

SUPPLEMENTARY METHODS

Participants

This was a nationwide cohort study conducted by the Ministry of Health, Labour and Welfare. Two 21st Century Longitudinal Newborn Surveys were initiated (in 2001 and 2010). These surveys aimed to evaluate countermeasures for addressing Japan's declining birthrate. The survey that started in 2010 targeted all babies born in Japan between May 10 and 24, 2010. When the participants became 6 months old, baseline questionnaires were sent to 43,767 households, of which 38,554 responded (response rate, 88%). Follow-up questionnaires were sent to the respondents annually thereafter. Birth record data from Vital Statistics of Japan were also linked to each targeted child.

The relationships between birth order and allergic diseases were analyzed using data from the first to ninth surveys, corresponding to 6 months to 9 years of age. There was no missing information on birth order.

Birth order

Birth order was defined based on the number of deliveries a mother had, excluding stillbirths, as recorded in the birth records. The birth records included birth weight, gestational age, singleton/multiple birth, sex, birth order, and parents' ages. Using these data, the participants were classified into first, second, and third or later-born children.

Allergic diseases

In the second to the ninth surveys, the participants were asked whether they had consulted an outpatient clinic at least once in the past year due to common diseases. In

the seventh survey only, the participants were asked whether they had consulted an outpatient clinic once or more during the past 12 months or 18 months due to bronchial asthma, food allergy, or atopic dermatitis. To investigate changes in the prevalence of each allergic disease with age, follow-up evaluations were performed at the ages of 6-18 months, 18-30 months, 30-42 months, 42-54 months, 54-66 months, 66 months-7 years, 7-8 years, and 8-9 years. A history of at least one outpatient consultation for bronchial asthma, food allergy, or atopic dermatitis during each follow-up period category was used as the primary outcome.

Statistical analysis

Baseline characteristics were compared among birth order categories. Moreover, to evaluate selection bias due to loss to follow-up, baseline characteristics were compared between children included in the analysis and those lost to follow-up.

Log-binomial linear regression analysis was performed to evaluate the relationship between birth order and outpatient consultation due to each allergic disease in each follow-up period from 6 months to 9 years of age. Using first-born children as a reference, crude relative risk and 95% CI were estimated for second and third or later-born children. After controlling for potential confounding factors, adjusted relative risk and 95% CI were recalculated.

We selected the following biological and socioeconomic factors as potential confounding factors. The biological factors were sex (dichotomous), singleton/multiple birth (dichotomous), full-term/preterm birth (< 37 weeks: dichotomous), and maternal age at delivery (< 25 years, 25-29 years, 30-34 years, \geq 35 years: categorical). The socioeconomic factors included maternal smoking habit (non-smoker, smoker < 10

cigarettes/day, smoker ≥ 10 cigarettes/day: categorical), parents' educational background (university or higher, junior college/vocational school, high school, junior high school, and others: categorical), and residential place of living at birth (ward, city, town, village: categorical). Sex, singleton/multiple birth, gestational age, maternal age at delivery, and place of birth/place of residence were retrieved from birth records.

Information on maternal smoking status was obtained by the baseline survey.

Information on parents' educational attainment was obtained by the second survey.

Potential confounding factors were selected from previous studies or based on background information concerning the relationship between the birth order and allergic diseases. Cases with missing data were excluded, and complete case analyses were performed. No imputation was performed for missing data.

Subgroup analysis was also conducted to examine effect modification by sex and early daycare attendance. Early daycare attendance was based on whether or not the child was attending daycare at the age of 1.5 years. An answer of "caregiver" to the question, "Who usually takes care of the child during the daytime on weekdays?" in the second survey was defined as a child who attended daycare early in childhood. Further analysis included an interaction term between birth order and early daycare attendance.

Statistical analyses were performed using Stata version 17 (StataCorp LLC, College Station, TX, USA).

Ethics approval

Ethics approval for this study was granted by the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University

Hospital, Ethics Committee (No. 1506-073). Informed consent was not required as census data were publicly available and longitudinal survey data were fully anonymized for secondary use.