Desert-dust exposure is associated with increased risk of asthma hospitalization in children

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Online Data Supplement

Methods

Study design

The present study used a case-crossover design, which is an analytic technique designed to assess the effect of transient exposure on the risk of acute illness, and has been increasingly used in epidemiological studies investigating acute effects of ambient air pollution (E1). In this design, the exposure frequency during a time window immediately before the illness onset (hazard period) is compared with the exposure frequency during control periods when no illness followed. As each case serves as its own referent, the design has the ability to control by design rather than by statistical modeling for potential confounding caused by fixed individual characteristics including measured and unmeasured variables (E2). The case-crossover design is able to control for time trends in the data through the use of information both before and after the events (E3).

In this study, four controls were matched to each hospitalization, ±2 weeks and ±4 weeks. In this approach, day of the week was also controlled by design. When the subjects were in the hospital on the control day, that day was excluded from the control because the patient was not at risk for hospitalization on that day, and a substitute control day was selected from ±3 weeks or ±5 weeks. The study protocol was approved by the Human Research Protection Program of the University of California, San Diego.

Setting

The study location was Toyama, Japan; a local prefecture about 50 km in diameter, with a population of about one million, and with no area-specific air pollution problems reported. It is located almost in the middle of Japan, facing the Japan Sea, and surrounded by 3000 m mountains (Figure E1). The usual main constituent of the aerosol particles in this area was reported as non-sea-salt derived SO_4^{2-} and NH_4^+ (E4). Aerosol particles presumably also contained diesel exhaust and other pollutants typically observed usually in urban locations in the study situation.

Toyama is occasionally susceptible to Asian dust events usually in spring, and thereby the study duration was determined as between February and

April each year, from 2005 to 2009, when exposure data (LIDAR data) was available.

Hospitalization data

Data were obtained from the hospitalization records of eight principal hospitals, which are located within 50 km from where the exposure data (LIDAR data) was obtained in Toyama, Japan (Figure E2). Asian dust comes in a large cloud (Figure E1 and E3) that sometimes covers all areas in Western Japan, and therefore we considered that the dust measurements were applicable to patients who were admitted in those hospitals (E5, E6). Potential cases were children aged 1-15 years, who had at least one hospitalization with the admission diagnosis of asthma in any of the eight principal hospitals in Toyama between February and April, from 2005 to 2009. 'Hospitalization' referred to actual inpatient admission, and did not include an emergency visit that did not end in admission. Children <12 months of age or with serious cardiovascular or respiratory diseases other than asthma were excluded, as the diagnosis of asthma in these groups may be un-reliable. We *a priori* defined the first hospitalization of the year as cases, and excluded the subsequent hospitalizations from the analysis because, after initial admission, patients were considered at higher risk for subsequent hospitalization.

Dust, air pollution, and meteorological data

Mineral-dust data and other air pollution data were obtained from The National Institute for Environmental Studies in Japan, and meteorological data were obtained from the Japan Meteorological Agency. The pollen data was obtained from the Japan Weather Association. In the local area during the study period, cedar was the major source of pollen, and cypress pollen was also observed in a lesser amount. The mineral-dust data as well as non-mineral-dust data were based on measurement by the LIDAR system with a polarization analyzer, which distinguishes mineral-dust particles (non-spherical particles) from non-mineral-dust particles (spherical particles); that is, while PM2.5 and PM10 differentiate the size of particles but do not differentiate mineral-dust from non-mineral dust (sphere or non-sphere), the LIDAR system does not differentiate the size of particles but does differentiate the shape of particles (E7-E11). Thus, the LIDAR system could specifically measure quantity of mineral dust. Daily (24-hour) average values were obtained for both a non-spherical extinction-coefficient, which was converted into mineral-dust particle mass concentration by a formula, and a spherical extinction coefficient, which was converted into non-mineral-dust particle mass concentration (E12, E13).

A heavy-dust-event day *a priori* was defined as the day when the daily average dust extinction coefficient in Toyama, measured by LIDAR under 1km height from the ground, recorded more than 0.1 /km, which corresponded to 0.1 mg/m^3 mineral-dust particles (E12, E13). This was the standard threshold for particulate matter, and the threshold for a public announcement of Asian dust arrival on the LIDAR homepage run by the Ministry of the Environment in Japan. For the main analysis, exposure status of a patient's hazard/control period was defined as exposed when at least one of the days during the hazard/control period was a heavy-dust-event day, and was defined as un-exposed when neither of the days during the hazard/control period was a heavy-dust-event day.

There were missing values for the non-spherical extinction coefficient on some snowy, foggy, or rainy days. These missing values were treated as 0 /km, which corresponded to 0 mg/m^3 in density, taking into account their capturing the particles to the ground, presumably resulting in a very low particulate concentration in the air.

