# Prenatal risk factors of indoor environment and incidence of childhood eczema in the Japan Environment and Children's Study

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**Abstract**

The quality of indoor environment is a risk factor for early childhood eczema and atopic dermatitis; however, its influence during pregnancy on childhood eczema in Japan has not been investigated. In this study, we aimed to determine the indoor environmental factors that are associated with eczema in children up to 3 years of age, using national birth cohort data from the Japan Environment and Children's Study (JECS).

Information on indoor environments and eczema symptoms until 3 years of age was collected using self-administered questionnaires to the mothers. A total of 71,883 and 58,639 mother-child pairs at 1.5- and 3-years-old, respectively, were included in the former analyses. To account for prenatal indoor risk factors, 17,568 (1.5-years-old) and 7,063 (3-years-old) children without indoor mold and/or ETS exposure were included in the final analysis. A higher mold index, gas heater use, parquet flooring use, and frequent insecticide use showed significantly increased risks for childhood eczema up to 3 years of age. These associations were consistent after stratification analysis among children whose parents did not have a history of allergies. The updated WHO guidelines on indoor air quality should be implemented based on recent findings regarding the effects of prenatal exposure to indoor dampness on health effects of children further in life, including asthma, respiratory effects, eczema, and other immunological effects.

**Keywords:** Indoor environments; Mold; Prenatal exposure; Childhood eczema; Japanese children; Birth cohort

## 1 Introduction

Atopic dermatitis (AD) is an eczematous common childhood disease categorized as a type of long-term inflammation that results in symptoms including itchiness, dryness, inflamedness, redness, and swelling (Leung et al., 2004). It typically manifests in early childhood, and the symptoms alleviate at school age. Genetic factors, immune system dysfunction, and environmental exposure are thought to cause AD (Asher et al., 1995). According to Phases I and III of the International Study of Asthma and Allergies in Childhood (ISAAC), the worldwide prevalence of eczema in children aged 6–7 years showed an increasing trend in both developed and developing countries (Asher et al., 2006). The prevalence of childhood AD in Japan has been reported as 12.8%, 9.8%, and 13.2% at 4 months old, 1.5 years old (1.5Y), and 3 years old (3Y), respectively (Ministry of Health, 2010). It gradually decreases in school-aged children (Katoh et al., 2019); however, these symptoms affect their quality of life.

We spend more than 90% of our time indoors, and young children spend most of this time in their homes. The indoor environment is a risk factor for childhood asthma, allergic rhinitis, and AD. Recent reviews identified volatile organic compounds (VOCs), particulate matter, and environmental tobacco smoke (ETS) as major indoor risk factors for allergic sensitization (Ahn, 2014; Halken, 2004; Narla and Silverberg, 2020). Moreover, indoor dampness, such as mold growth, moldy odor, condensation, and water leakage, has been reported as an additional risk factor for childhood eczema and AD (Lee et al., 2020; Mendell et al., 2011; Ukawa et al., 2013). In Sweden, Germany, and Korea, early life exposures to the indoor environment such as moldy and damp places, as well as pollutants emitted from combustion heaters and cookware, furniture, painting, floor covering, and wallpaper, are associated with the risk of childhood AD (Bornehag et al., 2005a; Herbarth et al., 2006; Lee et al., 2012). WHO guidelines for indoor air quality—dampness and mold—summarized the epidemiological evaluation of human health risks conducted in different countries and under different climatic conditions and revealed that the occupants of damp or moldy houses are at an increased risk for respiratory symptoms, respiratory infections, and exacerbation of asthma (WHO, 2009). However, most epidemiological studies included in the guidelines had cross-sectional study designs and focused on asthma, respiratory symptoms, and allergic rhinitis; studies assessing prenatal exposure and examining effects on eczema or atopic dermatitis as health outcomes have not been included. Recently, a few epidemiological studies have reported that prenatal exposure to ETS, visible mold, air dryness, keeping dogs at home, and home renovation during pregnancy were associated with childhood AD or eczema (Lee et al., 2020; Norbäck et al., 2021; Yang et al., 2015). A selective review suggested that early-life exposure to indoor environmental factors plays an important role in the development of childhood allergies (Lu et al., 2020a). A Korean birth cohort study on the childhood origin of asthma and allergic diseases (COCOA) revealed that home renovation during pregnancy was associated with higher levels of cord blood IgE (Yu et al., 2016). Similarly, a Canadian birth cohort study, the Kingston Allergy Birth Cohort, showed that candle use and keeping pets at home during pregnancy were associated with an increased risk of allergic sensitization at 2 years of age (Gallant and Ellis, 2020). History of parental allergic diseases was identified as one of the major risk factors for eczema and associated with their behavior and home environment (Asher et al., 1995).

We hypothesized that differences in the association between indoor environments and eczema would differ for parents with and without a history of allergy. Moreover, as revealed by several cross-sectional studies, current exposure to ETS and indoor dampness, such as condensation and mold problems, have been suggested as potential risk factors for childhood eczema (Bornehag et al., 2005b; Mendell et al., 2011; Norbäck et al., 2021; Saijo et al., 2004; Ukawa et al., 2013). Therefore, in this study, we aimed to investigate the prenatal indoor environmental factors and their association with childhood eczema up to 3 years, taking into account parental heredity of allergy, using data from The Japan Environment and Children’s Study (JECS)—a birth cohort study. The larger scale, longitudinal study design of a birth cohort allows us to exclude postnatal factors that influence childhood eczema and to focus exclusively on the associations between prenatal indoor risk factors and childhood eczema.

## 2 Materials and Methods

### 2.1 Study population

The JECS is an ongoing nationwide prospective birth cohort study in Japan that aims to identify the environmental factors affecting children's health and development (Michikawa et al., 2015; Michikawa et al., 2018). Fifteen Regional Centres were selected to cover all Japanese geographical areas (Hokkaido, Miyagi, Fukushima, Chiba, Kanagawa, Koshin, Toyama, Aichi, Kyoto, Osaka, Hyogo, Tottori, Kochi, Fukuoka, and South Kyushu/Okinawa). To maximize representativeness, baseline recruitment was performed in collaboration with local governments and cooperating healthcare providers. Children were followed up from birth until they reached the age of 13.

Pregnant women in the early stages of their pregnancy and living in an area located in a Regional Centre were recruited and enrolled in this study between January 2011 and March 2014. Figure 1 presents the flowchart of the study. A total of 104,062 fetal records in the *jecs-ta-20190930* dataset from the JECS, registered in the University Hospital Medical Information Network (UMIN) 000030786 (UMIN Clinical Trials Registry) were used. After excluding stillbirths and miscarriages (n=3,759), multiple births (n=1,891), unknown sex (n=18), and mothers who did not respond to early and late pregnancy questionnaires (n=2,164), a total of 96,230 mother-child pairs were included. Study population for the outcome of eczema at 1.5Y, participants who were missing the data of 1.5Y questionnaire (n=10,533) as well as eczema queries of the International Study of Asthma and Allergies in Childhood (ISAAC) (Asher et al., 1995; Asher et al., 2006) (n= 205), and moved their houses after birth up to 1.5Y (n=13,609) were excluded. Overall, 71,883 children were included in the analysis. As for the population of eczema at 3Y, participants who were missing the data of the 3Y questionnaire including eczema queries of the ISAAC in the 3-year questionnaire (n=16,180) and moved their houses after birth up to 3Y (n=21,411) were excluded. Overall, 58,639 children were included in the analysis. To examine associations with prenatal indoor risk factors on childhood eczema, 54,315 and 51,576 participants who had indoor mold and/or ETS exposure at 1.5Y and 3Y, respectively, were further excluded from both study populations. Finally, 17,568 and 7,063 children were included in the analysis at 1.5Y and 3Y, respectively.

