

BMJ Open Birth cohort study on the effects of desert dust exposure on children's health: protocol of an adjunct study of the Japan Environment & Children's Study

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ABSTRACT

Introduction: Desert dust is estimated to constitute about 35% of aerosol in the troposphere. Desertification, climatic variability and global warming all can contribute to increased dust formation. This study aims to examine possible health effects of desert dust exposure on pregnant women and their children. The purpose of this report was to present the study protocol.

Methods and analysis: This 4-year birth cohort study began in 2011 as an adjunct study of the Japan Environment & Children's Study (JECS) involving three regions: Kyoto, Toyama and Tottori. The JECS participants of the three regions above who also agreed to participate in this adjunct study were enrolled prior to delivery. Light Detecting and Ranging (LIDAR) with a polarisation analyser, which can distinguish mineral dust particles from other particles, is used for exposure measurements. Outcomes are allergic symptoms for mothers and development of asthma and other allergic or respiratory diseases for their children. Data are acquired in a timely manner by connecting local LIDAR equipment to an online questionnaire system. Participants answer the online questionnaire using mobile phones or personal computers.

Ethics and dissemination: The study protocol was approved by the ethics committees of Kyoto University, University of Toyama and Tottori University. All participants provided written informed consent. The results of this study will be published in peer-reviewed journals and disseminated to the scientific community and general public.

Trial Registration number: UMIN000010826.

INTRODUCTION

Desert dust and human health

Aerosol particles are produced by a variety of natural and anthropogenic processes, with desert dust estimated to constitute about

Strengths and limitations of this study

- In this cohort study, data on environmental exposure during the period from pregnancy to early infancy, as well as potential confounding sources, are collected. A comprehensive analysis of this information will allow us to explore the role of desert dust exposure on allergic/respiratory diseases.
- Web-based questionnaires connected to an environment measurement system allows for providing the questionnaire only at necessary times, and reduces the burden on participants.
- Participants' mobile phones or personal computers are used to access the web-based questionnaires. Those who do not use either type of device were excluded. One of the weak points of the study is the lack of consistency in the type of device used to answer the questionnaires.

35% of aerosol mass with diameter smaller than 10 µm.¹ Mulitza *et al*² reported a sharp increase in desert dust emissions that paralleled the advent of commercial agriculture in the Sahel region, suggesting that human-induced dust emissions have contributed to the atmospheric dust load for about 200 years. Desert dust particles are principally composed of rock-forming minerals such as quartz, and clay minerals such as mica and kaolinite. Additional particle analysis revealed the presence of microbial agents such as bacteria, fungi, fungal spores and viruses^{3–6} as well as anthropogenic atmospheric pollutants likely absorbed during transport.⁷

Recent evidence has revealed several possible negative effects of these dust particles

on human health. Administration of desert dust sand to murine bronchi exerted adjuvant effects in the airway^{8 9} and inhalation of desert dust by patients with mild asthma caused a significant decrease in forced expiratory volume.¹⁰ Epidemiological studies showed that desert dust events were associated with health outcomes such as exacerbated asthma in Spain, the Caribbean, Japan, Korea, China, Taiwan and other locations.^{11–21} Although many studies on urban pollution have examined direct associations and vulnerable populations, as well as possible countermeasures and their effectiveness^{22 23} only a few have quantified direct associations between desert dust and human health.²⁴ Several facets of desert dust exposure remain unknown, such as its long-term effects on healthy and vulnerable populations, who the vulnerable populations are, whether it increases the incidence of asthma or sensitisation against allergens, what components of the dust particles exert negative health effects, if there are any effect modifiers, how to reduce the effects and if it influences long-term disease progression such as outgrowing asthma. This information would be particularly important for future public health measures, because growing evidence suggests that the three main factors affecting desert dust activities—desertification, climatic variability and global warming—all can contribute to increased dust formation.^{2 25 26}

People in developed countries spend approximately 90% of their time indoors.²⁷ We found that the arrival of Asian dust (desert dust from China and Mongolia) caused a 50-fold increase in particulate counts outdoors and a 20-fold increase indoors (in apartments) under everyday conditions, with window and air purifier use dramatically affecting indoor particulate counts.²⁸ Minimising air pollutant exposure to reduce the risk of symptom exacerbation is viewed as a common sense solution and may lead to biased estimates of the impact of pollution exposure on health. For our cohort, we wanted to obtain information quickly on individual behaviour to lessen this bias and estimate how much risk from dust exposure can be reduced by avoidance behaviour.

