York city between 1998 and 2006 found that V and Ni were associated with wheezing symptoms among children aged 2 years or younger (Patel et al., 2009). A multi-city study using data from 106 counties in the US reported an increased risk of respiratory hospitalization associated with the same-day concentration of V and Ni (Bell et al., 2009). Another US study based on Medicare data comprising populations aged 65 years and over observed similar short-term associations for both chemical species (Bell et al., 2014). On the contrary, a study in Hong Kong did not find any association between the elements and respiratory emergency hospitalizations (Pun et al., 2014).

We found evidence suggesting a larger lung function decline was associated with dust and soil source-related $PM_{2.5}$ on AD days (Table S9). This was not observed with $PM_{2.5}$ mass or other sources. A study conducted at a nearby city of Fukuoka to study the relationship between suspended particulate matter (SPM) and asthma hospitalization of children under 12 years old did not find evidence of effect modification by AD (Ueda et al., 2010). In Seoul, Hong et al. (2010) found that AD did not substantially modify the potency of metals on the lung function of schoolchildren. Different definitions of AD have been used. For example, Nakamura et al. (2015) utilized multiple criteria such as the concentration of SPM, Light Detection and Ranging (LIDAR) extinction coefficient, and the correlation between SPM and LIDAR. The authors reported an association between AD days and emergency department visits for bronchial asthma and other respiratory diseases among children at a medical facility in Nagasaki. Kanatani et al. (2010) conducted a study in western Japan using LIDAR monitoring of mineral dust particles (non-spherical particles, a marker of AD events) and reported an association with asthma hospitalization among children. Watanabe et al. (2016) analyzed the same LIDAR data and reported reduced PEF in asthmatic adults attributable to heavy AD days. These findings indicate the potential impact of AD on asthmatics.

The current study contributes to existing evidence in several ways. First, it showed that severe asthmatics with active treatment were susceptible to specific chemical constituent/source of $PM_{2.5}$. Second, to our knowledge, the study is one of the first to investigate the health impact of exposures on asthmatics in an environment with generally low air pollutant concentrations. Lastly, the study reported possible effect modification by AD which increased the risk of exposure to specific particle source.

There are several limitations worth noting. Our exposure data came from a fixed monitoring station with no spatial information. The analysis was therefore unable to capture the spatial heterogeneity of chemical constituents or source-apportioned concentrations. Single-station measurements, which represent the average exposure levels in a population, were assigned as personal exposure in the current study. This might result in Berkson-type measurement error that produces little to no bias but reduces statistical power (Zeger et al., 2000). Another limitation is the potential confounding by covarying constituents. Our current method of adjustment did not account for potential confounding by covarying constituents, which could be addressed using different methods, for example, model residuals although results would

not be directly comparable (Mostofsky et al., 2012). Our study did not have information on indoor air pollution. Hence, for constituents with indoor sources, the discrepancy between the true ambient concentration and average personal exposure may introduce a classical error that can result in underestimation of associations (Mostofsky et al., 2012). We also had no information on airborne pollen which was prevalent during the spring season and might trigger/aggravate asthma symptoms. Further research is necessary to understand the mechanism of how air pollen might influence exposure to $PM_{2.5}$ constituents/source profiles. There was no data on daily mobility and activity of study participants, and no complete daily information on their respiratory symptoms, medications, and personal characteristics (e.g. height and weight) which might be necessary to account for between-subject variability. The source profiles resolved in the current study location might have unique particle mixtures that limit interpretability in another location, despite the same labels. Some chemical constituents might act as surrogates for other air pollutants including those not examined in this study. We have tested the sensitivity of effect estimates in multi-pollutant models, but the adjustment for other chemical species/sources might have resulted in a multicollinearity problem, making it difficult to identify the significant chemical species/sources given their correlation with the $PM_{2.5}$ total mass.

5. Conclusions

We conducted a study to examine the association of $PM_{2.5}$, its constituents, and sources with the lung function of severe asthmatic adults in urban Nagasaki, Japan. There was evidence of lung function deterioration associated with sulfate particles and $PM_{2.5}$ from oil combustion and traffic source. OC and $PM_{2.5}$ from secondary sulfate source were also associated with decreased respiratory capacity even though their estimates were not robust to the adjustment of other pollutants. Findings suggest that despite their ongoing treatment and the overall low air pollution level, asthmatic adults might still be affected by specific $PM_{2.5}$ constituents and sources. Further research with larger sample size, longer study period, and more personal exposure information to confirm the results will be beneficial.