### 2.2 Outcome measurements

Caregivers (typically mothers) were asked, through a questionnaire, about eczema when the children were 1.5Y and 3Y. The ISAAC questionnaire for 6–7 years old (Asher et al., 1995; Asher et al., 2006; Ellwood et al., 2005; Weiland et al., 2004) with a partially modified and validated Japanese translation was used for the definition of the eczema outcomes at each age. The caregivers were asked, *"Has your child ever had an itchy rash that was coming and going for at least 6 months? (yes/ no)"* If the answer was yes, they were then asked *"Has your child had this itchy rash at any time in the last 12 months? (yes/ no)?"* If the answer was yes, they were further asked, *"Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes? (yes/ no)"* If the answer was yes, we defined the children as eczema-positive at that age.

### 2.3 Exposure measurements

Information on the type of house, building age, building structure, and indoor environments, such as type of heating system (gas heater/kerosene heater/wood heater/electric heater/forced flue venting system heater: FF heater), floor materials (tatami/carpet on the tatami/parquet floor or tiles/carpet on the parquet floor), cleaning habits (every day/several times per week/once per week/1–2 times per week/seldom), mold growth (mold index: 0–5), furry pet keeping at home (yes/no), usage of room fragrance (yes/no), and frequency of spraying insecticide inside the home (never/< 1 time per month/1–3 times per month/once per week/several times per week/every day), were collected from the mother-reported questionnaire during the second or third trimester of pregnancy (Iwai-Shimada et al., 2018). The housing type was categorized as detached houses or apartments.

The building structures were categorized as detached wooden, detached reinforced concrete, wooden apartments, or reinforced concrete apartments. Building age was categorized as < 1 year/ ≥ 1, <3 years/ ≥ 3, <5 years/ ≥ 5, <10 years/ ≥ 10, <20 years/ ≥ 20 years/, or unknown.

Usage of the following types of heaters was inquired: gas heater (yes/no), kerosene heater (yes/no), wood stove (yes/no), electric heater (yes/no), and FF heater (yes/no). Several previous studies have assessed signs of indoor dampness based on the presence of mold growth, moldy odor, damp spots, condensation, water leakage, and high humidity in the bathroom (Bornehag et al., 2001; Mendell et al., 2011; Norback et al., 2013; Saijo et al., 2004; Saijo et al., 2010; Ukawa et al., 2013). In the present study, we assessed indoor dampness as mold index [0–5] calculated based on the presence of mold growth in five specific places: the kitchen, living room, bedroom, bathroom, and toilet. When mold was observed in all five locations, the mold index was assigned as 5. When the mold was not present in any of the five locations, the mold index was assigned as 0.

### 2.4 Other variables

Data on maternal age at delivery and gestational weeks were collected from transcripts of medical records. Information on maternal smoking during pregnancy, paternal smoking during pregnancy, ETS during pregnancy, history of maternal allergies, history of paternal allergies, and annual household income were collected from the mother-reported questionnaire during the first trimester of pregnancy. Data on annual household income and house renovation were collected from the mother-reported questionnaire during the second or third trimester of pregnancy. Maternal body mass index (BMI) before pregnancy was calculated using the weight and height data based on both medical records by a doctor in the first trimester and delivery and the mother-reported questionnaire during the first trimester of pregnancy. Data on renovation and ETS exposure of the children were collected from the mother-reported questionnaire when the child was 1.5Y and 3Y.

### 2.5 Statistical analysis

Chi-square, t-test, and Mann–Whitney U tests were used to assess the associations between the characteristics of the participants, as well as indoor environment factors, and childhood eczema at 1.5Y and 3Y. Multiple logistic regression analyses were used to analyze the effects of indoor environments during pregnancy on child eczema at 1.5Y and 3Y and estimate the odds ratios (ORs) and 95% confidential intervals (CIs). All variables listed in Section 2.3 were mutually adjusted in a model.

As hereditary factor is strongly associated with childhood eczema, stratification by the history of parental allergies was further conducted: "at least one of the parents has a history of allergies vs. no parents with a history of allergies." Since postnatal indoor risk factors on childhood eczema have been reported from previous cross-sectional epidemiological studies, we considered the isolation of prenatal risk factors for childhood eczema by excluding the population having postnatal ETS and/or indoor mold exposure. A history of maternal or paternal allergies was defined as positive when the mother or biological father gave a positive response to one of the following histories of allergies: bronchial asthma, allergic rhinitis or pollen allergy, AD, allergic conjunctivitis, food allergy, and eczema. The sex of the child, maternal smoking during pregnancy, annual household income, gestational age, maternal age at delivery, birth weight, and renovation were selected as covariates in the final model. A two-tailed test and a 5% level of significance were used for all analyses using JMP Pro 14 for Macintosh (SAS Institute, Cary, NC, USA).

### 2.6 Ethics statements

The protocol was approved by the Institutional Review Board on Epidemiological Studies of the Ministry of the Environment and by the Ethics Committees of all participating institutions (Ethical Number: No.100910001). The JECS was conducted in accordance with the Declaration of Helsinki and other national regulations. Written informed consent was obtained from all participating mothers and fathers.

## 3 Results

Table 1 presents demographic and indoor environment characteristics during pregnancy of the participants at 1.5Y and 3Y. The mean maternal age at delivery, maternal BMI before pregnancy, gestational week, child BMI, distributions of child sex and maternal and paternal history of allergies, and most of the characteristics of indoor environments during pregnancy at

1.5Y and 3Y were similarly distributed between two age groups. However, both maternal and paternal smoking during pregnancy were higher at 1.5Y than at 3Y. The mold index was slightly higher in the population of 1.5Y than in those of 3Y. Furthermore, within the same age group of 1.5Y and 3Y, the population after excluding postnatal mold and/or ETS exposures tended to have lower maternal and paternal smoking during pregnancy, live in newer houses (based on the building age), clean more frequently the living room, and have a lower frequency of insecticide use inside their homes. The prevalence of eczema at 1.5Y and 3Y was 9.1% and 9.5%, respectively. Within the same age group of 1.5Y and 3Y, the prevalence of eczema was higher in children whom postnatal ETS and/or mold exposures were excluded (1.5Y: 9.1%; 3Y: 9.5%) than in those before excluding postnatal risk factors (1.5Y: 11.5%; 3Y: 12.2%). The different pregnancy home environment factors were significantly correlated each other (Supplemental Table 1). For example, house type was associated with building structure and building age. Building age was associated with kerosene heater use, floor materials, and mold index of both prenatal and postnatal period, respectively. Moreover, prenatal mold index and ETS exposure were significantly correlated with postnatal mold index and ETS, respectively.

The associations between eczema at 1.5Y and 3Y and characteristics of the participants are shown in Supplemental Table 2. The prevalence of eczema at both ages was associated with male sex, heavier birth weight, history of maternal allergies, maternal ETS during pregnancy, building age, wood stove use, higher mold index during pregnancy, and annual household income.

The associations between prenatal indoor environment and eczema at 1.5Y are shown in Table 2 and Supplementary Table 3. Houses built more than 20 years ago (OR [95% CI]: 1.10 [1.02–1.18]), gas heater use (1.10 [1.01–1.20]), parquet floor use (1.15 [1.06–1.26]), frequent use of insecticide inside the house, and higher mold index (1–2: 1.27 [1.20–1.33] and ≥3: 1.36 [1.20–1.54]) than in those without a mold event (0) were associated with increasing the risk of eczema at 1.5Y (Table 2; total, n=71,883). On the other hand, furry pet keeping was inversely associated with the risk of eczema (0.88 [0.82–0.94]). In the stratification by parental heredity, houses built more than 20 years ago (1.14 [1.04–1.24]), parquet floor use (1.14 [1.02–1.26]), frequent use of insecticide inside the house, higher mold index, and furry pet keeping (0.89 [0.82–0.97]), associations remained significant among children whose at least one parent had a history of allergies (n=43,161). Among children whose parents had no history of allergies (n=10,328), carpet and parquet floor use, frequent use of insecticide, and a higher mold index were associated with the risk of eczema (Table 2).