The spherical extinction coefficient and the non-spherical extinction coefficient (/km) were converted to mass concentration (mg/m^3) by using the following formulae (E12, 13).

$$\text{Mass concentration } (mg/m^3) = F * \text{extinction coefficient } (/km)$$

F= 1000 (for non-spherical extinction coefficient, that is, for mineral-dust)

$$F=566-6.24 * X + 5.56\ e^{-2} * X*X - 4.62\ e^{-4} * X*X*X$$

(X=Relative humidity) (for spherical extinction coefficient, that is, for non-mineral-dust)

Gaseous NO_2 was measured by a wet photometric analysis or by a dry chemiluminescence analysis, gaseous SO_2 was measured by a dry ultraviolet absorption analysis, and gaseous Ox was measured by an ultraviolet absorption analysis. Suspended particulate matter (SPM), which was any particle collected with an upper 100% cut-off point of 10 μm aerodynamic diameter, and a 50% cut-off diameter for which is assumed to be approximately 7 μm, that is, PM7, was measured by a β ray attenuation method and pollen was measured by the Durham method. (E13-E15)

Statistical Analysis

Initially, a conditional logistic regression analysis was performed using hospitalization as the dependent variable and heavy-dust-event (>0.1 mg/m^3) as the independent variable (1; heavy dust event on any of the hazard/control period, 0; no heavy-dust-event on any of the hazard/control day) changing the hazard/control period from one to seven days to determine the crude odds ratio (OR) of heavy-dust-events for asthma hospitalization. Possible confounding climatic variables (daily average temperature, temperature difference from the previous day, temperature difference within the day, air pressure, air pressure difference from the previous day, humidity, and wind speed; variables were analyzed as continuous or dichotomous depending on the distribution of the variable) were examined if each had an increased OR for asthma hospitalization with various cut-off values and various lag-structures up to lag 0-6 (days 0 to 6). Cross-correlations of the variables were examined, and a conditional logistic regression analysis was conducted using outcome as the dependent variable (1; hospitalization, 0; control), and, as independent variables, heavy-dust event on any day during the previous 7 days, (0; no heavy-dust-event on any of the previous 7 days), and climatic variables that showed apparent ($p<0.1$) increase of OR for asthma hospitalization in the precedent analysis (average temperature, air pressure difference from the previous day, and humidity). Other air pollutants (gaseous NO_2, gaseous SO_2, gaseous Ox, non-mineral-dust particle, and pollen; variables were analyzed as five level nominal or dichotomous with various cut-off level; median, 80 percentile, 90 percentile and 95 percentile, and with various lag-structure up to 7 days) were examined if each had an increased OR for asthma hospitalization. The effect of these pollutants on the OR of heavy-dust event for asthma hospitalization was examined with a two-pollutant model approach in all the above models. We also determined the best-fitted model for each pollutant with a cut-off level and a lag-structure that showed the strongest association with asthma hospitalization among all the above models, Finally, we conducted a conditional logistic regression to obtain the best-fit OR using hospitalization as the dependent variable and, as independent variables, heavy-dust event, the climatic variables described above, and other air pollutants described above with a cut-off value and a lag structure that showed the strongest association with asthma hospitalization for each.

Additionally, we conducted the same conditional logistic regression analysis using particulate matter, which has been conventionally used as an exposure measurement for dust particles and does not differentiate mineral-dust particle from other particles.

The same conditional logistic regression analysis was conducted on each sub-group of sex and age defined *a priori* (ages 1-5 years, 6-12 years, and 13-15 years). A conditional logistic regression analysis was tried in each sub-group using hospitalization as the dependent variable and heavy-dust-event on the day (lag 0) or on the day with various lag-periods (lag 1 to lag 6) as the independent variable, to see when the risk for asthma hospitalization was increased by a heavy-dust-event in each group.

Also examined was how the OR increased in accordance with an increase in cut-off value for the mineral-dust level to examine if lower-level mineral-dust also influenced the asthma hospitalization.

R software (R version 2.9.2 for Windows; R Foundation, www.r-project.org) was used for statistical analysis.

Results

Associations between asthmatic hospitalizations and mineral-dust level with non-cumulative lag structure

Figure E5 shows crude ORs of heavy dust event for asthma hospitalizations on the day of admission (lag 0) or on the day some days before admission (lag 1 to lag 6), that is, by non-cumulative lag-structure. The risk for hospitalization was high on the day of heavy-dust-event (lag 0) and also on 4 to 6 days after the event (lag 4, lag5, and lag 6). In particular, the risk on the first day of the exposure was high for boys and for elementary school ages (6-12 years of age), while girls and infants (1-5 years of age) showed an increased risk later in the week.

Associations between asthmatic hospitalizations and mineral-dust level with various cut-off value

Figure E6 shows how the OR increased in accordance with an increase in cut-off value for the mineral-dust level (hazard/control period: a week). It seemed that mineral-dust level above 0.02 mg/m^3 raised the risk of hospitalization and we conducted a conditional logistic analysis excluding cases/controls with mineral-dust level above 0.08 mg/m^3, to investigate if lower-level mineral-dust (0.02 mg/m^3 to 0.08 mg/m^3, which was observed on about 25% days during the study period) raises the risk, compared with the mineral-dust level less than 0.02 mg/m^3. The odds ratio of mineral-dust level 0.02-0.08 mg/m^3 for hospitalization was 1.31 (95% CI: 1.07-1.60, p= 0.0097).