Mobile phone/internet use and its application to epidemiological studies

As of 2010, 95% of all Japanese households owned mobile phones²⁹ and 99% of households with individuals aged 20–49 years used the internet.³⁰ Appropriate leveraging of these web-based communication tools can enhance epidemiological research beyond conventional studies, particularly when targeting younger participants. The expected advantages over traditional methods include convenience for the participant, as well as potentially large cost savings and efficient data collection for the researcher.^{31–35} On the other hand, web-based surveys have several limitations, such as sampling problems, lack of participant access to computers with internet connections and internet privacy concerns.^{31 33 35}

More studies are likely needed to quantify better the risks and benefits of conducting web-based survey research.³¹

Our birth cohort examines possible effects of desert dust exposure on health outcomes, using web-based questionnaires connected to an environment measurement system, allowing for the collection of information within a short time frame. This report aims to inform the relevant research community of our study objectives, design and progress.

Objectives

This study has the following objectives: (1) long-term effects; examine possible effects of desert dust exposure on the development of allergies or asthma in infants, (2) short-term effects; worsening of respiratory and allergic symptoms in pregnant women and (3) perform further analysis to examine the modification potential of long-term and short-term effects, including the degree to which the effect is lessened by avoidance behaviour, or enhanced by coexistence of other pollutants including pollen, identification of groups vulnerable to dust exposure, exploration of possible local differences in effects of desert dust exposure, and what in the dust particle exerts the effects, and to understand further the benefits and limitations of web-based questionnaires by comparing demographic characteristics between web-based survey responders and non-responders and examining the consistency of web-based answers to paper-based answers. The primary hypothesis is that the development of asthma at the age of four in those exposed to high level of desert dust is more than 1.5 times greater than those exposed to low level of desert dust.

METHODS AND ANALYSIS

Setting: the Japan Environment & Children's Study and its adjunct study 'Effects of desert dust exposure on children's health'

The Japan Environment & Children's Study (JECS) is an ongoing birth cohort study that began in 2011 and evaluates the impact of various environmental factors on children's health and development. A total of 100 000 children and their parents took part across 15 regions in Japan^{36 37} with follow-up programmes to examine health periodically from the early stages of pregnancy until the participating child reaches 13 years of age.

Exposure to environmental factors is assessed by chemical analyses of bio-specimens including blood, household environment measurements and computational simulations using monitoring data, as well as questionnaires.³⁶ The main eligibility criteria are: (1) residence in the study areas, (2) expected delivery date between 1 August 2011 and mid-2014 and (3) capable of participating in the study without difficulty.³⁶ The JECS allows additional investigations, or adjunct studies, pertaining to the main study. 'Effects of desert dust exposure on children's health' is our adjunct study involving three JECS regional centres in

Kyoto, Toyama and Tottori (figure 1). These regions are located in western Japan, with Kyoto in a basin while Toyama and Tottori face the Sea of Japan. All three regions have urban, suburban and local areas, but the Kyoto region is the most urban of these three, and includes part of Kyoto city (population, 1.5 million). The Toyama region includes Toyama city (population, 420 000), and the Tottori region includes Yonago city (population, 150 000). There are no known area-specific air pollution problems in these regions. Asian dust is a seasonal event, and areas in western Japan, including these regions, experience yellowish air for several days in spring and autumn, when dust blows from the Asian continent. The year-average suspended particulate matter (SPM) levels in the study regions are around $15 \mu\text{g}/\text{m}^3$, and day-average SPM can increase up to $70 \mu\text{g}/\text{m}^3$ during Asian dust events. For PM_{2.5}, the year-average levels in these regions are about $10\text{--}15 \mu\text{g}/\text{m}^3$, and day-average PM_{2.5} can increase up to $50 \mu\text{g}/\text{m}^3$ during Asian dust events and on some other days (eg, when pollutant plumes arrive from the Asian continent).