Financial interest

All authors have no competing financial interest.

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Appendix A. Supplementary data

Supplementary material is available at http://dx.doi.org/XXXXX.

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599 **Table 1** Characteristics of study subjects.
600

	Male (n = 11)					Female (n = 24)				
Characteristic[a]	**Mean**	**SD**	**Median**	**Min**	**Max**	**Mean**	**SD**	**Median**	**Min**	**Max**
Age (years)	52.7	10.8	47	38	65	50.4	12.8	51	20	65
Lung Function										
Number of measurement (day)	199.4	87.5	186	31	276	212.6	58.7	226.5	78	276
PEF (L/min)	499.3	86.4	530	280	690	328.7	88.2	340	130	640
Monthly maximum PEF (L/min)	516.1	76.8	530	380	690	355.9	91.8	360	160	640
Decrease from monthly maximum (%)	-4.3	4.7	-3.4	-46.2	0	-8	7.5	-6.1	-51.7	0
Decrease ≥ 15% (event/person)	6.9	14.7	0	0	49	28.9	46.7	3.5	0	158
First decrease [b] ≥ 15% within a week period (event/person)	1.6	2.4	0	0	8	3.7	3.4	2	0	10

[a] All non-smokers.
[b] include morning and evening measurements

Table 2 Summary of fine particulate matter ($PM_{2.5}$), its chemical constituents, sources, and weather variables.

	Mean	SD	Median	IQR	% of $PM_{2.5}$ total mass
$PM_{2.5}$ (μg/m^3)	18.5	8.34	17.79	10.13	–
Carbon (μg/m^3)					
OC	2.82	1.34	2.60	1.80	15.2
EC	1.17	0.80	1.00	0.77	6.3
Ion (μg/m^3)					
SO_4^{2-}	5.44	2.93	5.00	3.70	29.4
NH_4^+	2.36	1.41	2.20	1.70	12.8
NO_3^-	0.95	1.37	0.46	1.14	5.1
Metal (μg/m^3)					
Al	0.0711	0.0638	0.0530	0.0635	0.384
As	0.0014	0.0012	0.0011	0.0010	0.008
Cd	0.0002	0.0002	0.0002	0.0001	0.001
Cu	0.0023	0.0016	0.0022	0.0016	0.013
Fe	0.0899	0.0619	0.0820	0.0560	0.486
K	0.0001	0.0001	0.0001	0.0001	0.001
Mn	0.0056	0.0040	0.0047	0.0042	0.030
Ni	0.0013	0.0008	0.0011	0.0007	0.007
Pb	0.0078	0.0077	0.0057	0.0047	0.042
Ti	0.0063	0.0046	0.0053	0.0045	0.034
V	0.0026	0.0019	0.0021	0.0016	0.014
Zn	0.0259	0.0207	0.0220	0.0190	0.140
Source (μg/m^3)					
Oil combustion & traffic	2.30	1.96	1.95	2.64	12.4
Dust & soil	3.42	2.96	2.72	3.05	18.5
Secondary sulfate	7.09	5.12	6.29	6.65	38.3
Secondary nitrate	2.21	3.57	0.82	2.86	11.9
Sea salt	1.01	1.08	0.76	1.00	5.4
Industrial	1.82	2.57	1.05	1.66	9.8
Weather					
Temperature (°C)	15.8	4.4	16.5	5.9	–
Relative humidity (%)	69.7	12.3	68	17	–