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Table E1 Correlations between each pollutants and climatic factors

	Mineral dust	Non-M. dust	Pollen	Gaseous NO_2	Gaseous SO_2	Gaseous Ox
Mineral dust	1	0.014	0.168	0.013	0.241	0.189
Non-mineral d.	0.014	1	-0.078	-0.149	0.052	0.046
Pollen	0.168	-0.078	1	0.013	0.082	0.002
Gaseous NO_2	0.013	-0.149	0.013	1	-0.357	-0.672
Gaseous SO_2	0.241	0.052	0.082	0.357	1	-0.018
Gaseous Ox	0.189	0.046	0.002	-0.672	-0.018	1
Ave. Temp	0.310	0.050	0.217	-0.038	0.166	0.466
Air pressure	-0.055	-0.024	0.035	0.249	0.080	-0.367
Air Pre. Diff.	0.036	0.058	-0.006	-0.189	-0.155	0.029
Humidity	-0.280	0.125	-0.280	-0.082	-0.315	-0.305

Non-M dust; non-mineral dust, Ave. Temp; average temperature, Air Pre Diff.; air pressure difference from the previous day

Table E2 Crude odds ratio of each climatic variables for asthma hospitalization

	Odds ratio	(95%CI)	p value
Temperature on the day (°C)	0.992	(0.973-1.012)	0.429
Temperature on the previous day (°C)	0.979	(0.959-0.999)	0.035
Temp. diff. within the day (°C)	1.014	(0.989-1.039)	0.279
Humidity on the day (%)	0.994	(0.987-1.001)	0.087
Humidity on the previous day (%)	0.992	(0.985-0.999)	0.028
Wind speed on the day (m/s)	0.987	(0.953-1.022)	0.446
Air pressure on the day (hPa)	1.006	(0.9923-1.020)	0.382
Air press. diff. from previous day (hPa)	0.987	(0.973-1.001)	0.074

Definition of abbreviations: CI = confidence interval, Temp. diff. = temperature difference, Air press. diff. = air pressure difference

ONLINE FIGURE LEGENDS

Figure E1 Location of Toyama prefecture, Japan and representative distributions of Asian dust on May. 5 2010 forecasted by Chemical weather FORecasting System (CFORS)

CFORS calculates the distributions numerically with CPU-cluster utilizing information about atmospheric conditions, land surface usage, and emission inventories.

Figure E2 Locations of LIDAR and the eight hospitals in Toyama

Figure E3 Representative Moderate Resolution Imaging Spectroradiometer (MODIS) image on Mar. 21, 2002

Figure E4 Crude odds ratios for the relationship between asthma hospitalizations and heavy dust events defined by suspended particulate matter (daily average level above 0.1 mg/m^3 of suspended particulate matter) on the day of the admission (lag 0) or the previous 1-7 days (lag 0-1 to lag 0-7)

Error bars represent 95% CIs.

Figure E5A Crude odds ratios of heavy-dust-event for asthma hospitalizations on the day of admission (lag 0) or on the day some days before admission (lag 1 to lag 6), that is, by non-cumulative lag structure.

Error bars represent 95% CIs.

Figure E5B Crude odds ratios of heavy-dust-event for asthma hospitalizations on the day of admission (lag 0) or on the day some days before admission (lag 1 to lag 6) in each sex group.

Error bars represent 95% CIs.

Figure E5C Crude odds ratios of heavy-dust-event for asthma hospitalizations on the day of admission (lag 0) or on the day some days before admission (lag 1 to lag 6) in each age group.

Error bars represent 95% CIs.

Figure E6 Crude odds ratios for asthma hospitalizations with various cut-off values in exposure-status of mineral-dust particle level on any day during the previous week of admission

Error bars represent 95% CIs.

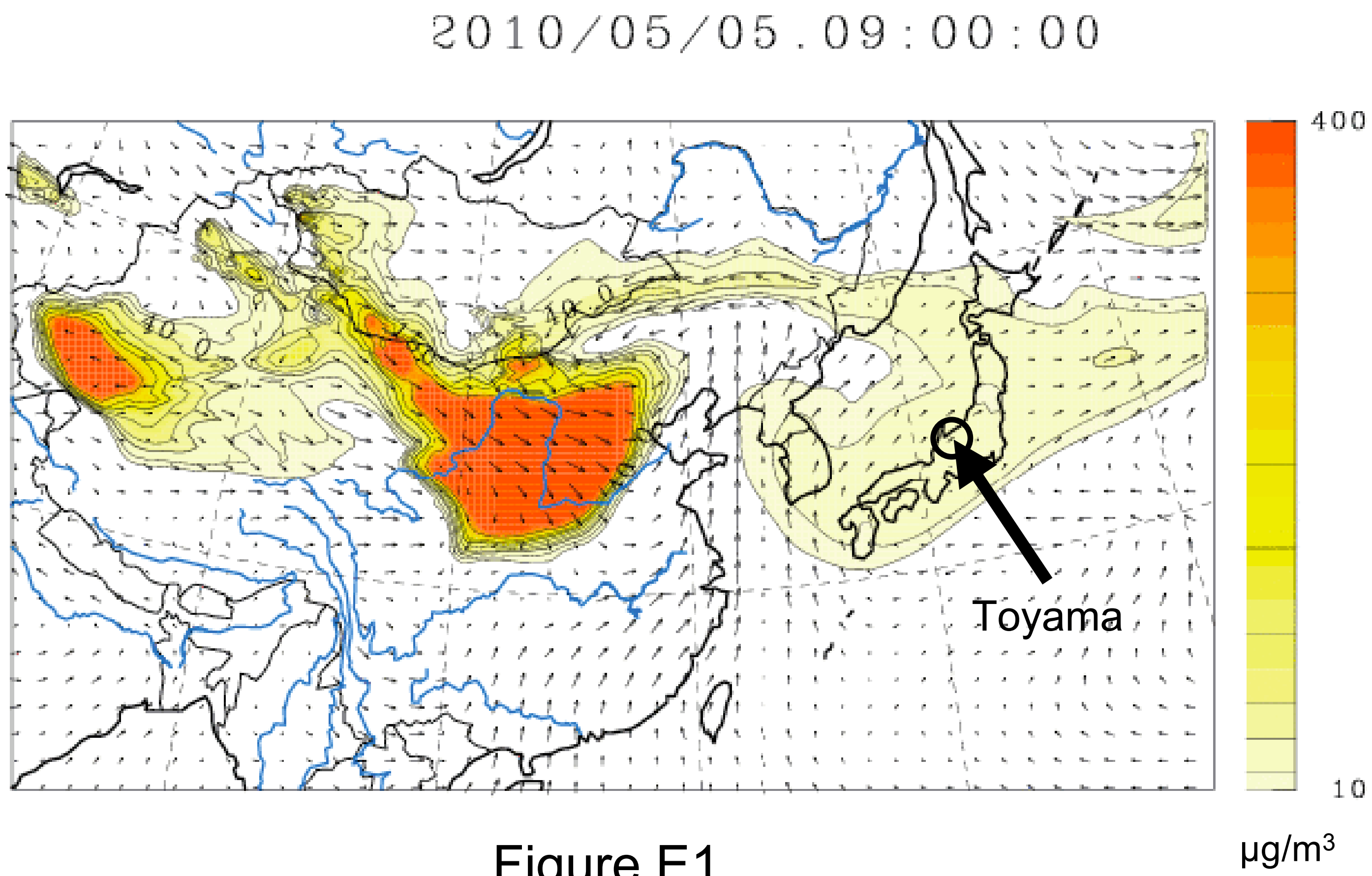


Figure E1

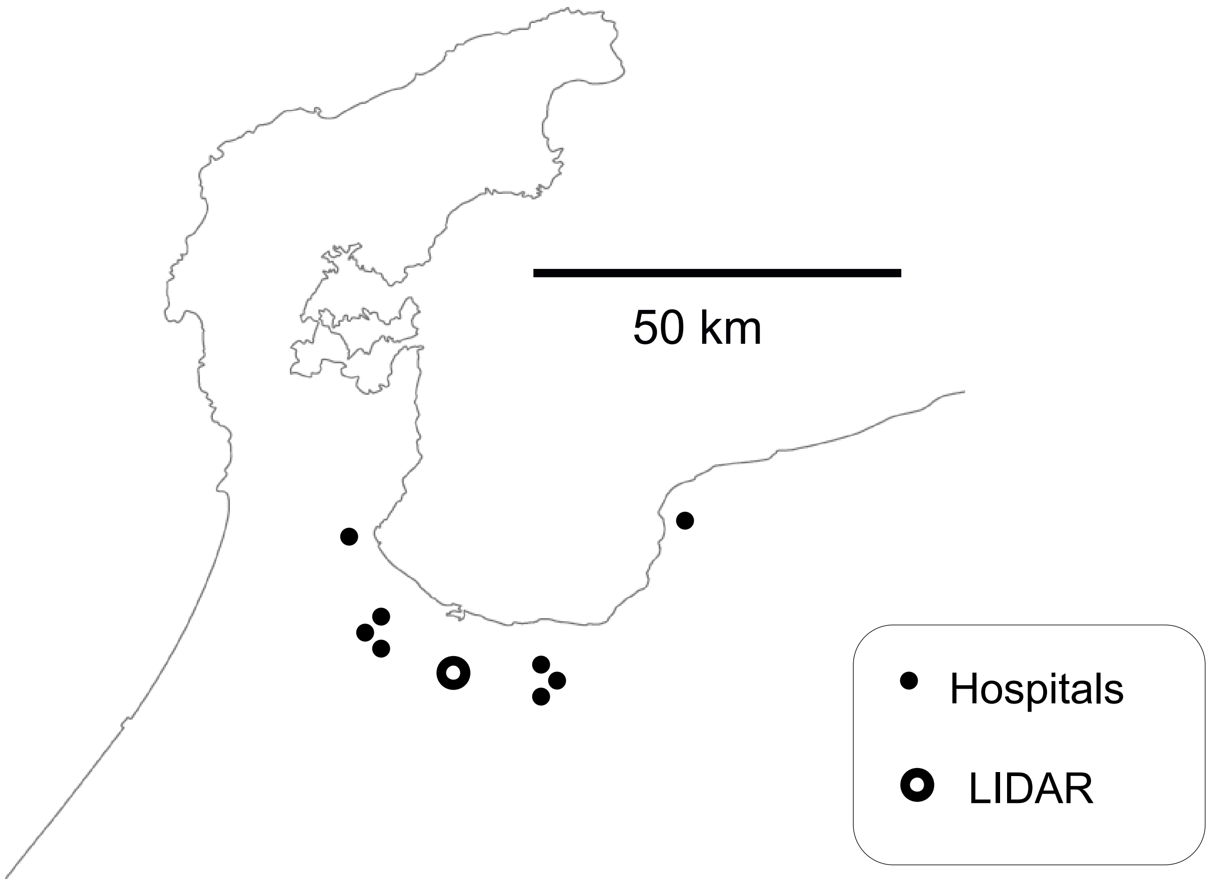


Figure E2

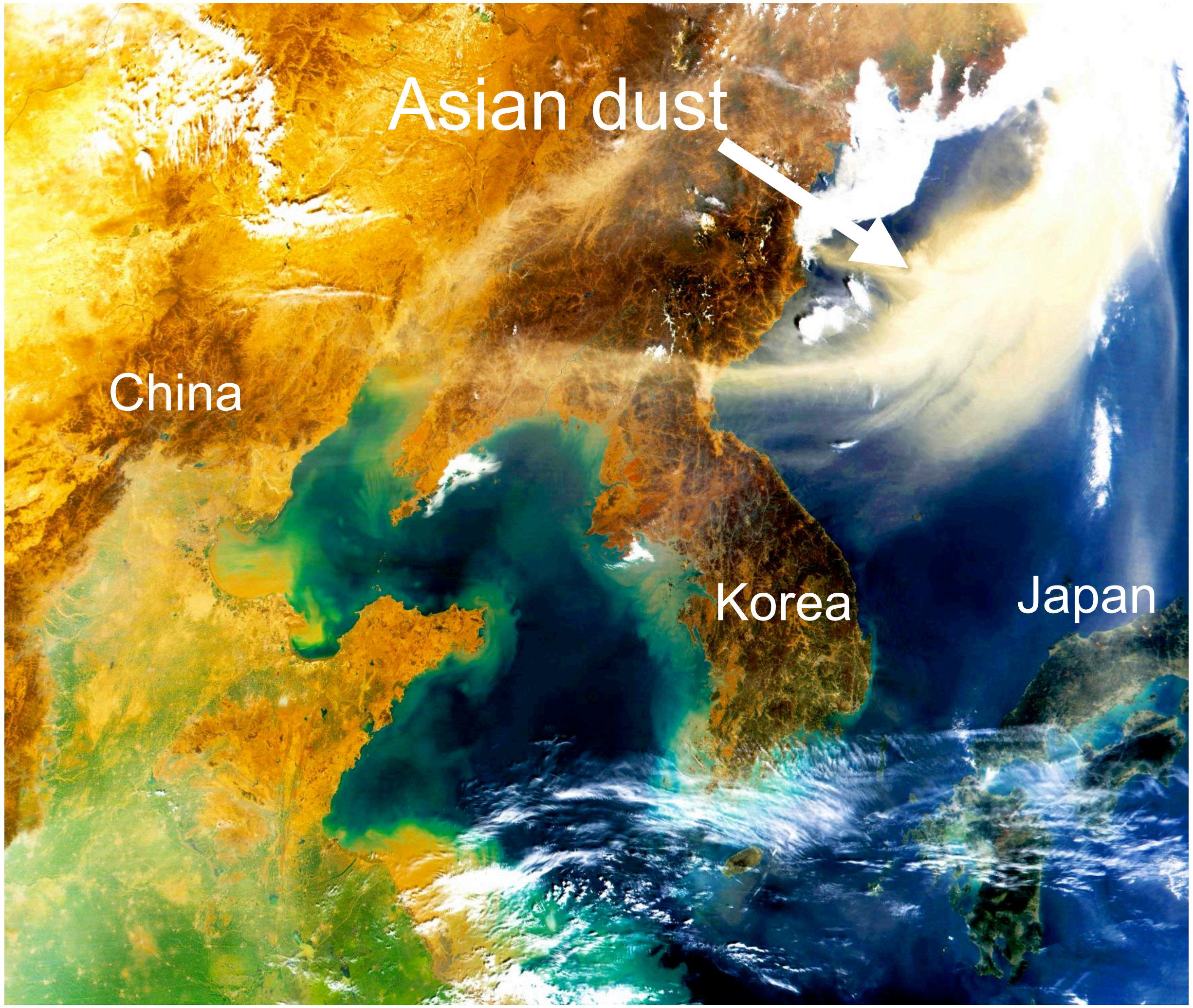
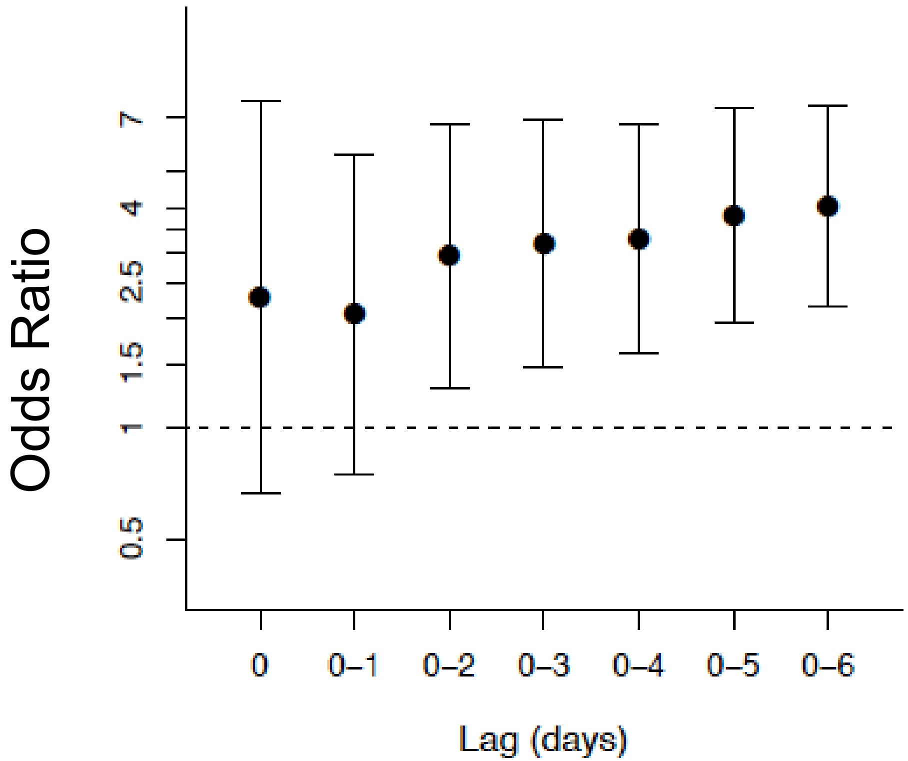


Figure E3



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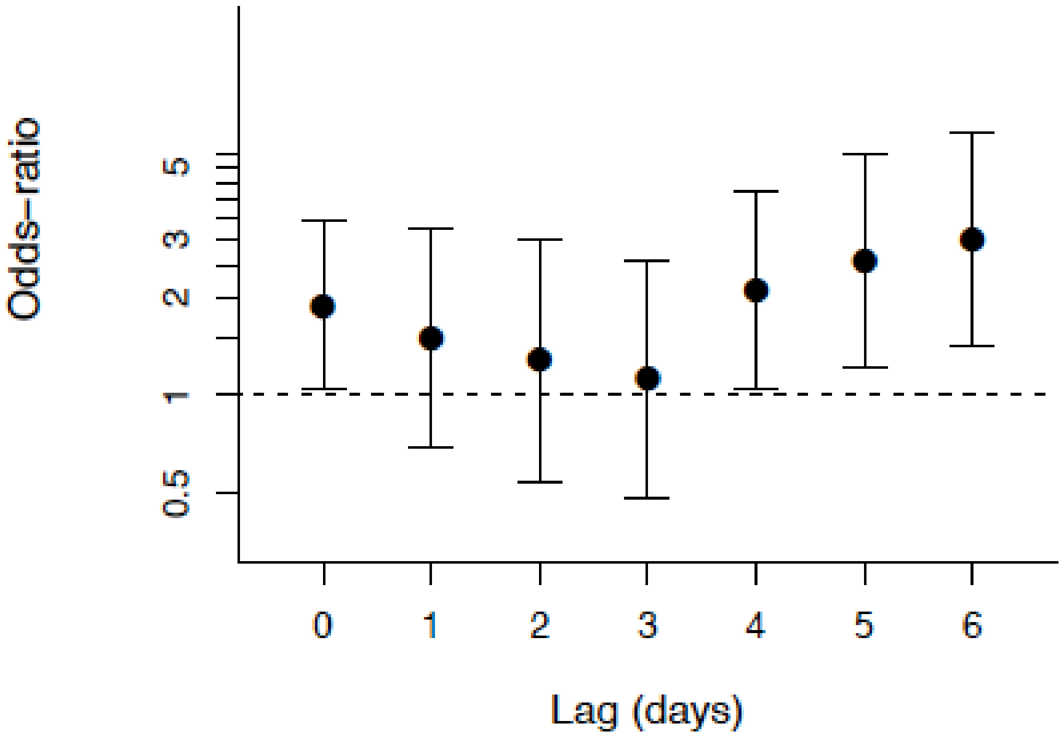