To isolate prenatal indoor risk factors for childhood eczema, postnatal ETS and indoor mold exposure were excluded (Table 2; total, n=17,568). Use of FF heater (1.67 [1.14–2.45]) and parquet flooring (1.24 [1.01–1.54]) increased the risk of childhood eczema. Regarding the frequency of insecticide spray use, once/month (1.20 [1.05–1.37]) and several times/week (1.38

[1.03–1.85]) use increased the risk of eczema, with “never use” as the reference. A significantly higher OR was observed for houses with a higher mold index (≥3; 1.61 [1.00–2.58]) than for those without the presence of mold (0). In contrast, furry pet keeping during pregnancy was associated with decreased risk of eczema (0.85 [0.73–0.99]). After stratification by heredity (Supplementary Table 3), although the number of children in each subgroup was limited, older building age, FF heater use (1.66 [1.02–2.69]), parquet floor use (1.35 [1.03–1.76]), and insecticide use once/month (1.19 [1.01–1.41]) showed significant to moderate associations with the risk of eczema among 1.5Y children who have at least one of parent with history of allergies (Supplementary Table 3, n=10,202). Among children whose parents had no history of allergies (Supplementary Table 3, n=2614), carpet use (2.59 [1.24–5.41]) was associated with the risk of eczema. On the other hand, living in an apartment (0.60 [0.42–0.86]) was inversely associated with the risk of eczema at 1.5Y.

The associations between prenatal indoor environment and eczema at 3Y are shown in Table 3 and Supplementary Table 4. Gas heater use (1.10 [1.01–1.21]) and higher mold index (1–2: 1.08 [1.02–1.15] and ≥3: 1.19 [1.04–1.37]) than in those without the presence of mold (0) were associated with risk of eczema at 3Y (Table 3: total, n=58,639). Among children with at least one parent with a history of allergies (n=36,199), prenatal risk factors in indoor environment did not show any significant associations with eczema. On the other hand, carpet use on the parquet floor (1.39 [1.05–1.83]), insecticide use <1 time/month (1.26 [1.04–1.53]) and once a week, and having higher mold index were associated with risk of eczema among children whose parents had no history of allergies (Table 3, n=8,491).

To isolate prenatal indoor risk factors for childhood eczema, postnatal ETS and indoor mold exposure were excluded. Electric heater use was inversely associated with the risk of eczema at 3Y (Table 3: total, n=7,063). The same association was observed among children whose parents had no history of allergies after stratification by parental heredity (Supplementary Table 4). However, other indoor risk factors during pregnancy were not associated with eczema.

## 4 Discussion

In this study, we investigated the associations between prenatal risk factors of indoor environment and childhood eczema at 1.5Y and 3Y in the nationwide birth cohort JECS. We examined which factors of indoor environments during pregnancy are associated with early childhood eczema in two different life stages (1.5Y and 3Y). The design of the large-scale birth cohort study allowed us to eliminate the influence of parental heredity by stratifying with/without a history of parental allergies (at least one/none of the parents have a history of allergies). The presence of indoor mold (mold index > 0), frequent use of insecticide spray, and use of parquet floor materials were associated with childhood eczema. Due to prenatal mold index and ETS exposure were strongly correlated with postnatal mold index and ETS, respectively (Supplemental Table 1), we further limited the population to those who were not exposed to ETS and/or mold after birth to isolate prenatal risk factors on childhood eczema at 1.5Y and 3Y. The results showed that FF heater use, parquet floor use, insecticide use, and indoor mold exposure (mold index ≥3) were associated with eczema at 1.5Y but not at 3Y. The evidence for these associations, except for mold exposure, was more clearly observed in children at 1.5Y than at 3Y, suggesting that the effects of prenatal risk factors of indoor environments may be more visible at an earlier age of 1.5Y and may disappear or become weaker at 3Y.

### *4.1 Mold exposure*

Indoor mold exposure during pregnancy was associated with eczema at 1.5Y and 3Y. These associations were also demonstrated among children whose parents had no history of allergy, indicating that prenatal mold exposure is a possible risk factor for childhood eczema regardless of parental heredity. In the subsequent stratified analysis by limiting the population to those who were not exposed to ETS and/or mold after birth, the significance of mold exposure became weaker or disappeared. Our findings showed that the postnatal indoor environment factors may be important risk factors for eczema later in life. However, in the results at both 1.5Y and 3Y, the ORs of the presence of eczema on mold index ≥3 were above 1.0 (1.5Y: OR=1.61, *p=0.050*; 3Y: 1.93, *p=0.125*) without significant associations, probably owing to the limited number of participants. This indicates that extremely unfavorable indoor dampness (mold index ≥3) during pregnancy is a potential risk factor for early childhood eczema until 3Y, regardless of postnatal indoor risk factors. Participants who were not exposed to postnatal indoor risk factors might have better indoor environments than the ones who were exposed. For example, our results show that the mold index (mean) at 1.5Y and 3Y were 0.81 and 0.80, respectively (Table 1). On the other hand, the mold index of the participants limited to those who were not exposed to postnatal ETS and mold at 1.5Y and 3Y were 0.38 and 0.26, respectively. Therefore, participants who continued to live in the absence of ETS and mold exposures after childbirth had lower mold index than those exposed to ETS and mold during the prenatal and postnatal period, showing that a higher mold index was a risk factor for their children's eczema. To the best of our knowledge, this is the first study to report that mold exposure at home during pregnancy is a possible indoor risk factor for childhood eczema until 3Y while considering parental heredity and postnatal indoor risk factors.

Several studies reported that some indoor environmental factors during pregnancy, such as dampness, air dryness, stuffy air, new furniture, renovation, pet-keeping, carpet use, and ETS, were associated with asthma and allergies (Chen et al., 2011; Gallant and Ellis, 2020; Havstad et al., 2011; Jedrychowski et al., 2013; Lee et al., 2020; Liu et al., 2012; Lu et al., 2020b; Norbäck et al., 2021; O'Connor et al., 2018; Yi et al., 2012). A Chinese retrospective study reported that signs of dampness, such as mold, mold odor, and condensation during pregnancy, were associated with eczema as defined by ISAAC in children aged 3–6 years (Norbäck et al., 2021). In the same study, Lu et al. reported that both perinatal and current exposure to indoor mold, moldy odor, and condensation on window panes during winter were associated with an increased onset and decreased remission of eczema during pre-school years (Lu et al., 2021). A Korean birth cohort study examined the associations between the timing of mold exposure (prenatal and postnatal) and development of AD and reported that prenatal mold exposure was significantly associated with AD in 1-year-old children. However, exposure to mold in the first year of life is not associated with the risk of AD (Lee et al., 2020). Although both prenatal and postnatal mold exposures have been separately considered, the effect of mold in the first year of life was not eliminated in the model of prenatal period.

Our study showed that the significant associations between higher mold index and increased eczema were consistent after stratification by parental heredity. This result indicates that prenatal indoor mold exposure can be a critical risk factor for childhood eczema regardless of the parental history of allergies. However, the mechanism underlying the relationships between indoor dampness, such as mold exposure, during pregnancy and the risk of childhood eczema remains unknown. One hypothesis is that exposure to indoor mold during the prenatal period can affect the development of AD via immunomodulation, possibly through IgE-related allergic inflammation. This hypothesis is supported by the study by Yu et al., which reported that mold exposure during infancy was associated with increased total serum IgE levels, indicating that exposure to indoor dampness may induce IgE-mediated allergic inflammation in the first year of life (Yu et al., 2015). In addition, Lee et al. reported that prenatal exposure to higher levels of dampness-induced indoor microbiomes and fungi was associated with the risk of AD in early life (Lee et al., 2020). The signs of dampness at home are indicators of a low ventilation rate (Engvall et al., 2005). Considering these observations, indoor dampness during pregnancy might induce IgE-mediated allergic inflammation during the development of AD. However, only few studies have examined the mechanisms underlying the risk of indoor dampness during pregnancy for childhood AD or eczema, and thus, the underlying mechanisms remain unknown. Further studies are needed to identify mechanisms underlying the association between indoor dampness during pregnancy and the development of eczema in early life.

### *4.2 Insecticide use*

In the present study, frequent use of spray insecticides during pregnancy was significantly associated with the risk of eczema at 1.5Y, but not at 3Y, after excluding postnatal risk factors of the indoor environment. Furthermore, a trend for a higher risk of eczema was observed with the more frequent use of spray insecticides ($p < 0.001$, data not shown). A Chinese retrospective cohort study on the lifetime development of allergies such as asthma, rhinitis, and eczema suggested that burning mosquito coils was associated with lifetime eczema (Norback et al., 2019). Pyrethroids are a common class of residential insecticides (Saillenfait et al., 2015);

experimental *in vitro* studies have reported immunotoxicological properties of synthetic pyrethroids (Diel et al., 1998), and adverse respiratory effects in humans have been reported in epidemiological studies (Osimitz et al., 2006; Osimitz et al., 2009; Salome et al., 2000). Insecticide aerosols trigger asthmatic symptoms and decrease lung function in patients (Salome et al., 2000). Maternal agricultural work was associated with a 26% upregulation of T-helper 2 cytokines based on the California birth cohort study, Center for the Health Assessment of Mothers and Children of Salinas (Duramad et al., 2006). Pyrethrum was also reported to cause allergic contact dermatitis in humans (Osimitz et al., 2006). However, studies on the adverse dermal effects of synthetic pyrethroids in humans are lacking. A review indicated that pyrethroids are generally thought to have low toxicity and have not been specifically associated with dermal reactions (Osimitz et al., 2009).

Our study only assessed the frequency of insecticide spraying using a self-reported questionnaire and did not quantify exposure levels of the mothers and the indoor environment. Therefore, the biological mechanisms for the associations between the use of insecticides during pregnancy and childhood eczema are yet to be elucidated. As such, the effect of using insecticide at home during pregnancy on the risk of childhood eczema must be interpreted with caution.

### *4.3 Types of floor materials*

The use of parquet floors, including compressed wooden flooring during pregnancy, was associated with a risk of childhood eczema at 1.5Y regardless of parental heredity (Table 2). At 3Y, the same association was observed in children whose parents had no history of allergies (Table 3). Parquet floorings contain synthetic chemicals, such as phthalates and other plasticizers, which are used for glue, floor wax, and coating, and flame retardants for compressed wooden flooring (van der Veen and de Boer, 2012; Wormuth et al., 2006). High levels of phthalates in house dust (Ait Bamai et al., 2013), phosphorous flame retardants in house dust (Tajima et al., 2014), and urinary metabolites (Bastiaensen et al., 2020) were associated with the use of compressed wood as dwelling floor materials. As shown in our previous studies, higher levels of phthalates and flame retardants were associated with increased allergic symptoms, such as wheezing, rhino-conjunctivitis, and eczema in children (Ait Bamai et al., 2016; Ait Bamai et al., 2018; Ait Bamai et al., 2014; Araki et al., 2020; Araki et al., 2018). Considering these observations, the use of compressed wood as floor material at home during pregnancy may be indirectly associated with childhood eczema, and these synthetic chemicals might mediate between the compressed wood floor and eczema symptoms. However, the participants' exposure levels to such chemicals, as well as the levels in indoor environments, were not quantified in this study. Therefore, the association of a compressed wood floor at home during pregnancy and childhood eczema should be interpreted with caution.

### *4.4 Types of heating systems*

We examined the type of heating system used during pregnancy as a risk factor for childhood eczema and hypothesized that the use of non-electric heaters, such as combustible heaters (e.g. kerosene, gas, and wood heaters), may be associated with the risk of childhood eczema. Our results showed that gas heater use during pregnancy was associated with a risk of eczema only at 1.5Y, whereas electric heater use during pregnancy was associated with eczema at 3Y. Previous cross-sectional studies have reported that non-electric heater use is associated with asthma (Cong et al., 2014) and AD (Ukawa et al., 2013) among Japanese schoolchildren. In a German case-control study, a gas heater with an exhaust pipe connection was associated with a significantly elevated risk of eczema (Schäfer et al., 1999). These results are consistent with our findings. In contrast, in a Taiwanese case-control study, no significant associations were reported between the use of a gas heater and AD (Yang et al., 2000). Exposure to $NO_2$ emissions or particulate matter from gas heating affects physiological skin parameters (Song et al., 2011); therefore, when gas, kerosene, or wood stoves are used, adequate ventilation may be necessary to maintain skin physiology under normal conditions. We recategorized "non-electric heaters" and "combustible heaters" from the queries of the questionnaire and examined whether the use of non-electric heaters or combustible heaters is associated with the risk for eczema. The use of combustible heaters showed an association with the risk of eczema in children whose mothers did not have a history of allergies. However, the association was not significant, which may be due to misclassifications of heating sources in the self-reported questionnaire.

### 4.5 Strengths and limitations

An important strength of this study is that we used nationwide prospective birth cohort study data, which represent the general population of Japan (Michikawa et al., 2015). Therefore, our findings can be generalized to the Japanese population. Upon comparing the current study population with all JECS participants, their baseline characteristics were comparable (Michikawa et al., 2015). Moreover, information on health outcomes and indoor environments were repeatedly collected from pregnancy up to 3Y, allowing us to eliminate postnatal indoor risk factors of childhood eczema, such as ETS and mold exposures, and to examine the effects limited only to prenatal indoor risk factors of eczema. Moreover, owing to the study design, we could eliminate other factors that directly affect the indoor environments after birth by excluding participants who moved houses after delivery and adjusting the pre- and postnatal renovation in the model as a covariate. Therefore, the influence of postnatal indoor environments should be minimal in the current model.

Nevertheless, this study has some limitations. First, the information used in this study was collected using self-administered questionnaires. The outcome definition of eczema was based on the ISAAC questionnaire, which is generally used for children aged 6–7 years (Asher et al., 1995). Furthermore, no biological examinations and/or medical diagnoses of eczema were available. The definition of eczema may lead to misclassifications, especially for the outcome at 1.5Y, owing to the misclassifications of infantile eczema. However, in this study, the prevalence of eczema at 1.5Y and 3Y as defined based on the ISAAC questionnaire was comparable to that in another Japanese birth cohort study, the Hokkaido study (Kishi et al., 2021). Therefore, the probability of misclassification can be minimal. Second, exposure assessments of indoor environments during pregnancy were based on self-reported questionnaires. Exposure to chemicals, such as VOCs, PM, $NO_2$, $SO_2$, SVOCs, and mite allergens in indoor air and/or house dust was not assessed. The indoor chemicals emitted from mold, gas heaters, parquet floors, and insecticides may be directly associated with childhood eczema. However, our study showed that indoor mold exposure and the use of gas heaters, parquet floors, and insecticides at home during pregnancy are risk factors for childhood eczema, even in the absence of chemical analyses. Third, the questionnaire in this study did not cover information on other important indoor dampness signs, such as moldy odor, visible mold, water leakage, condensation water leakage, and flooding (Norback et al., 2013; Ukawa et al., 2013; WHO, 2009). Therefore, factors for other indoor dampness are not considered in this study. Fourth, information related to either ventilation or window opening was not available from the questionnaires; thus, these factors were not considered. Ventilation and exchange of indoor air are useful activities to prevent high humidity and pollutants in indoor environments and adverse health outcomes (Callesen et al., 2014; Cong et al., 2014; Shajahan et al., 2019; Sherman and Hodgson, 2004; Sundell et al., 2011). Hence, we could not eliminate the effects of ventilation on our findings. Finally, repeating several statistical analyses increases the probability of a type I error; therefore, interpretation of the results in this study needs to be made with caution.