Sample selection

JECS participants in the three regions who also agreed to participate in this adjunct study were enrolled before delivery. Enrolment started in August 2011 and ended in March 2014. All participants provided written informed consent. Of the 7038 eligible pregnant women who enrolled in the JECS in Kyoto, Toyama or Tottori regional centres in 2011 and 2012, 3425 provided consent forms for this adjunct study as of the end of 2012 (figure 2). The median duration between enrolment and expected delivery was 95 days (mean, 98 days; maximum, 218 days) as of the end of 2012. Eligible participants who enrolled after 2012 were added to the study in an ongoing manner. Mobile phones/personal computers are not provided to potential participants who do not have them, in view of the high penetration of these devices in the target population.



Figure 1 Investigated regions in the adjunct study.

Study design

Study design protocols are shown in figures 3 and 4. Those who participated in the JECS at Kyoto, Toyama or Tottori regional centres were informed of this adjunct study. Those who agreed to participate were provided access to the URL for the baseline web-based questionnaire. The URL of the web-based questionnaire for assessing individual exposure level and allergic symptoms is sent to the participants' mobile phones on the day dust is observed and on some randomly selected days during the Asian dust season (February–May, and October–November). Symptom development is compared between exposed days and non-exposed days. The effect modification potential of avoidance behaviours, vulnerability characteristics and coexistence of other air pollutants including pollen are investigated using the two-factor model with interaction terms. Exposure to SPM and PM_{2.5}, which have been used to investigate the effects of particulate matter, are also examined. Sampling of particulate matter in the air (total suspended particulate) is also conducted at each location every day during the Asian dust season, with a plan to perform chemical/biological analysis to explore what components in the dust exert the effects, or what can be effect modifiers. A web-based questionnaire for child outcomes is sent every 6 months after the child is born until the child reaches the age of 4 years. Participants answer the questionnaire using their personal mobile phones or personal computers by the set time limit (within 28 h after issue). The development of asthma or

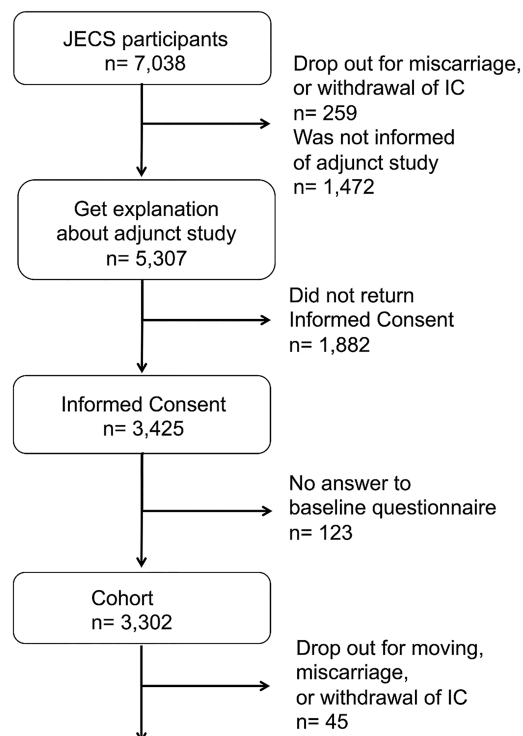


Figure 2 Participants in the Japan Environment & Children's Study (JECS) and the adjunct study as of the end of 2012.

other allergic diseases is compared between those exposed to high or low levels of desert dust. Time to development of asthma or other allergic diseases between the two groups is also examined.

Sample size

The primary objective of this study was to assess the association between desert dust exposure and asthma development in children. A sample of 9000 children will give 80% power to detect an OR of 1.5 at the 5% significance level between children exposed to high and low levels of desert dust, assuming the incidence of asthma in those with low exposure is 1.5%. We also evaluated the sample size needed for our secondary objective, which is to assess the association between desert dust exposure and allergic symptom worsening in pregnant women, and confirmed that the sample size used for the primary objective is sufficient.

Measurements

Demographics

On study enrolment, baseline information such as history of asthma or any other allergic diseases is collected via the web-based questionnaire. In addition, various lifestyle parameters such as diet, exercise, family environment and housing environment are obtained during the course of the JECS. Serum samples are collected three times during pregnancy for the JECS, and the remaining serum will be used to measure levels of vitamin D and inflammatory cytokines in some participants. Details of measurement items are presented in [table 1](#) and the questionnaire is shown in online supplementary appendix.