Figure E5A

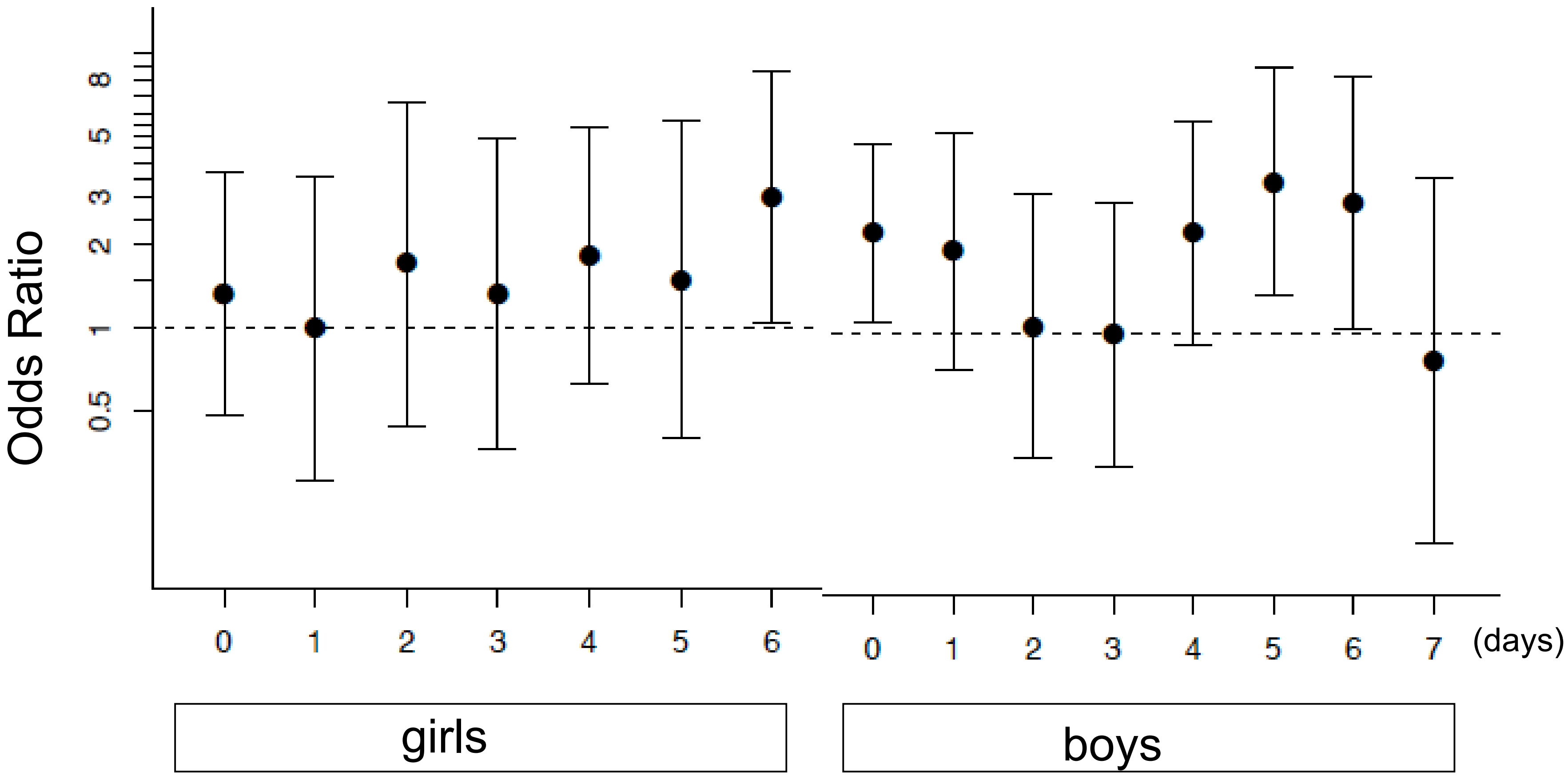
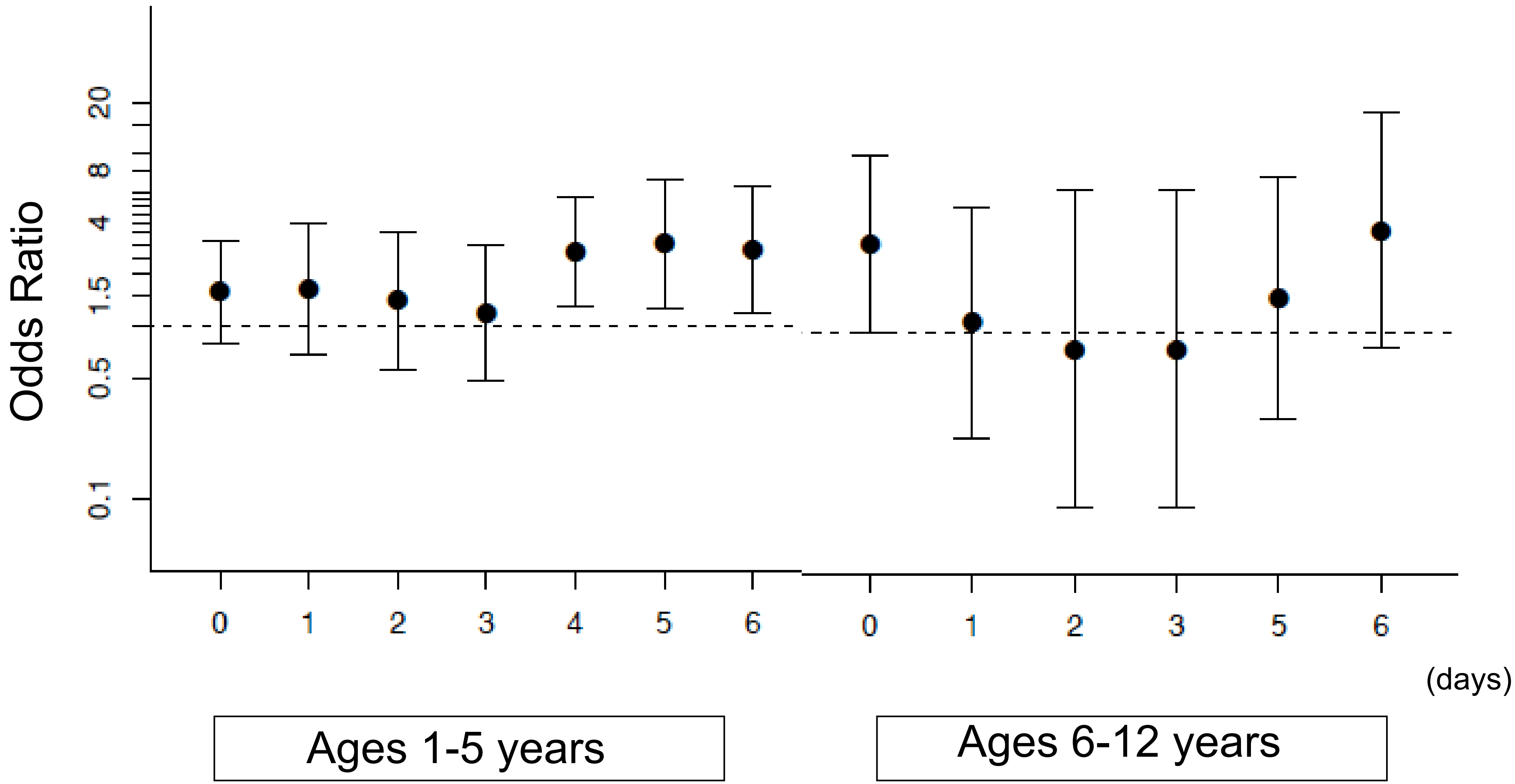