## 5 Conclusions

Our findings indicated that a higher mold index, gas heater use, parquet flooring use, and frequent insecticide use before infant birth was significant risks for childhood eczema in early childhood, especially at 1.5 years of age. These associations remained consistent after stratification analysis among children whose mothers did not have a history of allergies, indicating that these factors are independent of genetic factors. Furthermore, a higher incidence of mold exposure was a risk factor, regardless of parental heredity. Our findings should be interpreted with caution because neither chemical analyses nor biological evaluations were conducted to characterize the indoor environments and to validate eczema outcomes.


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**Table 1.** Characteristics of participants and indoor environments during pregnancy

| | | Children at 1.5Y | | | | Children at 3Y | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Included postnatal indoor factors¶ N = 71,883 | | Excluded postnatal indoor factors¶ N = 17,568 | | Included postnatal indoor factors¶ N = 58,639 | | Excluded postnatal indoor factors¶ N = 7,063 | |
| | | N | % | N | % | N | % | N | % |
| Maternal age at delivery (y) | Mean, SD | 31.6 | 4.9 | 31.7 | 4.8 | 31.9 | 4.9 | 32.1 | 4.7 |
| Maternal BMI before pregnancy (kg/m²) | Mean, SD | 21.2 | 3.3 | 21.0 | 3.1 | 21.2 | 3.2 | 21.0 | 3.1 |
| Gestational week | Mean, SD | 38.8 | 1.5 | 38.8 | 1.6 | 38.8 | 1.5 | 38.8 | 1.5 |
| Child BMI at 1.5y (kg/m²) | Mean, SD | 16.5 | 2.2 | 16.4 | 2.3 | 16.5 | 2.2 | 16.4 | 2.4 |
| Child BMI at 3y (kg/m²) | Mean, SD | n.a. | | | | 16.0 | 1.5 | 15.9 | 1.4 |
| Child sex | Boy | 36947 | 51.4 | 8976 | 51.1 | 30198 | 51.5 | 3638 | 51.5 |
| | Girl | 34936 | 48.6 | 8592 | 48.9 | 28441 | 48.5 | 3425 | 48.5 |
| Eczema at 1.5y old | Yes | 8258 | 11.5 | 1594 | 9.1 | n.a | n.a | n.a | n.a |
| Eczema at 3y old | Yes | n.a | n.a | n.a | n.a | 7158 | 12.2 | 674 | 9.5 |
| Maternal allergy | Yes | 36524 | 50.8 | 8478 | 48.3 | 29743 | 50.7 | 3375 | 47.8 |
| Paternal allergy | Yes | 17181 | 45.8 | 4188 | 45.3 | 14075 | 45.7 | 1728 | 45.5 |
| Maternal smoking during pregnancy | Yes | 11348 | 15.8 | 2351 | 13.4 | 8758 | 14.9 | 811 | 11.5 |
| Paternal smoking during pregnancy | Yes | 33559 | 46.7 | 7138 | 40.6 | 26892 | 45.9 | 2652 | 37.5 |
| Environmental tobacco smoke | Seldom | 45821 | 63.7 | 13075 | 74.4 | 37764 | 64.4 | 5485 | 77.7 |
| | 1 day/week | 8497 | 11.8 | 1728 | 9.8 | 6927 | 11.8 | 656 | 9.3 |
| | 2 day/week - everyday | 17376 | 24.2 | 2722 | 15.5 | 13799 | 23.5 | 907 | 12.8 |
| House type | Detached house | 37580 | 52.3 | 9485 | 54.0 | 32988 | 56.3 | 4130 | 58.5 |
| | Apartment | 33208 | 46.2 | 7840 | 44.6 | 24843 | 42.4 | 2837 | 40.2 |
| Structure of house | Wooden detached | 32546 | 45.3 | 8090 | 46.0 | 28530 | 48.7 | 3481 | 49.3 |
| | Reinforced concrete detached | 5034 | 7.0 | 1395 | 7.9 | 4458 | 7.6 | 649 | 9.2 |
| | Wooden apartment | 7648 | 10.6 | 1874 | 10.7 | 5604 | 9.6 | 664 | 9.4 |
| | Reinforced concrete apartment | 25560 | 35.6 | 5966 | 34.0 | 19239 | 32.8 | 2173 | 30.8 |
| | Others | 639 | 0.9 | 122 | 0.7 | 465 | 0.8 | 47 | 0.7 |
| Building age | < 3 years | 13251 | 18.4 | 5112 | 29.1 | 11576 | 19.7 | 2367 | 33.5 |
| | >= 3 , <10 years | 18061 | 25.1 | 4699 | 26.7 | 15057 | 25.7 | 1876 | 26.6 |
| | >= 10 , <20 years | 16136 | 22.4 | 3288 | 18.7 | 12820 | 21.9 | 1216 | 17.2 |
| | >= 20 years | 17840 | 24.8 | 3200 | 18.2 | 14352 | 24.5 | 1184 | 16.8 |
| | Unknown | 6115 | 8.5 | 1151 | 6.6 | 4478 | 7.6 | 371 | 5.3 |
| Renovation | Yes | 2464 | 3.4 | 675 | 3.8 | 2109 | 3.6 | 297 | 4.2 |
| Gas heater use | Yes | 5875 | 8.2 | 1489 | 8.5 | 4940 | 8.4 | 628 | 8.9 |
| Kerosene heater use | Yes | 35160 | 48.9 | 7722 | 44.0 | 28330 | 48.3 | 2950 | 41.8 |
| Wood stove use | Yes | 506 | 0.7 | 104 | 0.6 | 409 | 0.7 | 33 | 0.5 |
| Electric heater use | Yes | 39867 | 55.5 | 9920 | 56.5 | 32673 | 55.7 | 3999 | 56.6 |
| FF-heater use | Yes | 1066 | 1.5 | 235 | 1.3 | 842 | 1.4 | 101 | 1.4 |
| Furry pet keeping | Yes | 12193 | 17.0 | 2746 | 15.6 | 10041 | 17.1 | 1054 | 14.9 |
| Floor materials | Tatami | 8180 | 11.4 | 1625 | 9.2 | 6587 | 11.2 | 583 | 8.3 |
| | Carpet on the tatami | 6106 | 8.5 | 1083 | 6.2 | 4798 | 8.2 | 374 | 5.3 |
| | Parquet floor or tiles | 26033 | 36.2 | 7134 | 40.6 | 21661 | 36.9 | 2981 | 42.2 |
| | Carpet on the parquet floor | 29897 | 41.6 | 7399 | 42.1 | 24238 | 41.3 | 2998 | 42.4 |
| Frequency of cleaning living room | Seldom | 1540 | 2.1 | 268 | 1.5 | 1232 | 2.1 | 96 | 1.4 |
| | 1 time/ week | 21992 | 30.6 | 5007 | 28.5 | 18045 | 30.8 | 1993 | 28.2 |
| | 1-2 times/ week | 4154 | 5.8 | 751 | 4.3 | 3368 | 5.7 | 234 | 3.3 |
| | Several/ week | 31407 | 43.7 | 7979 | 45.4 | 25612 | 43.7 | 3166 | 44.8 |
| | Everyday | 12522 | 17.4 | 3503 | 19.9 | 10188 | 17.4 | 1548 | 21.9 |
| Frequency of spraying insecticide inside home | Never | 48136 | 67.0 | 12743 | 72.5 | 39206 | 66.9 | 5147 | 72.9 |
| | < 1 time/ month | 14313 | 19.9 | 2948 | 16.8 | 11752 | 20.0 | 1200 | 17.0 |
| | 1-3 times/ month | 4654 | 6.5 | 947 | 5.4 | 3801 | 6.5 | 349 | 4.9 |
| | Once/ week | 1424 | 2.0 | 260 | 1.5 | 1160 | 2.0 | 106 | 1.5 |
| | Several times/ week | 2524 | 3.5 | 479 | 2.7 | 2065 | 3.5 | 176 | 2.5 |
| | Every day | 418 | 0.6 | 88 | 0.5 | 351 | 0.6 | 42 | 0.6 |
| Mold Index (0 - 5) | Mean, SD | 0.81 | 0.8 | 0.38 | 0.6 | 0.8 | 0.8 | 0.26 | 0.5 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Mold Index (0 - 5) | 0 | 27983 | 38.9 | 11982 | 68.2 | 23068 | 39.3 | 5476 | 77.5 |
| | 1 - 2 | 41274 | 57.4 | 5435 | 30.9 | 33434 | 57.0 | 1543 | 21.8 |
| | >=3 | 2626 | 3.7 | 151 | 0.9 | 2137 | 3.6 | 44 | 0.6 |
| Household income (Million Yen/year) | < 2 | 3401 | 4.7 | 4621 | 3.4 | 2640 | 4.5 | 1744 | 2.5 |
| | >= 2, 4 < | 22727 | 31.6 | 590 | 26.3 | 18159 | 31.0 | 176 | 24.7 |
| | >= 4, 6 < | 22578 | 31.4 | 5769 | 32.8 | 18539 | 31.6 | 2340 | 33.1 |
| | >= 6, 10 =< | 18383 | 25.6 | 5399 | 30.7 | 15419 | 26.3 | 2326 | 32.9 |
| | Missing | 4794 | 6.7 | 1189 | 6.8 | 3882 | 6.6 | 477 | 6.8 |