Exposure

Asian dust days were defined in the protocol as days during which the Light Detecting and Ranging (LIDAR) system measured more than 0.07/km of desert dust (day median) at an altitude of 135 m based on previous

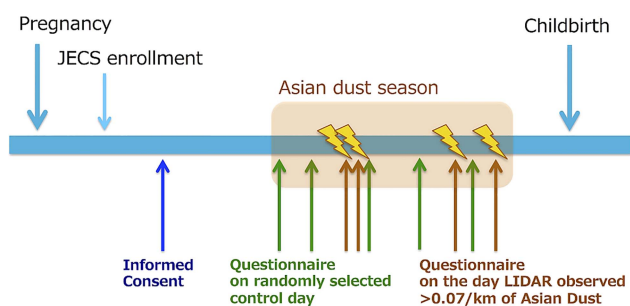


Figure 3 Adjunct study protocol during pregnancy.

A web-based questionnaire for assessing individual exposure level and allergic symptoms is issued on the day dust is observed (brown) and on some randomly selected days (green) during the Asian dust season (February–May, and October–November) (JECS, Japan Environment & Children's Study; LIDAR, Light Detecting and Ranging).

studies.^{17 18} LIDAR is an optical remote sensing technology that measures properties of scattered light to obtain information on a distant target. In combination with a polarisation analyser, it can distinguish non-spherical dust particles from other spherical particles.^{17 38–41} On Asian dust days, a self-administered questionnaire is automatically issued to participants and the URL is sent to their mobile phones and/or personal computers. The various questions asked are shown in the online supplementary appendix. An identical questionnaire is sent for comparison on other days during the Asian dust season to randomly-selected participants with about 10% probability each day. SPM and PM_{2.5} are also measured at each location, and the same analysis will be performed for exposure measurements.

Outcome

For outcome measurement of allergic disease development in infants (long-term effects on infants), a self-administered questionnaire is sent to mothers via mobile phone every 6 months after childbirth. The questionnaire includes the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire⁴² and physicians' diagnoses of asthma and other allergic diseases (see online supplementary appendix). We defined asthma development as persistent wheezing and/or physician's diagnosis of asthma or asthmatic bronchitis. For measurement of day-to-day symptoms (short-term effects on pregnant mothers), a self-administered questionnaire including items from a Japanese version of the Allergy Control Score⁴³ is issued to participants via mobile phones and/or personal computers. We will compare the proportion of those with any symptom (symptom score above 0) between Asian dust days and control days.

Statistical analysis plan

(1) For the primary analysis (long-term effects on infants), we compare the development of asthma at the age of four between highly exposed and lowly exposed (lower than the first quantile and higher than the

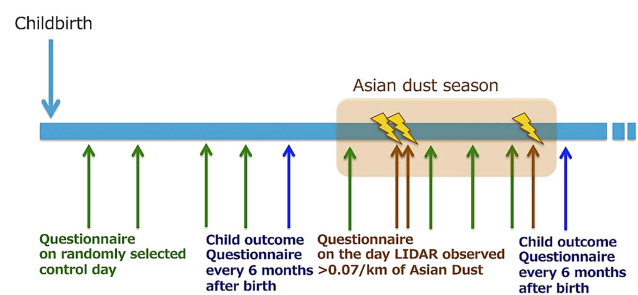


Figure 4 Adjunct study protocol after birth. A web-based

questionnaire for assessing the child's exposure level is issued on the day dust is observed (brown) and on some randomly selected days (green). A web-based questionnaire for assessing child outcomes is sent every 6 months after the child is born until the child reaches 4 years of age (LIDAR, Light Detecting and Ranging).