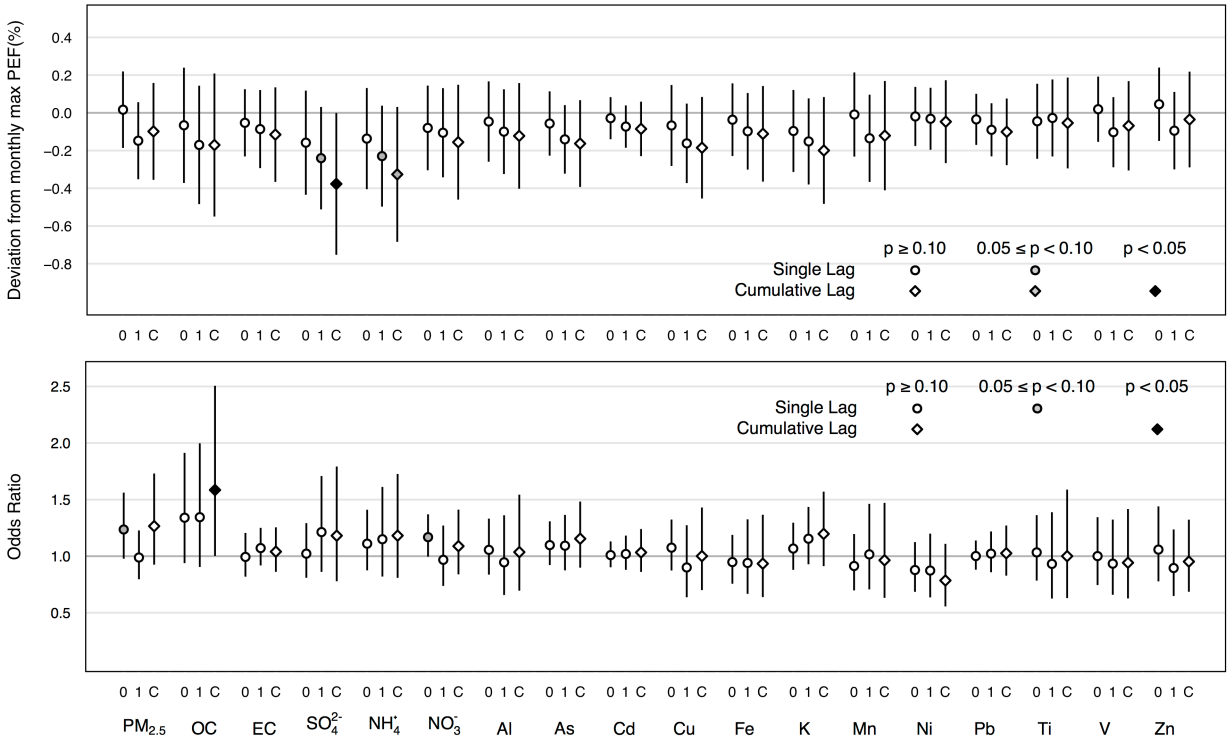
642 **Figure Legends**

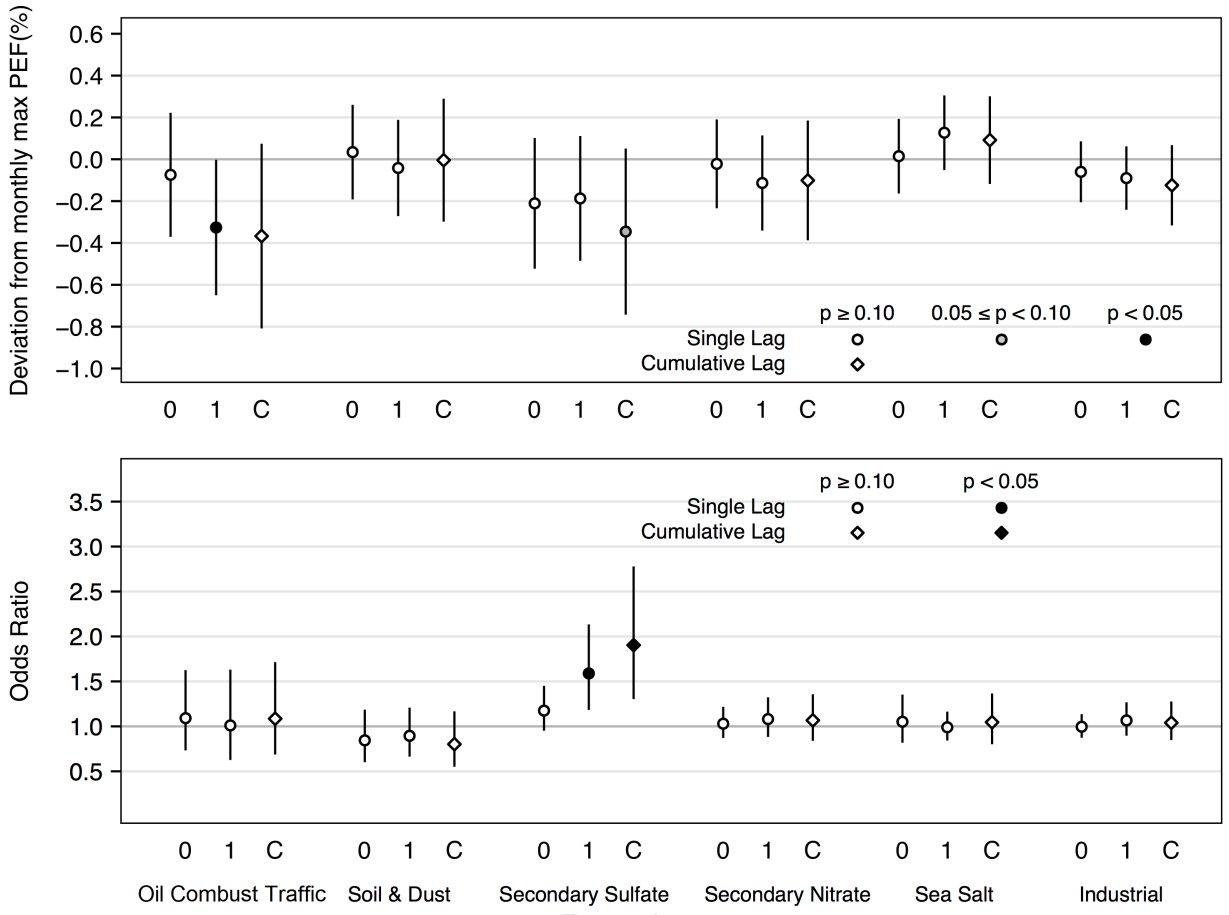
643

644 **Fig. 1.** Percent change of PEF rate from personal monthly maximum (top panel) and odds
645 ratios of the first 15% or more decrease of PEF from personal monthly maximum (bottom
646 panel) within a rolling 1-week interval for an IQR increase of $PM_{2.5}$ total mass or chemical
647 constituents at lag 0, lag 1, and the average denoted by "C" or cumulative lag. Refer to Table
648 2 for the IQR values.

649

650 **Fig. 2.** Percent change of PEF rate from personal monthly maximum (top panel) and odds
651 ratios of the first 15% or more decrease of PEF from personal monthly maximum (bottom
652 panel) for an IQR increase of the PMF-resolved source-specific $PM_{2.5}$ concentration at lag 0,
653 lag 1, and the average denoted by "C" or cumulative lag. Refer to Table 2 for the IQR values.




Deviation from monthly max PEF(%)
0.6
0.4
0.2
0.0
−0.2
−0.4
−0.6
−0.8
−1.0
p ≥ 0.10
0.05 ≤ p < 0.10
p < 0.05
Single Lag
Cumulative Lag
0 1 C 0 1 C 0 1 C 0 1 C 0 1 C 0 1 C
Odds Ratio
3.5
3.0
2.5
2.0
1.5
1.0
0.5
p ≥ 0.10
p < 0.05
Single Lag
Cumulative Lag
0 1 C 0 1 C 0 1 C 0 1 C 0 1 C 0 1 C
Oil Combust
Traffic
Soil & Dust
Secondary Sulfate
Secondary Nitrate
Sea Salt
Industrial

Highlights:

- Lung function of asthmatic adults was inversely associated with sulfate in $PM_{2.5}$.
- $PM_{2.5}$ from oil combustion & traffic reduced peak expiratory flow rate (PEF).
- Reduction associated with $PM_{2.5}$ from dust & soil was larger on Asian Dust days.
- No evidence linking total mass and selected metals to reduced lung function.
- Sensitivity to specific constituents/sources was suggested despite low $PM_{2.5}$ level.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: