

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

TABLE I. Risk factors for current wheeze at age 5 years: univariate analysis

Variable (n)*	Current wheeze			
	Frequency (%)	Yes, n (%)	OR (95%CI)	P value
Male sex (n = 922)	515 (56)	132 (26)	1.63 (1.18-2.25)	.003
Maternal asthma ever (n = 922)	177 (19)	56 (32)	1.88 (1.31-2.71)	.001
Paternal asthma ever (n = 922)	112 (12)	26 (23)	1.08 (0.68-1.73)	.74
Breast-fed (n = 872)	618 (71)	125 (20)	0.94 (0.66-1.34)	.73
Maternal smoking during pregnancy (n = 920)	128 (14)	42 (33)	1.93 (1.28-2.90)	.002
Maternal smoking age 5 years (n = 900)	159 (18)	44 (28)	1.50 (1.01-2.21)	.04
Paternal smoking during pregnancy (n = 920)	237 (26)	63 (27)	1.42 (1.01-2.00)	.05
Paternal smoking age 5 years (n = 900)	213 (24)	57 (27)	1.45 (1.02-2.08)	.04
SES				
High (n = 801)	502 (62)	80 (16)	Reference group	
Intermediate (n = 801)	150 (19)	38 (25)	1.79 (1.15-2.77)	.009
Low (n = 801)	149 (19)	42 (28)	2.07 (1.35-3.18)	.001
Cat owner at birth (n = 913)	218 (24)	50 (23)	1.12 (0.78-1.61)	.55
Cat owner age 5 y (n = 892)	193 (22)	44 (23)	1.13 (0.77-1.65)	.54
Dog owner at birth (n = 913)	170 (17)	45 (27)	1.41 (0.96-2.07)	.08
Dog owner age 5 y (n = 892)	138 (16)	33 (24)	1.21 (0.79-1.86)	.38
Atopy (SPT) age 5 y (n = 815)	224 (28)	78 (43)	2.53 (1.79-3.58)	<.001
Day-care attendance				
Home or child-minder (n = 845)	265 (31)	66 (25)	Reference group	
Nursery				
Any age (n = 845)	580 (69)	99 (17)	0.62 (0.44-0.88)	.008
<6 mo (n = 580)	41 (7)	8 (20)	0.73 (0.32-1.66)	.45
6-12 mo (n = 580)	94 (16)	9 (10)	0.32 (0.15-0.67)	.003
>12 mo (n = 580)	445 (77)	82 (18)	0.68 (0.47-0.98)	.04
Position in sibship				
First-born (n = 922)	442 (48)	92 (21)	Reference group	
Any older siblings (n = 922)	480 (52)	111 (23)	1.14 (0.84-1.56)	.40
1 older sibling (n = 480)	342 (71)	76 (22)	1.09 (0.77-1.53)	.63
2 older siblings (n = 480)	107 (22)	26 (24)	1.22 (0.74-2.01)	.43
>2 older siblings (n = 480)	31 (7)	9 (29)	1.56 (0.69-3.49)	.28

SPT, Skin prick test.

*Number of subjects with available data.

by multivariate analysis. Because one of the most important predictors of wheezing during childhood (maternal smoking) was not independent of the SES, these variables were modeled both separately and jointly. The variable regarding the presence of older siblings was also included in the multiple logistic regression model. In the model that included maternal smoking (but not SES), male sex (adjusted odds ratio [95% CI], 1.49 [1.01-2.20], $P = .046$), maternal asthma (1.72 [1.10-2.68], $P = .017$), maternal smoking in pregnancy (2.15 [1.26-3.66], $P = .005$), and allergic sensitization at age 5 years (2.47 [1.66-3.67], $P < .001$) were significantly and independently associated with an increased risk for current wheeze at age 5 years. Entering nursery between 6 and 12 or after 12 months of age was associated with a reduced risk for current wheeze at age 5 years (0.25 [0.11-0.60], $P = .002$; and 0.65 [0.44-0.98], $P = .04$, respectively; Fig 1). The effect of day-care on wheeze did not materially change when we examined its potential interaction with the other relevant variables (maternal asthma, maternal smoking, and position in sibship). For multivariate models which included the SES, see the Online Repository.