¶: Postnatal indoor factors represents postnatal indoor mold and/or ETS exposure; n.a.: not applicable

FF-heater: forced flue venting system heater

**Table 2.** Associations between indoor environment during pregnancy and childhood eczema at 1.5Y with/without postnatal indoor factors†.

| Indoor environment during pregnancy | | Included postnatal indoor factors | | | | | | | | | Excluded postnatal indoor factors | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Total[a] (n =71883) | | | At least one of parent with allergies[b] (n =43161) | | | None of the parents with allergies[b] (n =10328) | | | Total[c] (n =17568) | | |
| | | N | OR | (95% CI) | *N* | OR | (95% CI) | *N* | OR | (95% CI) | N | OR | (95% CI) |
| House Type | Detached house | 18550 | | *Ref.* | 22584 | | *Ref.* | 5559 | | *Ref.* | 9275 | | *Ref.* |
| | Apartment | 16703 | 1.01 | (0.96, 1.06) | 20206 | 1.03 | (0.97, 1.09) | 4322 | 0.89 | (0.76, 1.05) | 7665 | 0.93 | (0.83, 1.04) |
| Building age | < 3 years | 6837 | 1.05 | (0.97, 1.13) | 8319 | 1.08 | (0.99, 1.18) | 2465 | 0.67 | (0.42, 1.05) | 5022 | 0.99 | (0.86, 1.15) |
| | >= 3 , <10 years | 9177 | | *Ref.* | 11094 | | *Ref.* | 1793 | | *Ref.* | 4607 | | *Ref.* |
| | >= 10 , <20 years | 7934 | 1.02 | (0.96, 1.10) | 9656 | 1.04 | (0.96, 1.13) | 2338 | 1.16 | (0.73, 1.84) | 3208 | 1.14 | (0.97, 1.33) |
| | >= 20 years | 8864 | **1.10** | (**1.02, 1.18**) | 10707 | **1.14** | (**1.04, 1.24**) | 2520 | 0.95 | (0.56, 1.61) | 3118 | 1.13 | (0.95, 1.34) |
| | Unknown | 2746 | 0.94 | (0.85, 1.04) | 3385 | 0.98 | (0.87, 1.11) | 848 | 1.29 | (0.65, 2.55) | 1102 | 1.10 | (0.86, 1.40) |
| Gas heater use | Yes | 3018 | **1.10** | (**1.01, 1.20**) | 3605 | 1.07 | (0.96, 1.18) | 684 | 0.83 | (0.60, 1.14) | 1449 | 1.15 | (0.95, 1.38) |
| Kerosene heater use | Yes | 17037 | 0.99 | (0.94, 1.05) | 20912 | 0.96 | (0.90, 1.02) | 5379 | 0.95 | (0.81, 1.13) | 7481 | 1.05 | (0.93, 1.18) |
| Wood stove use | Yes | 257 | 1.11 | (0.84, 1.45) | 304 | 1.17 | (0.85, 1.62) | 81 | 1.43 | (0.71, 2.91) | 100 | 1.03 | (0.53, 2.00) |
| Electric heater use | Yes | 20289 | 0.99 | (0.94, 1.04) | 24548 | 0.97 | (0.91, 1.03) | 5254 | 1.02 | (0.87, 1.19) | 9670 | 0.93 | (0.83, 1.05) |
| FF heater use | Yes | 541 | 1.17 | (0.97, 1.41) | 638 | 1.21 | (0.97, 1.50) | 148 | 1.06 | (0.58, 1.94) | 226 | **1.67** | (**1.14, 2.45**) |
| Furry pet keeping | Yes | 5864 | **0.88** | (**0.82, 0.94**) | 7043 | **0.89** | (**0.82, 0.97**) | 1786 | **0.80** | (**0.65, 0.98**) | 2664 | **0.85** | (**0.73, 0.99**) |
| Floor materials | Tatami | 3789 | | *Ref.* | 4708 | | *Ref.* | 1337 | | *Ref.* | 1579 | | *Ref.* |
| | Carpet on the tatami | 2858 | 1.05 | (0.94, 1.17) | 3486 | 1.00 | (0.87, 1.14) | 953 | **1.40** | (**1.02, 1.92**) | 1041 | 1.11 | (0.84, 1.47) |
| | Parquet floor or tiles | 13404 | **1.15** | (**1.06, 1.26**) | 16141 | **1.14** | (**1.02, 1.26**) | 3359 | **1.38** | (**1.05, 1.80**) | 6960 | **1.24** | (**1.01, 1.54**) |
| | Carpet on the parquet floor | 14789 | 1.08 | (1.00, 1.18) | 17953 | 1.09 | (0.99, 1.21) | 4165 | **1.38** | (**1.07, 1.78**) | 7237 | 1.16 | (0.94, 1.43) |
| Frequency of cleaning livingroom | Everyday | 6230 | 0.94 | (0.88, 1.01) | 7393 | 0.93 | (0.86, 1.01) | 1638 | 0.94 | (0.76, 1.17) | 3399 | 0.91 | (0.79, 1.05) |
| | Several/ week | 15713 | | *Ref.* | 18995 | | *Ref.* | 4167 | | *Ref.* | 7765 | | *Ref.* |
| | 1 time/ week | 1989 | 1.07 | (0.96, 1.18) | 2467 | 1.02 | (0.91, 1.16) | 3224 | 1.04 | (0.87, 1.23) | 4912 | 1.04 | (0.91, 1.17) |
| | 1-2 times/ week | 10873 | 1.02 | (0.96, 1.08) | 13397 | 1.00 | (0.94, 1.07) | 669 | 1.27 | (0.96, 1.67) | 723 | 0.95 | (0.72, 1.24) |
| | Seldom | 752 | 1.00 | (0.85, 1.17) | 908 | 0.99 | (0.82, 1.21) | 266 | 0.76 | (0.46, 1.27) | 258 | 1.45 | (0.99, 2.13) |
| Frequency of spraying insecticide | Never | 23680 | | *Ref.* | 28670 | | *Ref.* | 6838 | | *Ref.* | 12427 | | *Ref.* |
| | Once/ month | 7315 | **1.14** | (**1.07, 1.21**) | 8764 | **1.13** | (**1.05, 1.21**) | 1913 | 1.04 | (0.86, 1.25) | 2890 | **1.20** | (**1.05, 1.37**) |
| | 1-3 times/ month | 2381 | **1.19** | (**1.08, 1.30**) | 2836 | **1.15** | (**1.03, 1.29**) | 601 | 1.30 | (0.98, 1.73) | 937 | 1.01 | (0.80, 1.28) |
| | Once/ week | 689 | **1.26** | (**1.07, 1.47**) | 818 | 1.14 | (0.93, 1.40) | 219 | **1.62** | (**1.06, 2.47**) | 255 | 1.13 | (0.74, 1.74) |
| | Several times/ week | 1270 | **1.27** | (**1.12, 1.43**) | 1546 | **1.24** | (**1.07, 1.44**) | 335 | 1.14 | (0.77, 1.68) | 464 | **1.38** | (**1.03, 1.85**) |
| | Every day | 223 | **1.53** | (**1.17, 2.00**) | 259 | 1.34 | (0.96, 1.87) | 58 | **2.54** | (**1.27, 5.08**) | 84 | 0.92 | (0.42, 2.00) |
| Mold Index (0 - 5) | 0 | 13282 | | *Ref.* | 16377 | | *Ref.* | 3975 | | *Ref.* | 11619 | | *Ref.* |
| | 1 - 2 | 20862 | **1.27** | (**1.20, 1.33**) | 25109 | **1.27** | (**1.20, 1.35**) | 5640 | 1.13 | (0.95, 1.34) | 5291 | 1.10 | (0.98, 1.23) |
| | >=3 | 1414 | **1.36** | (**1.20, 1.54**) | 1675 | **1.34** | (**1.16, 1.55**) | 349 | **1.53** | (**1.05, 2.24**) | 147 | **1.61** | (**1.00, 2.58**) |