Table 1 Summary of adjunct study measurements and data collection items

Phase	Measurements
Registration	Expected date of childbirth History of diseases including asthma and other allergic diseases (yes/no for each disease) Status of asthma (clinic visit, therapy, attacks), if applicable Height (cm) and BMI* Education level* (7 categories) Family members (age and sex of other children)* Family income* (10 categories) Smoking history*/partner's smoking history* (5 categories for each: never/stopped before pregnancy/stopped after pregnancy/current)/second-hand smoke exposure* (5 categories) Diet status (daily intake amount of vitamins and fat in Food Frequency Questionnaire)* Housing type* (5 categories)/age of house* (7 categories)/use of unvented heater* (yes/no)/cleaning frequency* (10 categories)/use of air purifier*/use of dehumidifier*/use of humidifier*/presence of mould*/pet ownership* (yes/no for each) Attitude towards UV exposure (3 categories)
Pregnancy period	Hours spent outside on the day (4 categories)
– Asian dust day	Use of mask on the day (yes/no)
– Control day	Open or closed window on the day (yes/no) Air purifier use on the day (yes/no) Airing of futon/laundry on the day (yes/no for each) Symptom score and medication use (Allergy Control Score) Serum 25(OH)D (ng/mL)/serum immunoglobulin* (IU/mL)/inflammatory cytokines (pg/mL)
At birth	Labour date* Child's sex* Attitude towards UV exposure for babies
After birth	Hours child spent outside on the dust day (4 categories)
– Asian dust day	Open or closed windows on the dust day (yes/no)
– Control day	Air purifier use on the dust day (yes/no) Airing of futon/laundry on the day (yes/no for each)
Every 6 months after birth	Lifetime wheezing or whistling/wheezing or whistling in the past 6 months/sleep disturbances due to wheezing/clinic visits or hospitalisation for respiratory symptoms (yes/no for each) Self-reported physician diagnoses of asthma and other diseases (yes/no for each) UV exposure status (4 categories)

*Refer to the Japan Environment & Children's Study (JECS).

BMI, body mass index; UV, ultraviolet.

fourth quantile of the cumulative value of day-average dust levels from birth, respectively) infants. Time to development of asthma or other allergic diseases between the two groups is also examined applied by Cox's proportional hazards models. (2) For short-term effects on pregnant mothers, we will compare the proportion of those with any symptom (symptom score above 0) between Asian dust days (dust level $\geq 0.07/\text{km}$) and control days (dust level $< 0.07/\text{km}$) for the primary analysis, and will also conduct sensitivity analysis including a comparison of the log score between these days. The generalised estimating equation is used to adjust interindividual correlations, as appropriate. (3) For further analysis to examine for possible confounders and possible effect modifiers of long-term and short-term effects, the following factors will be examined: distance from main roads (< 30 , $30\text{--}50$ and > 50 m), housing type (concrete, wooden, apartment, detached, others), age of house, use of unvented heater, cleaning frequency, use of air purifier, use of dehumidifier, use of humidifier, presence of mould in the house, pet ownership, amount of house dust, number and sex of siblings

and other family members, bottle fed or breast fed, body weight at 6 months or 1 year, serum vitamin D concentration, vitamin D intake from diet and ultraviolet (UV) exposure status during pregnancy, UV exposure status after birth, socioeconomic status (income, education level), history of asthma and other allergic disease of parents, smoking in the house, local pollen level, local SO_2 , NO_2 and oxygen levels, local spherical particulate level (particulates other than desert dust) and local meteorological variables (air pressure and its change from the previous day, average temperature and its change from the previous day, lowest temperature, humidity). Data will be analysed as follows: (1) each factor will be examined for the association with the outcomes using threshold models with various cut-off values, and the best model will be determined based on Quasilikelihood under the Independence model Criterion (QIC) values; (2) factors associated with the outcomes ($p < 0.1$) will be evaluated for confounder potential and/or effect modification potential by two-factor model analysis with respective interaction terms; (3) assuring that multicollinearity is not a problem, we will put all the confounders into the

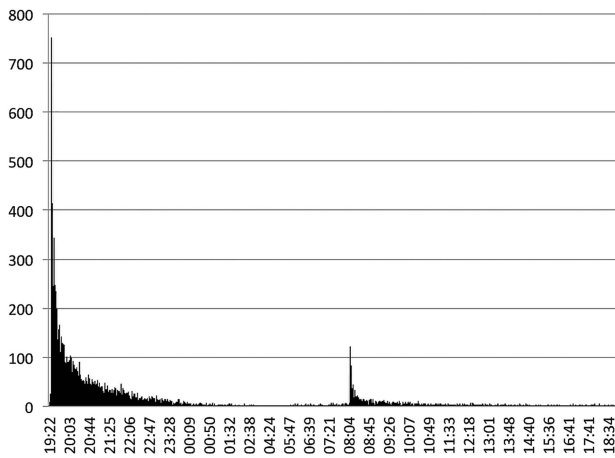


Figure 5 Distribution of answers.

desert dust model and determine the best model using a subtraction method.