Wheeze phenotypes

We investigated the effect of age of entry to nursery on the natural history of wheezing within the first 5 years of life by analyzing its association with previously established phenotypes of wheeze.²³ Of 815 children with a full prospective data set, 439 never wheezed with the first 5 years of life, and 201 were

classified as transient early wheezers, 47 as late-onset wheezers, and 128 as persistent wheezers. We used children who have never wheezed and those who did not attend a nursery as reference groups. The results of the univariate analysis are presented in Table II. Entering a nursery between the ages of 6 and 12 months significantly reduced the risk of persistent wheeze (0.40 [0.17-0.94], $P = .04$). A weak association was observed for late-onset wheeze (0.24 [0.06-1.09], $P = .06$). Although statistical significance was not reached, the data suggested that children who attended a nursery appeared to be at an increased risk of having transient early wheeze. We acknowledge that some of the findings presented in Table II are indicative only of the reported associations because multivariate analysis was not performed.

The overall effect of day-care attendance on current wheeze and wheeze phenotypes did not materially change when data were analyzed with subjects assigned into those starting at nursery before and after 12 months of age (see this article's Tables E1 through E3 in the Online Repository at www.jacionline.org).

Lung function, atopic sensitization, rhinitis, and eczema

We found no association between day-care attendance and lung function at ages 3 or 5 years (Fig 2).

Entering nursery in the first 6 months of life was associated with an increased risk of atopy (2.47 [1.23-4.95], $P = .01$). No

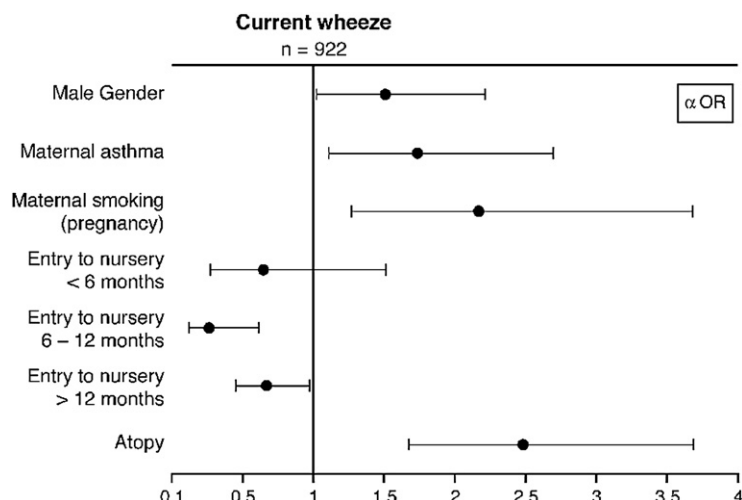


FIG 1. Adjusted odds ratios (95% CI) for factors independently related to current wheeze using logistic regression. Multivariate model included sex, parental asthma, exposure to parental smoking, day-care attendance, presence of older siblings, and allergic sensitization at age 5 years.

TABLE II. Results of the univariate analysis of the relation between age of entry into nursery and wheeze phenotypes

Age of entry into nursery	Wheeze phenotypes (n)					
	Transient early (201)		Persistent (128)		Late-onset (47)	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Any age (542)	1.17 (0.80-1.71)	.42	0.71 (0.46-1.09)	.12	0.51 (0.27-0.95)	.03
<6 mo (39)	1.21 (0.53-2.75)	.65	1.00 (0.40-2.53)	.99	0.31 (0.04-2.43)	.26
6-12 mo (90)	1.35 (0.77-2.36)	.30	0.40 (0.17-0.94)	.04	0.24 (0.06-1.09)	.06
>12 mo (413)	1.12 (0.75-1.67)	.58	0.75 (0.48-1.18)	.22	0.59 (0.31-1.13)	.10

Reference groups: never-wheezers (n = 439) and children not attending a nursery (n = 244).

associations were observed between age of entry to day-care and rhinoconjunctivitis or eczema.

Having older siblings was inversely associated with rhinoconjunctivitis (0.72 [0.54-0.97], $P = .03$), but position in sibship was not related to the other atopic phenotypes investigated (univariate analysis presented in Table III).

DISCUSSION

Principal findings

Our data suggest that children who attended nursery had a reduced risk of current wheeze at age 5 years compared with children cared for at home or by a child-minder. This effect was independent of atopic sensitization. The observed protective effect appeared strongest for children who entered the nursery between 6 and 12 months of age. With respect to the natural history of early childhood wheezing, the protective effect of day-care attendance was strong for persistent wheezing. Although statistical significance was not reached, our results indicated that children who attended a nursery may be at an increased risk of transient early wheeze. We observed no association between the age of entry into day-care and lung function, rhinoconjunctivitis, or eczema, but starting at nursery in the first 6 months of life was associated with an increased risk of atopy. In addition, we found no association between the presence and number of older siblings and wheezing. Having older siblings reduced the risk of rhinoconjunctivitis, whereas position in sibship was not related to the other atopic phenotypes investigated.

Limitations of the study

One of the limitations of our study is that some of the outcomes are based on parental report. Furthermore, although we imply that day-care attendance is a proxy measure of the exposure to various infectious agents, we did not have a direct measure of exposure to infections. However, over recent years several reports have shown that children attending day-care centers experience more infections than children cared for at home.²⁵⁻²⁹ Day-care centers may also be an important source of exposure to endotoxin.^{30,31} Recently, Hoffjan et al³² investigated the effect of interactions between a number of genetic polymorphisms and day-care exposure in the first 6 months of life on the cytokine response profiles and atopic phenotypes in the first year of life. The authors identified 6 gene-environment interactions between day-care and the early-life immune phenotypes (some of these were accounted for by the increased number of virus infections, whereas the others were independent of virus infections). These data suggest that in addition to the increased number of virus infections, there are other factors associated with this environment that may contribute to the day-care effect.

Another limitation is the small number of children who started nursery within the first 6 months of life (n = 41), and this may be the reason for failing to reach statistical significance in some of the results related to this group. In the UK and the majority of European countries, government regulations provide paid maternity leave for at least 6 months, and consequently, children are usually looked after by their mothers at home during the first 6 months of life.

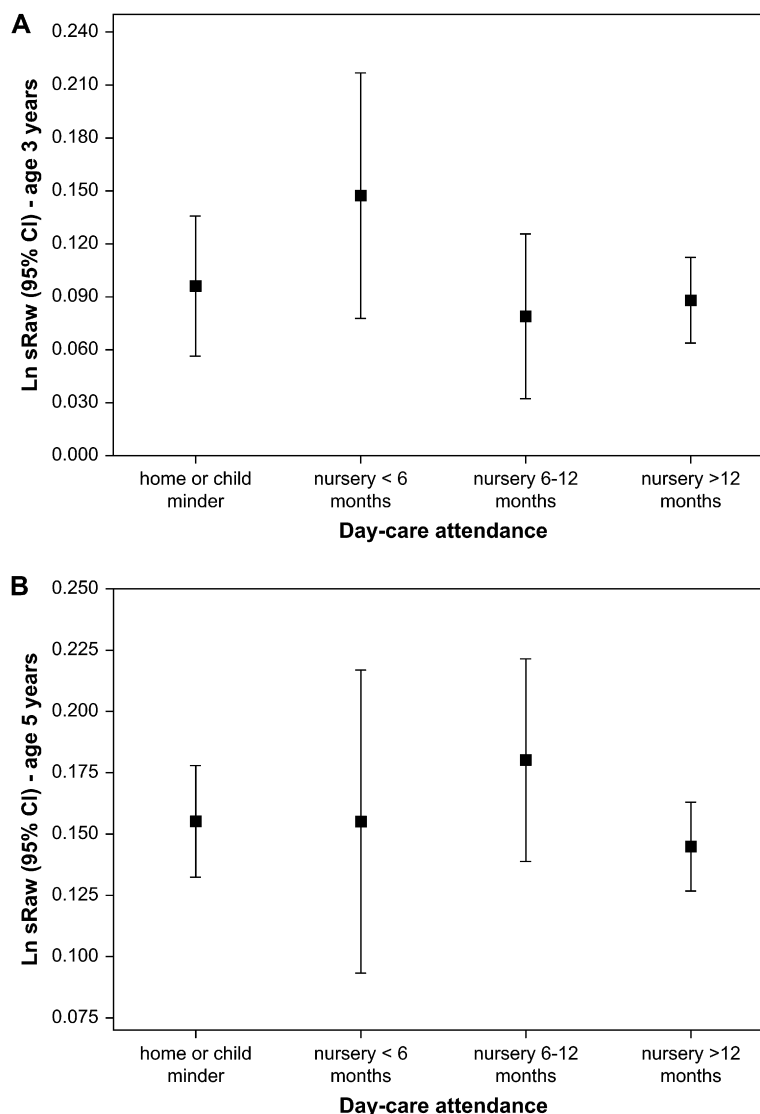


FIG 2. Relationship between day-care attendance and lung function (*Ln sRaw*, natural logarithm of specific airway resistance) at ages 3 (**A**) and 5 (**B**) years.

We included children cared for by a child-minder in the same group as those looked after at home. We made this decision because in our study population, the average number of children cared for by a child-minder was 3, which is much closer to the average number of children in families than the number of children in nurseries (where the average number was 70). We therefore argue that the environmental exposures among children cared for by child-minder are similar to those in homes rather than nurseries. In addition, the results did not materially differ when we performed the analysis with the 2 groups separately (data not shown).

The major strength of our study is careful longitudinal phenotyping from birth in an unselected population, with very high follow-up rate (in excess of 90%). Because asthma and allergic diseases start early in life and may progress or remit over time, the optimal study design to investigate them is a birth cohort, because it overcomes problems of recall bias and permits accurate phenotyping. In our study, we accurately defined symptoms, preschool lung function, and allergic status, and assessed day-care

attendance contemporaneously. Most previous studies that investigated the effect of day-care were cross-sectional studies or cohort studies among selected, predominately high-risk populations; none had a measure of lung function in preschool age.

Meaning of the study

Previous studies investigating the relationship between day-care attendance and wheeze have produced conflicting results, reporting reduced risk,^{11,12,15,16} increased risk,¹⁴ or no association.^{17,18} Furthermore, the protective effect demonstrated in some studies was observed only in selected groups.^{12,13} Celedon et al¹² showed that day-care attendance in early life was associated with a decreased risk of recurrent wheezing and asthma at the age of 6 years, but only among children without maternal history of asthma. In contrast, day-care attendance increased the risk of subsequent wheezing in children of mothers with asthma. In a study from Netherlands, day-care protection against wheezing occurred only among sensitized children.¹³ The protective effect

TABLE III. Day-care attendance, position in sibship, and rhinoconjunctivitis, eczema, and atopy (univariate analysis)

	Atopy		Rhinoconjunctivitis		Eczema	
	OR (95% CI)*	P value	OR (95% CI)*	P value	OR (95% CI)*	P value
Age of entry into nursery						
Attended at any age	1.07 (0.75-1.53)	.69	1.00 (0.72-1.39)	.69	1.02 (0.75-1.37)	.91
<6 mo	2.47 (1.23-4.95)	.01	0.86 (0.40-1.85)	.71	1.50 (0.77-2.90)	.23
6-12 mo	1.06 (0.60-1.87)	.85	0.88 (0.51-1.52)	.65	1.16 (0.72-1.88)	.53
>12 mo	0.98 (0.67-1.42)	.90	1.04 (0.74-1.46)	.81	0.95 (0.70-1.30)	.76
No. of older siblings						
Any older siblings	0.99 (0.72-1.34)	.93	0.72 (0.54-0.97)	.03	0.90 (0.69-1.18)	.45
1 older	0.89 (0.63-1.26)	.52	0.68 (0.49-0.94)	.02	1.01 (0.76-1.35)	.94
2 older	1.19 (0.74-1.93)	.47	0.78 (0.48-1.25)	.30	0.73 (0.47-1.14)	.16
>2 older	1.39 (0.60-3.21)	.44	1.03 (0.47-2.25)	.94	0.49 (0.22-1.13)	.09

*Unadjusted ORs with 95% CIs.

of day-care observed in our study was independent of maternal history of asthma and child's sensitization status.

There is evidence to support that the age of entry into day-care may influence the outcomes.^{11,33,34} Ball et al¹¹ showed that the inverse association between day-care and recurrent wheeze and asthma later in life was observed for children who entered the day-care before the age of 6 months. In Norway (where the majority of children start with day-care after 12 months of age), there was no association between day-care and asthma at age 10 years,¹⁷ and a recent Swedish study demonstrated that day-care attendance was associated with an increased risk for asthma and wheeze at age 6 years.¹⁴ However, most children in Sweden enter public day-care after the age of 18 months. Our results suggest that the risk of current wheeze at age 5 years was reduced in all children who attended a nursery, irrespective of the age of entry. This association appeared strongest among children who started the nursery between the age of 6 and 12 months. It is worth noting that during this period, the immature immune system gradually loses maternal antibody protection and starts to produce its own immunoglobulins.³⁵ Different exposures at this time point may promote the effective maturation of the immune responses.

Our findings on the relationship between day-care attendance and wheeze phenotypes are similar to previous reports^{11,16,36} indicating a higher risk for transient wheeze and a reduced risk for wheeze later in life.

Recently, Karmaus and Botezan³⁷ reviewed the literature published since 1965 on whether a higher number of siblings protect against the development of allergy and asthma. The sibling effect was less consistent for asthma/wheeze than for other allergic conditions. Of 31 studies reporting on asthma/wheeze in relation to the number of siblings, 22 found a negative, 1 a positive, and the others no association. We did not observe any association between the presence or number of older siblings and current wheeze in 5-year-old children, but the presence of older siblings was protective against rhinoconjunctivitis. Our data suggest that position in sibship and nursery attendance may be the markers of different exposures.

Implications

In recent years, the increasing demands in the developed societies have resulted in many lifestyle changes. Families are becoming smaller, and an increasing number of young children are looked after by child-minders or attend crowded day-care centers. It is well documented that children in the nursery environment have more respiratory, gastrointestinal, and other

infections than children cared for at home.^{25,26,28,29,38} The risk appears to be age-related, and the younger the child, the higher is the risk.²⁷

The effect of day-care on wheezing appears to be influenced by the starting age at day-care, which in turn is influenced by regulations on paid maternity leave, which vary among countries (eg, UK, 6 months; Norway, 12 months; Sweden, 18 months).

According to the British government Department for Education and Skills, day nursery provision has tripled over the period 1990 to 2001, whereas the number of child-minders has been steadily decreasing. On average, 70 children were enrolled in a nursery, whereas a child-minder cared for fewer than 4 children. In 2005, more than 700,000 children were attending full day-care settings, and nearly all (93%) were preschool children, with 21%, 24%, and 28% under 2 years old, 2 years old, and 3 years old, respectively.³⁹ The number of children attending full day nursery in the UK has been consistently increasing, whereas epidemiologic data suggest contemporaneous plateau or a decrease in the prevalence of wheezing.^{3,5,6} Further information is essential to ascertain whether the increasing trends in day-care attendance may act as a potential protective cofactor in preventing early childhood wheezing.

CONCLUSION

Day-care attendance was associated with reduced risk of current wheeze at age 5 years, and the effect appeared strongest if children entered the nursery between 6 and 12 months of age. No independent association was observed between the presence and number of older siblings and wheezing. Having older siblings reduced the risk of rhinoconjunctivitis. Day-care attendance and position in sibship may influence the atopic march, but different effects are observed for different phenotypes.

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Clinical implications: The protective effect of day-care attendance on the development of childhood wheezing may be strongest for children who enter day-care between 6 and 12 months of age.

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METHODS

Study design

The MAAS is a prospective study that follows the development of asthma and other atopic disorders in a cohort of infants.

Setting

The setting is the maternity catchment area of Wythenshawe and Stepping Hill Hospitals, including of 50 square miles of South Manchester and Cheshire, UK, a stable mixed urban-rural population. The study was approved by the Local Research Ethics Committee. Informed consent was obtained from all parents.

Participants

All pregnant women were screened for eligibility at booking antenatal visits (8th to 10th week of pregnancy). The study was explained to the parents, and informed consent for initial questionnaires and skin prick testing was obtained. Both parents completed a questionnaire about their and their partner's history of asthma and allergic diseases and smoking habits.

When informed consent had been obtained, pregnant women and their partners were skin prick tested. If the pregnant woman's partner was not present at the antenatal clinic visit, an invitation was sent for him to attend an open-access evening clinic at Wythenshawe Hospital for skin prick testing and a questionnaire. Once both parents had completed questionnaires and skin prick testing, a full explanation of the proposed future follow-up for the child was given.

Of the 1499 couples who met the inclusion criteria (≤ 10 wk of pregnancy, maternal age ≥ 18 y, questionnaire and skin test data available for both parents), 288 declined to take part in the study. Of 1211 couples who initially agreed to take part, 1085 had a successful full-term pregnancy (>36 wk gestation) and gave consent to a further follow-up. Of those, 133 were prenatally randomized into an environmental control group (see below), and 952 were followed as an observational arm of the cohort.

Allocation to study groups. Children were assigned to risk groups according to parental sensitization status. Nested within the cohort is a primary prevention study in which a subgroup of children at high risk (both parents atopic) without pets in home was randomized to either stringent environmental control (allergen impermeable covers for the parental and infant bed, hot washing of bedding weekly, high-efficiency particulate air vacuum cleaner, hard floor for the nursery) or a normal regimen. Children randomized to the environmental control group were excluded from this analysis.

Follow-up. The children were followed prospectively and attended review clinics at ages 1, 3, and 5 years (± 4 wk). We completed assessment at age 5 years in April 2003.

Variables

Symptoms and demographic data. Validated respiratory questionnaires were interviewer-administered at ages 1, 3, and 5 years to collect the information on symptoms, physician-diagnosed illnesses, and treatments received.

We also collected information on environmental tobacco smoke exposure, pet ownership, and contact and childcare arrangements.

Socioeconomic status was based on paternal occupation (adopted from the National Statistics Socio-economic Classification); children were assigned into 3 categories (high, intermediate, and low SES). Complete information on the definition of SES was available on 801 subjects.

Specific airway resistance. At age 3 and 5 years, we performed measurements of specific airway resistance (sR_{aw}) to assess airway function in all children who were willing to cooperate. Measurements of sR_{aw} were made by using a constant volume whole-body plethysmograph (Master-screen Body 4.34; Jaeger, Würzburg, Germany). Flow and volume were measured with a heated differential pressure screen-type pneumotachograph with a resistance of $0.036 \text{ kPa}^{-1}\text{s}$ and a dead space of 160 mL. Pressure measurements were made with a pressure transducer (Nr.660.99007; Hube Control AG, Wuerenlos, Switzerland) with an input range of ± 100

Pa, a resolution of 0.05 Pa, and a linear response up to 10 Hz. The plethysmograph was calibrated daily. Sensors in an ambient unit supplied with the plethysmograph recorded ambient data on temperature, humidity, and barometric pressure. The pneumotachograph was volume calibrated according to the American Thoracic Society recommendations using a 2-L syringe at flow rates of 0 to 1.5, 1.5 to 5, and >5 L/s. The half value period was calibrated to ensure a specific leakage in the box of 4 to 7 seconds.

The pressure transducer was calibrated using a 50-mL motor driven piston pump to generate sinusoidal variations of plethysmographic pressure. Electronic body temperature, pressure, and saturation compensation was applied throughout, using a time-shift of 60 ms.

sR_{aw} is measured by a single-step procedure from the simultaneously measured changes of respiratory flow and changes of plethysmographic pressure, omitting the measurement of thoracic gas volume. Measurements were performed during tidal breathing by using a facemask, which was adapted by fitting a standard pediatric facemask with a noncompressible mouthpiece made from silicone tubing. The end of the tubing was made rigid with an aluminum splint. The purpose of this was to maintain stable airway opening, prevent nose-breathing, and support the cheeks. The procedure was explained to the accompanying adult and the use of the facemask demonstrated to the child. The children were encouraged to sit in the plethysmograph alone, but if they refused, the accompanying adult, usually a parent, accompanied the child in the plethysmograph cabinet with the child seated on the parent's knee. The door of the plethysmograph was closed and the subject asked to breathe through the facemask.

Children were encouraged to breathe at a rate of 30 to 45 breaths per minute. If a parent accompanied the child, adults were asked to inhale and hold their breath for approximately 20 seconds. sR_{aw} measurements were made once a stable breathing pattern had been re-established. Once a stable breathing pattern was established, at least 3 measurements of sR_{aw} were performed, and each was calculated from the medians of 5 consecutively measured technically acceptable loops (each child performed at least 15 loops). The mean of these 3 measurements of effective sR_{aw} was used in the analysis. The measured values of sR_{aw} were corrected for the influence of the pneumotachograph screen and for the volume displacement caused by the subject (or subject + parent).

