

Day-care attendance, position in sibship, and early childhood wheezing: A population-based birth cohort study

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Background: There are conflicting data on the effect of day-care attendance and position in sibship on the development of wheezing.

Objective: To investigate the relationship between day-care attendance and position in sibship with early childhood wheeze.

Methods: Prospective population-based birth cohort. At age 5 years, we collected information on parentally reported symptoms ($n = 922$); lung function was ascertained using plethysmography ($n = 745$) and allergic sensitization by skin testing ($n = 815$). Participants were assigned into categories according to the age of entry to day-care (0-6, 6-12, >12 mo) and number of older siblings (0, 1, 2, >2).

Results: Current wheeze was reported by 203 participants (22%); 224 (28%) were sensitized. In the multivariate model, sensitization (odds ratio, 2.47; 95% CI, 1.66-3.67), male sex (1.49, 1.01-2.20), maternal asthma (1.72, 1.10-2.68), and maternal smoking during pregnancy (2.15, 1.26-3.66) significantly increased the risk of wheezing. Entering day-care between 6 and 12 or after 12 months of age was significantly and inversely associated with current wheeze (0.25, 0.11-0.60; and 0.65, 0.44-0.98, respectively). Entry into nursery between 6 and 12 months reduced the risk of persistent wheezing ($P = .04$). We found no association between day-care attendance and lung function. Entering nursery in the first 6 months of life was associated with increased risk of atopy (2.47, 1.23-4.95). Having older siblings was associated only with rhinoconjunctivitis (0.72, 0.54-0.97).

Conclusion: Day-care attendance was associated with a reduced risk of current wheezing in 5-year-old children. The protective effect appeared strongest for children who entered day-care between the ages of 6 and 12 months. (*J Allergy Clin Immunol* 2008;122:500-6.)

Key words: Day-care, siblings, wheezing, birth cohort

The prevalence of asthma and wheeze has increased substantially over the last decades, but the reasons for this increase remain unclear.¹ The International Study of Asthma and Allergies in Childhood has revealed large variations in the prevalence of wheeze both between and within countries and provided the framework to explore these discrepancies further.² The latest data from the International Study of Asthma and Allergies in Childhood phase 3 suggest that in the mid-1990s, the prevalence of wheeze increased in most centers where the prevalence had been low, and decreased or remained unchanged in most centers where the prevalence had been high.³ In the United Kingdom (UK), although there is still evidence of an ongoing increase in the prevalence of wheeze among young children,⁴ in some areas the rate of rise in asthma has slowed,⁵ and even a downward trend has been reported.⁶

Numerous host and environmental risk and protective factors for wheezing have been identified^{1,7} and several hypotheses proposed to explain the increasing trends in prevalence.^{8,9} One of these (the hygiene hypothesis) proposes that decrease in exposure to infections and microbial products in early childhood may alter the maturation of the immune system. This could account for the observed increasing trends of asthma and other allergic disease, particularly in the developed countries.¹⁰

Contact with other children in nurseries or older siblings at home has been used as an indirect measure of exposure to infectious agents (although it must be emphasized that the size of exposure differs between the 2 settings). Thus, children with older siblings or attending a nursery early in life should be at lower risk of developing asthma/wheeze compared with those not receiving the protection offered by increased exposure to infectious agents via contact with older siblings or other children at day-care centers. However, studies investigating the associations among day-care attendance, the number of older siblings, and wheeze have produced conflicting results.¹¹⁻¹⁸ Results from birth cohort studies suggest that childhood wheezing illness is not a single disease but a spectrum of distinct phenotypes that may have different etiologies and different risk factors^{11,17,19,20}; only few studies investigating the effect of day-care or older siblings have taken this into account.

We hypothesized that day-care attendance and position in sibship have an effect on both presence and natural history of

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Abbreviations used

MAAS: Manchester Asthma and Allergy Study
OR: Odds ratio
SES: Socioeconomic status
UK: United Kingdom

wheezing in early childhood, and explored this hypothesis within the context of a large population-based birth cohort.

METHODS

Study population

The Manchester Asthma and Allergy Study (MAAS) is an unselected population-based birth cohort study described in detail elsewhere.^{19,21} Participants were recruited prenatally and followed prospectively, attending review clinics at ages 1, 3, and 5 years (± 4 wk). The study was approved by the Local Research Ethics Committee. Written Informed consent was obtained from all parents. For detailed methods, see this article's Online Repository at www.jacionline.org.

Definitions of exposures and outcomes

A validated questionnaire²² was interviewer-administered to collect information on parentally reported symptoms, physician-diagnosed illnesses, and treatments received. We also collected information on environmental tobacco smoke exposure, socioeconomic status (SES), pet ownership, and contact and childcare arrangements.

Day-care attendance. Data were derived from parental reports at first-year and third-year reviews. Children were assigned into 4 categories according to the type and age of entry into day-care: (1) no nursery (looked after at home or by child-minder, a person registered to look after 1 or more children in her/his own home), (2) entry into nursery before 6 months, (3) entry into nursery between 6 and 12 months, and (4) entry into nursery after 12 months of age.

Position in sibship. Data were derived from parental reports at recruitment, first-year, third-year, and fifth-year reviews. We created the following 4 categories: (1) no older siblings, (2) 1 older sibling, (3) 2 older siblings, and (4) more than 2 older siblings.

In addition, data were analyzed according to the attendance at day-care ever, entry into nursery before or after 12 months of age, and the presence or absence of older siblings.

Wheeze. According to parentally reported history of wheeze, *current wheeze* at age 5 years was defined as a positive response to the question, "Has your child had wheezing or whistling in the chest in the last 12 months?" On the basis of prospectively collected data, children were assigned to the following wheeze phenotypes^{23,24}: *no wheezing*, no wheeze during the first 3 years of life, no wheezing ever by age 5 years; *transient early wheezing*, wheezing during the first 3 years, no wheezing in the previous 12 months at age 5 years; *late-onset wheezing*, no wheeze during the first 3 years, wheezing in the previous 12 months at age 5 years; and *persistent wheezing*, wheezing during the first 3 years, wheezing in the previous 12 months at age 5 years.

Rhinoconjunctivitis. *Rhinoconjunctivitis* was defined as parentally reported presence of nasal symptoms and itchy eyes without a cold in the previous 12 months at age 5 years.

Eczema. *Eczema* was defined as parentally reported eczema ever at age 5 years.

Lung function. Specific airway resistance was measured at ages 3 and 5 years by using plethysmography as previously described.^{23,24} Children were asymptomatic at the time of assessment of lung function.

Atopic sensitization. Atopic sensitization was ascertained at age 5 years by skin prick testing (*Dermatophagoides pteronyssinus*, cat, dog, grasses, molds, milk, egg; Bayer, Elkhart, Ind) and defined as a wheal at least 3 mm greater than the negative control.

Statistical analysis

Statistical analysis was performed by using SPSS 13.0. (SPSS Inc, Chicago, Ill). Initially, risk factors were assessed by univariate analysis to see how each potential explanatory variable affected the presence of wheeze at age 5 years. Factors that were significantly associated with wheeze in the univariate analysis were examined in multiple logistic regression analysis adjusting for sex, parental asthma, environmental tobacco smoke exposure, day-care attendance, presence of older siblings, and allergic sensitization at age 5 years. The relationship between wheeze phenotypes and age of entry to day-care were investigated by logistic regression. The results are presented as odds ratios (ORs) and 95% CIs. Because the number of subjects in some wheeze phenotypes groups was too small to produce a viable multiple regression model, we did not perform the multivariate analysis.

RESULTS

Of 1085 children born into the cohort, 133 participants at high risk of atopy (both parents atopic) were prenatally randomized into a stringent environmental intervention¹⁹ and thus excluded from this analysis. Of 952 children who took part in the observational cohort, 922 (515 male) were reviewed at age 5 years (96.8% follow-up rate). Of those 922 participants, 77 (8.35%) have not provided information on day-care attendance. In the observational cohort, there was no difference between children with the information of day-care ($n = 845$) and those without ($n = 77$) for demographic characteristics including sex, maternal asthma, and position in sibship. Of 845 children with the information on day-care, 265 (31%) were looked after at home or by a child-minder, and 580 (69%) attended a nursery. Forty-one subjects (7%) entered nursery before the age of 6 months, 94 (16%) between 6 and 12 months, and 445 (77%) after 12 months. A total of 442 (48%) children were first-born. Of the 480 participants with older siblings, 342 (71%) had 1, 107 (22%) 2, and 31 (7%) more than 2 older siblings.

Skin prick tests were performed on 815 children; 536 children had lung function measured at age 3 years, and 745 at age 5 years. Current wheeze at age 5 years was reported by 203 (22%) participants, and 224 (28%) subjects were sensitized to at least 1 of the allergens.

Current wheeze at age 5 years

Univariate analysis. The results of the univariate analysis are presented in Table I. Nursery attendance at any age was associated with reduced risk of current wheeze. Analysis of the age of entry into day-care revealed that children who started attending a nursery between 6 and 12 months and after the age of 12 months had a significantly lower risk for wheeze at age 5 years compared with children who did not attend nursery (OR [95% CI], 0.32 [0.15-0.67] and 0.68 [0.47-0.98], respectively). No association was observed between current wheeze and the presence or number of older siblings.

The other significant associates of current wheeze in the univariate analysis were male sex, maternal history of asthma, environmental tobacco smoke exposure, SES, and allergic sensitization. No association was observed for paternal history of asthma, breast-feeding, older siblings, and cat or dog ownership. Maternal smoking in pregnancy was not independent of the SES and was more common among families with low SES compared with those with high SES (23.4% vs 7.6%; $P < .001$).

Multivariate analysis. Factors that were significantly associated with current wheeze in the univariate analysis were examined

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