†: Postnatal indoor factors represents postnatal indoor mold and/or ETS exposure

FF-heater: forced flue venting system heater.
Odds ratios (OR) and 95% confidential intervals (CI) were adjusted following covariates:
a: Adjusted for child sex, maternal age at delivery, gestational age, birth weight, maternal smoking during pregnancy, annual household income, maternal history of allergies, renovation, ETS exposure at 1.5Y, and mold index at 1.5Y.
b: Adjusted for child sex, maternal age at delivery, gestational age, birth weight, maternal smoking during pregnancy, annual household income, renovation, ETS exposure at 1.5Y, and mold index at 1.5Y.
c: Adjusted for child sex, maternal age at delivery, gestational age, birth weight, maternal smoking during pregnancy, and annual household income, renovation, and maternal history of allergies.

**Table 3.** Associations between indoor environment during pregnancy and childhood eczema at 3Y with/without postnatal indoor factors†.

| Indoor environment during pregnancy | | Included postnatal indoor factors | | | | | | | | | Excluded postnatal indoor factors | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Total[a] (n=58639) | | | At least one of parent with allergies[b] (n=36199) | | | None of the parents with allergies[b] (n=8491) | | | Total[c] (n=7063) | | |
| | | N | OR | (95% CI) | *N* | OR | (95% CI) | *N* | OR | (95% CI) | N | OR | (95% CI) |
| House Type | Detached house | 32988 | | *Ref.* | 22584 | | *Ref.* | 5559 | | *Ref.* | 9275 | | *Ref.* |
| | Apartment | 24843 | 1.01 | (0.96, 1.07) | 15412 | 1.00 | (0.94, 1.07) | 3354 | 0.98 | (0.82, 1.16) | 2837 | 0.98 | (0.82, 1.17) |
| Building age | < 3 years | 11576 | 1.05 | (0.97, 1.13) | 7388 | 1.07 | (0.97, 1.17) | 1611 | 1.00 | (0.79, 1.28) | 2367 | 1.13 | (0.91, 1.40) |
| | >= 3 , <10 years | 15057 | | *Ref.* | 11094 | | *Ref.* | 1793 | | *Ref.* | 4607 | | *Ref.* |
| | >= 10 , <20 years | 12820 | 0.96 | (0.89, 1.03) | 7863 | 0.97 | (0.89, 1.06) | 1925 | 0.94 | (0.75, 1.17) | 1216 | 0.88 | (0.68, 1.14) |
| | >= 20 years | 14352 | 0.97 | (0.90, 1.04) | 8779 | 0.98 | (0.89, 1.07) | 2119 | 0.95 | (0.75, 1.21) | 1184 | 0.82 | (0.62, 1.09) |
| | Unknown | 4478 | 0.85 | (0.76, 0.95) | 2585 | 0.91 | (0.79, 1.04) | 647 | 0.63 | (0.43, 0.92) | 371 | 0.88 | (0.57, 1.34) |
| Gas heater use | Yes | 4940 | **1.10** | **(1.01, 1.21)** | 3115 | 1.11 | (0.99, 1.23) | 605 | 1.05 | (0.76, 1.43) | 628 | 1.02 | (0.77, 1.37) |
| Kerosene heater use | Yes | 28330 | 1.00 | (0.94, 1.06) | 17372 | 0.98 | (0.92, 1.05) | 4520 | 1.10 | (0.92, 1.31) | 2950 | 1.03 | (0.86, 1.25) |
| Wood stove use | Yes | 409 | 1.07 | (0.79, 1.45) | 245 | 1.06 | (0.74, 1.52) | 79 | 1.73 | (0.88, 3.43) | 33 | 0.82 | (0.25, 2.73) |
| Electric heater use | Yes | 32673 | 0.97 | (0.91, 1.02) | 20632 | 0.98 | (0.91, 1.04) | 4463 | 1.03 | (0.87, 1.22) | 3999 | **0.82** | **(0.68, 0.97)** |
| FF heater use | Yes | 842 | 1.07 | (0.87, 1.32) | 528 | 1.15 | (0.91, 1.47) | 125 | 0.69 | (0.32, 1.49) | 101 | 1.01 | (0.52, 1.97) |
| Furry pet keeping | Yes | 10041 | 0.96 | (0.90, 1.03) | 5994 | 0.96 | (0.88, 1.05) | 1509 | 1.01 | (0.82, 1.24) | 1054 | 0.98 | (0.77, 1.25) |
| Floor materials | Tatami | 6587 | | *Ref.* | 4708 | | *Ref.* | 1337 | | *Ref.* | 1579 | | *Ref.* |
| | Carpet on the tatami | 4798 | 0.93 | (0.82, 1.05) | 2825 | 0.90 | (0.78, 1.05) | 790 | 1.22 | (0.86, 1.74) | 374 | 1.06 | (0.68, 1.65) |
| | Parquet floor or tiles | 21661 | 1.08 | (0.99, 1.19) | 13744 | 1.06 | (0.95, 1.19) | 2895 | 1.33 | (0.99, 1.78) | 2981 | 0.83 | (0.60, 1.15) |
| | Carpet on the parquet floor | 24238 | 1.04 | (0.95, 1.14) | 14841 | 1.01 | (0.91, 1.13) | 3518 | 1.39 | (1.05, 1.83) | 2998 | 0.79 | (0.57, 1.09) |
| Frequency of cleaning livingroom | Everyday | 10188 | 0.98 | (0.92, 1.06) | 6178 | 0.97 | (0.89, 1.06) | 1402 | 1.09 | (0.87, 1.36) | 1548 | 1.09 | (0.88, 1.35) |
| | Several/ week | 25612 | | *Ref.* | | | *Ref.* | 15880 | | *Ref.* | | | *Ref.* |
| | 1 time/ week | 3368 | 0.95 | (0.85, 1.06) | 2046 | 0.98 | (0.86, 1.13) | 557 | 0.99 | (0.71, 1.38) | 234 | 0.63 | (0.35, 1.13) |
| | 1-2 times/ week | 18045 | 1.00 | (0.94, 1.06) | 11246 | 1.00 | (0.93, 1.07) | 2755 | 1.04 | (0.86, 1.25) | 1993 | 1.14 | (0.94, 1.38) |
| | Seldom | 1232 | 0.85 | (0.70, 1.02) | 750 | 0.87 | (0.70, 1.09) | 217 | 0.60 | (0.32, 1.11) | 96 | 0.92 | (0.44, 1.93) |
| Frequency of spraying insecticide | Never | 39206 | | *Ref.* | 28670 | | *Ref.* | 6838 | | *Ref.* | 12427 | | *Ref.* |
| | Once/ month | 11752 | 1.06 | (0.99, 1.13) | 7394 | 1.03 | (0.96, 1.12) | 1638 | **1.26** | **(1.04, 1.53)** | 1200 | 1.06 | (0.86, 1.32) |
| | 1-3 times/ month | 3801 | 1.00 | (0.90, 1.11) | 2394 | 0.94 | (0.83, 1.06) | 498 | 1.23 | (0.89, 1.70) | 349 | 0.88 | (0.60, 1.31) |
| | Once/ week | 1160 | 1.04 | (0.87, 1.25) | 684 | 0.99 | (0.79, 1.24) | 183 | **2.04** | **(1.32, 3.15)** | 106 | 0.94 | (0.47, 1.89) |
| | Several times/ week | 2065 | 1.03 | (0.90, 1.19) | 1292 | 1.01 | (0.86, 1.19) | 300 | 1.11 | (0.73, 1.71) | 176 | 0.78 | (0.44, 1.40) |
| | Every day | 351 | 1.15 | (0.84, 1.56) | 224 | 1.12 | (0.77, 1.61) | 51 | 1.98 | (0.88, 4.47) | 42 | 0.97 | (0.34, 2.77) |
| Mold Index (0 - 5) | 0 | 23068 | | *Ref.* | 16377 | | *Ref.* | 3975 | | *Ref.* | 11619 | | *Ref.* |
| | 1 - 2 | 33434 | **1.08** | **(1.02, 1.15)** | 20805 | 1.12 | (0.94, 1.34) | 4762 | **1.22** | **(1.03, 1.45)** | 1543 | 1.08 | (0.88, 1.33) |
| | >=3 | 2137 | **1.19** | **(1.04, 1.37)** | 1412 | 1.10 | (0.70, 1.73) | 280 | **1.70** | **(1.14, 2.54)** | 44 | 1.93 | (0.83, 4.46) |

†: Postnatal indoor factors represents postnatal indoor mold and/or ETS exposure.
FF-heater: forced flue venting system heater.
Odds ratios (OR) and 95% confidential intervals (CI) were adjusted following covariates:
a: Adjusted for child sex, maternal age at delivery, gestational age, birth weight, maternal smoking during pregnancy, annual household income, maternal history of allergies, ETS exposure at 3Y, and mold index at 3Y.
b: Adjusted for child sex, maternal age at delivery, gestational age, birth weight, maternal smoking during pregnancy, annual household income, ETS exposure at 3Y, and mold index at 3Y.
c: Adjusted for child sex, maternal age at delivery, gestational age, birth weight, maternal smoking during pregnancy, and annual household income, and maternal history of allergies.

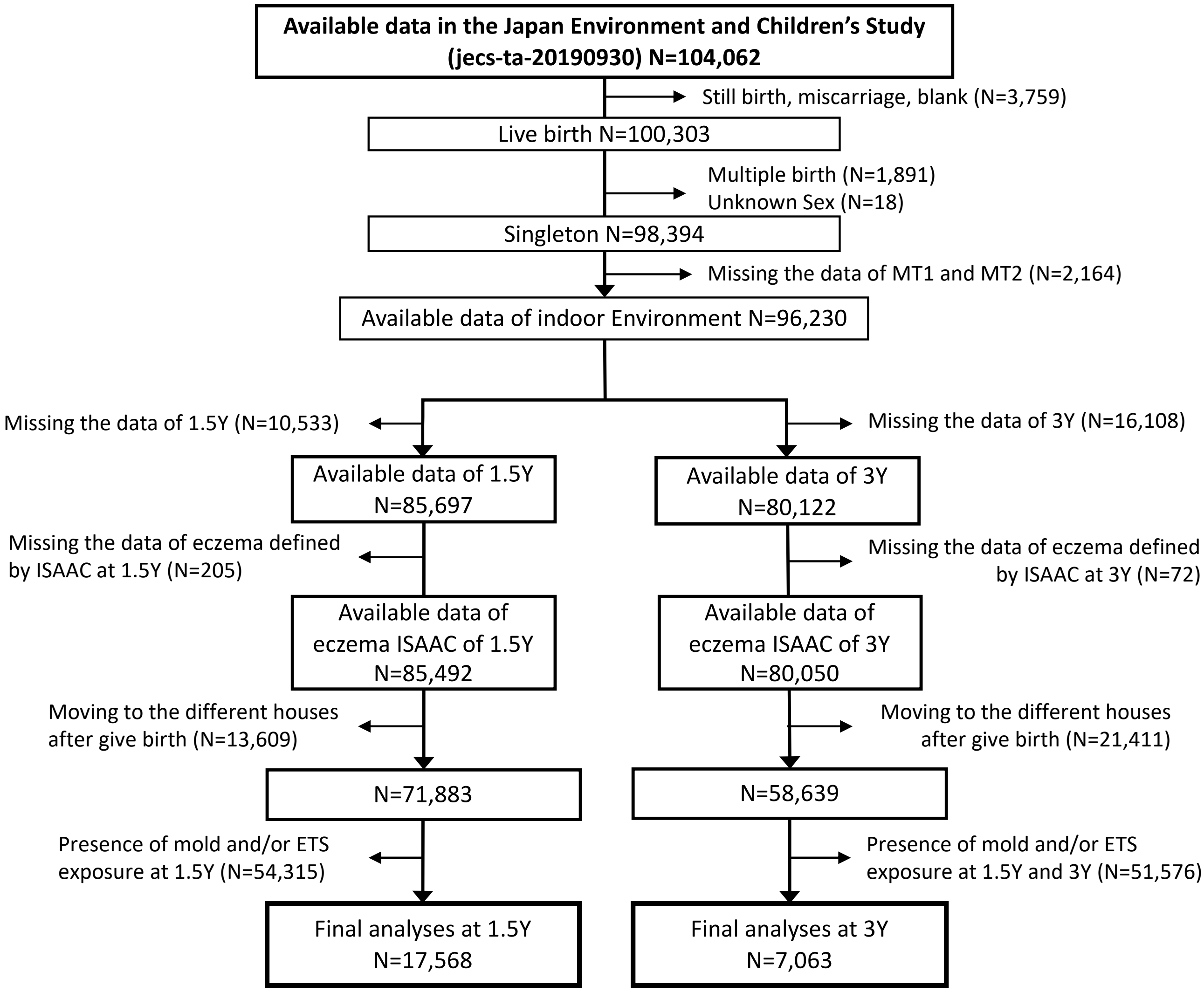


**Figure 1. Study population**