Progress

Study status

We completed participant enrolment in March 2014. We will follow the children until mid-2018.

Response rate

Of those who presented consent forms to participate in this adjunct study, 3302 (97%) completed the baseline questionnaire by the end of 2012. A total of 24 256 questionnaires were issued in the evening on Asian dust days and control days during Asian dust seasons (October–November in 2011; February–May and October–November in 2012), and 88% (21 345/24 256) were completed by the set time limit (within 28 h after issue). About half of the participants answered within 1 h after the email notification (questionnaire issue), and about half of the remaining participants answered within 1.5 h after an email reminder was sent the next morning (figure 5). Forty-five participants dropped out by the end of 2012 due mainly to moving outside the study area, withdrawal of consent or miscarriage (figure 2).

DISCUSSION

The intent of this cohort study is to collect data on environmental exposure during the period from pregnancy to early infancy and to control for potential confounding sources. Our task of collecting individual data on behaviour related to dust exposure on the same day by sending an automatic email to participants based on LIDAR system measurements was successful, as demonstrated by the high response rate of 88% as of the end of 2012. To our knowledge, this is the first study that connects an environmental measurement system to a questionnaire system, thereby reducing the burden on participants by providing the questionnaire only at necessary times.

The introduction of LIDAR data for exposure measurements in epidemiological studies is a recent endeavour.^{17 18 21} PM_{2.5} and PM₁₀ have long been used to investigate the effects of particulate matter on health outcomes. PM_{2.5} and PM₁₀ differentiate particulate size, but cannot differentiate sources, while LIDAR measurements differentiate desert dust and particulates from other sources, but do not differentiate size.^{38–41} In general, pollution plumes consist of a mixture of different particulate sources and sizes, making assessments of their contributions to health complicated. In this study, we will examine particulate levels from other sources, which are measured by LIDAR as spherical particulates, for possible confounders and effect modifiers. Further, SPM (\approx PM₇) and PM_{2.5} are also measured at each location, and we will conduct the same analysis for SPM and PM_{2.5}, for comparison. These efforts will also contribute to understanding the adverse effects of particulates on health and help develop effective protection measures for vulnerable populations.

Web-based questionnaires provide benefits of an automatic validation check, automatic reminder and automatic random selection of control participants. Participant selection, however, is generally considered a significant weak point of web-based studies, particularly those that also recruit participants online.³¹ Our study tried to resolve this issue by recruiting participants through an ongoing cohort study that targets a relatively young population, where nearly universal internet access is achieved (about 99%). Other concerns associated with web-based surveys include lack of participant access to computers with internet connections, internet privacy concerns and response inconsistency across different media. We attempted to overcome these issues by using participants' individual mobile phones and/or personal computers, a secure server equipped with a firewall and password protection and uploading no personal data other than email addresses on the server.

One of the limitations of our study relates to the inconsistent use of devices; some participants used mobile phones of different types, while others used personal computers. Moreover, the generalisability of the results may become a concern, given that this adjunct study follows only about one-quarter of the newborns in the study areas; those who do not use mobile phones or personal computers were excluded, and some attrition occurred mainly due to individuals moving outside the study area. However, participant characteristics as of the end of 2012 were similar overall to those reported by the Japanese government^{44–47} (data not shown), and only minor attrition was observed (45/3425 over the course of about a year). Thus, we believe that our cohort is representative of Japanese families with small children.

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Competing interests None.

Patient consent Obtained.

Ethics approval The study protocol was approved by ethics committees of Kyoto University, Toyama University, and Tottori University.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Researchers interested in collaborations or further information are invited to contact KTK, MD, MAS at kanatani.kumiko.2r@kyoto-u.ac.jp.

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