Figure E5B



Odds Ratio
20
8
4
1.5
0.5
0.1
0
1
2
3
4
5
6
0
1
2
3
5
6
(days)
Ages 1-5 years
Ages 6-12 years

Figure E5C

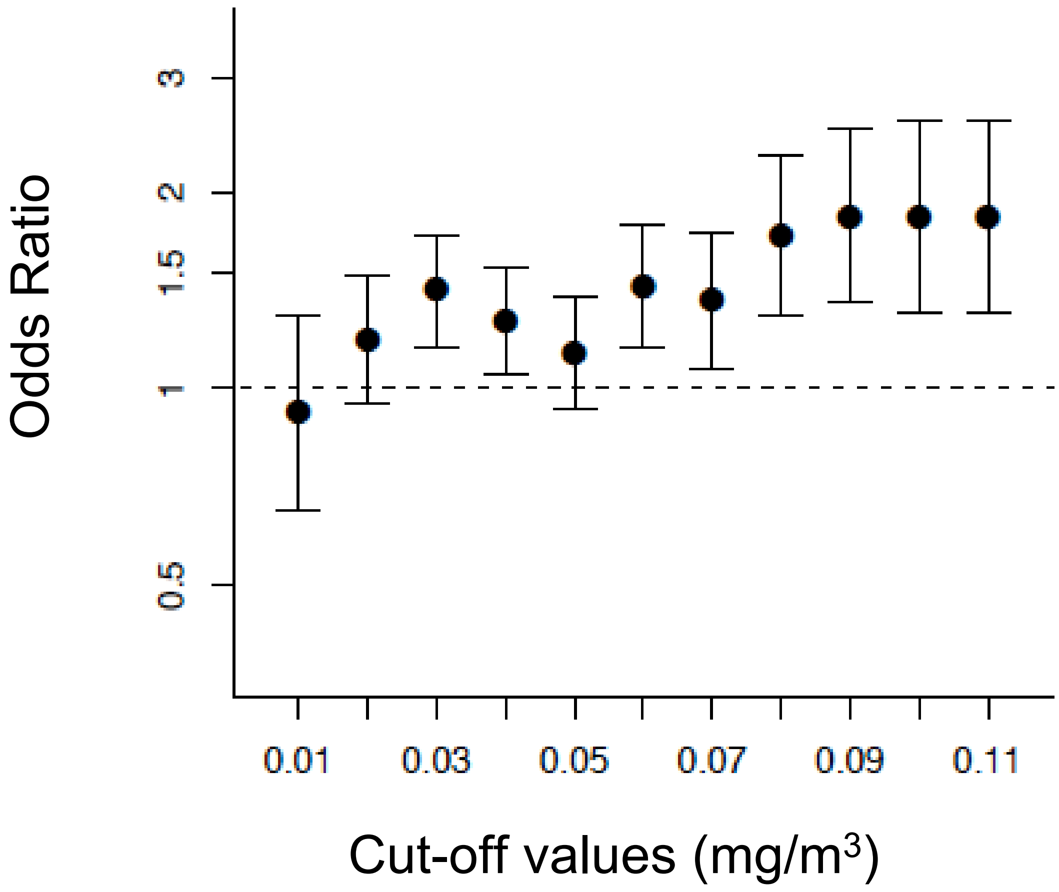

Odds Ratio
3
2
1.5
1
0.5
0.01
0.03
0.05
0.07
0.09
0.11
Cut-off values (mg/m³)

Figure E6