Children were asymptomatic at the time of assessment of lung function. A total of 536 children successfully performed lung function measurement at age 3 years, and 745 had sR_{aw} measured at age 5 years.

Allergic sensitization. We ascertained allergic sensitization at age 3 and 5 by skin prick testing (*D pteronyssinus*, cat, dog, mixed grasses, egg, milk, positive and negative controls). Sensitization was defined as wheal at least 3 mm greater than the negative control to at least 1 allergen tested.

RESULTS

Multivariate analysis

The results did not materially change in the model in which we included SES, but not maternal smoking. In this model, the independent significant associates of wheezing were the age of entry into day-care between 6 and 12 months (adjusted odds ratio [aOR], 0.31; 95% CI 0.12-0.77; $P = .01$), maternal asthma (aOR, 1.67; 95% CI, 1.01-2.76; $P = .05$) and allergic sensitization (aOR, 2.87; 95% CI, 1.88-4.36; $P < .001$).

In the multivariate model that included both maternal smoking and SES, the age of entry to day-care between 6 and 12 months remained an independent and significant associate of wheezing (aOR, 0.30; 95% CI, 0.12-0.76; $P = .01$). The other significant associates of wheezing were maternal asthma (aOR, 1.68; 95% CI, 1.02-2.78; $P = .04$) and allergic sensitization (aOR, 2.90; 95% CI, 1.90-4.42; $P < .001$). However, neither maternal smoking in pregnancy (aOR, 1.62; 95% CI, 0.89-2.96) nor SES (aOR, 1.56; 95% CI, 0.92-2.67 for low SES) remained significant associates of wheezing, suggesting that the high collinearity between

maternal smoking and SES rendered this multivariate regression model insufficiently robust; such a model may not accurately represent the relationship between the predictors and the outcomes.

It is worth emphasizing that the age of entry to day-care between 6 and 12 months remained an independent and significant associate of wheezing in all multivariate models, suggesting that our findings for day-care are independent of SES.

TABLE E1. Day-care attendance and current wheeze at age 5 years: univariate analysis

Variable	Current wheeze			
	Frequency (%)	Yes, n (%)	OR (95% CI)	P value
Day-care attendance (n = 845)				
Home or child-minder	265 (31)	66 (25)	Reference group	
Nursery				
Any age	580 (69)	99 (17)	0.62 (0.44-0.88)	.005
<12 mo	135 (23)	17 (13)	0.43 (0.24-0.78)	.005
>12 mo	445 (77)	82 (18)	0.68 (0.47-0.98)	.04

TABLE E2. Risk factors for current wheeze at age 5 years:
multivariate analysis*

Variable	aOR (95% CI)	P value
Sex (male)	1.50 (1.01-2.21)	.04
Maternal asthma ever	1.73 (1.11-2.70)	.02
Maternal smoking during pregnancy	2.22 (1.35-3.63)	.002
Entry into nursery before 12 mo	0.37 (0.19-0.70)	.002
Entry into nursery after 12 mo	0.65 (0.44-0.98)	.04
Atopy (SPT) at age 5 years	2.46 (1.66-3.64)	<.001

SPT, Skin prick test.

*Multivariate model included sex, parental asthma, exposure to parental smoking, day-care attendance, presence of older siblings, and allergic sensitization at age 5 y.

TABLE E3. Results of the univariate analysis of the relation between age entry into nursery and wheeze phenotypes

Age of entry to nursery	Wheeze phenotypes (n)					
	Transient early (201)		Persistent (128)		Late-onset (47)	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Any age (542)	1.17 (0.80-1.71)	.42	0.71 (0.46-1.09)	.12	0.51 (0.27-0.95)	.03
<12 mo (129)	1.31 (0.79-2.17)	.30	0.57 (0.29-1.11)	.10	0.26 (0.08-0.92)	.04
>12 mo (413)	1.21 (0.75-1.67)	.57	0.75 (0.48-1.18)	.22	0.59 (0.31-1.13)	.10

Reference groups: never-wheezers (n = 439) and children not attending a nursery (n = 244).