

Early Daycare Is Associated with an Increase in Airway Symptoms in Early Childhood but Is No Protection against Asthma or Atopy at 8 Years

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Rationale: Daycare exposes young children to more infections early in life and may thereby prevent the development of asthma and allergy.

Objectives: To prospectively study the effect of daycare on the development of asthma and allergic sensitization during the first 8 years of life.

Methods: In the Prevention and Incidence of Asthma and Mite Allergy birth cohort 3,963 newborn children were followed prospectively for 8 years. Daycare use and respiratory health were assessed yearly by questionnaires. At 8 years, sensitization to airborne allergens and airway responsiveness were measured. Daycare was defined as early (aged 0–2 yr), late (aged 2–4 yr), or none (no daycare before age 4 yr). Associations of daycare and/or older siblings with asthma symptoms (wheezing, shortness of breath, and inhaled steroids taken in the last year), airway responsiveness, and allergic sensitization were assessed in a longitudinal repeated-event analysis.

Measurements and Main Results: Children with early daycare had more wheezing in the first years of life, but less wheezing and steroid use between 4 and 8 years of age. At the age of 8 years, early daycare was not protective for asthma symptoms (adjusted odds ratio [aOR], 0.99; 95% confidence interval [CI], 0.74–1.32), allergic sensitization (aOR 0.86; 95% CI, 0.63–1.18), or airway hyperresponsiveness (aOR, 0.80; 95% CI, 0.57–1.14). The transient reduction in airway symptoms between age 4 and 8 years was only observed in children without older siblings.

Conclusion: Early daycare is associated with an increase in airway symptoms until the age of 4 years, and fewer symptoms between the ages of 4 and 8 years. We found no protection against asthma symptoms, hyperresponsiveness, or allergic sensitization at the age of 8 years.

Keywords: daycare; siblings; allergic sensitization; airway hyperresponsiveness; childhood asthma

Will parents who send their children to daycare thereby prevent the development of asthma and allergies at the cost of more airway infections in infancy? Previous studies have not been able to give a conclusive answer to this important dilemma.

A preventive effect of daycare attendance on the development of asthma has been suggested, based on the hypothesis that infections early in life may reduce the later development of allergic diseases (1). Daycare has been consistently associated

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Daycare exposes young children to more infections early in life, and may thereby prevent the development of asthma and allergy. Only a few longitudinal studies have investigated this association and these have given conflicting results.

What This Study Adds to the Field

Our study suggests that children who attend daycare experience more airway symptoms at an early age, but do not develop fewer asthma symptoms and/or allergies at the age of 8 years.

with increased prevalence of infections in early life (2–5). Because daycare is a modifiable factor it could be important for asthma prevention programs. However, convincing evidence that daycare is indeed associated with a reduction in asthma/allergy in the long term is lacking (6–10). The fact that multiple studies reported an increased risk of asthma in children with infections in early childhood further adds to the controversy (10–15).

In the Prevention and Incidence of Asthma and Mite Allergy birth cohort, daycare and the development of asthma and allergy were assessed prospectively in 3,963 children up to 8 years. At 8 years airway hyperresponsiveness and specific IgE in serum were measured. This enabled us to examine age-specific associations between daycare and the presence of older siblings on the one hand, and asthma symptoms and allergic sensitization on the other. Some of the results of this study have been previously reported in the form of an abstract (16).

METHODS

Study Population

Recruitment took place in the years 1996 to 1997. After birth the baseline study population consisted of 3,963 children. Questionnaires for parental completion, based on the ISAAC core questionnaires (17) were sent to the parents during pregnancy, at the child's ages of 3 and 12 months, and yearly thereafter up to the age of 8 years. At 8 years 3,518 children were invited for venipuncture to assess specific IgE for common allergens. Also, all children with an allergic mother ($n = 988$) and a random subset of children with a nonallergic mother ($n = 566$) were invited for a medical examination, including spirometry and measurement of airway responsiveness by means of a methacholine challenge (18). See Figure 1 for a population flowchart. Details of the Prevention and Incidence of Asthma and Mite Allergy study design

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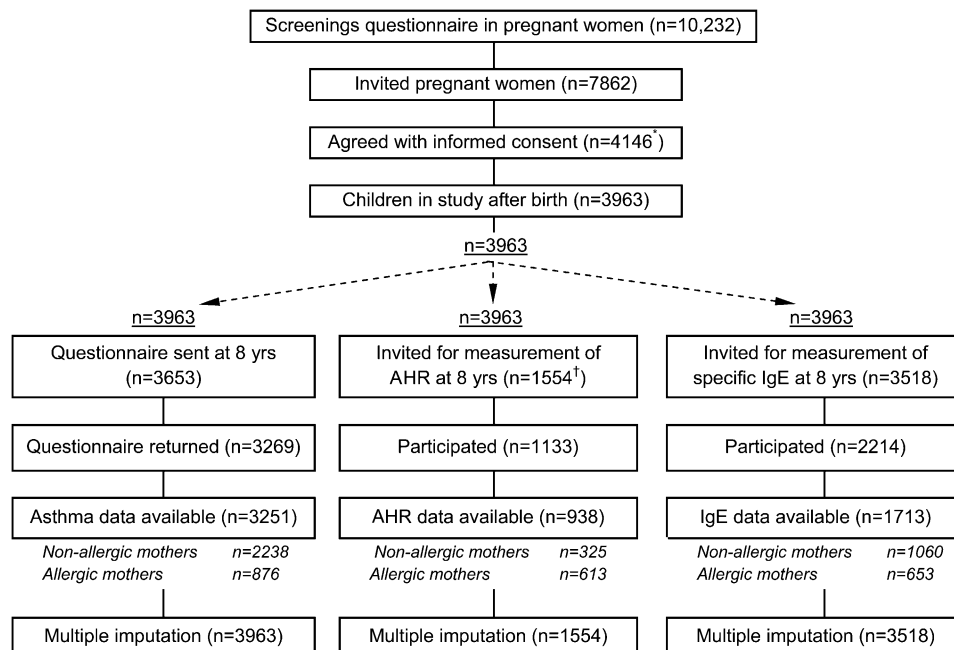


Figure 1. Population flowchart. All 3,963 eligible children could enter each of the three arms of flowchart. *A total of 1,327 allergic mothers (32%) and 2,819 non-allergic mothers (68%) were included, which is a good reflection of the general Dutch population. †Invited for the hospital-based medical examination, including airway hyperresponsiveness (AHR), were all children of allergic mothers ($n = 988$) and a random sample (22%, $n = 566$) of the children of nonallergic mothers who were still in the study at 8 years of age.

have been published previously (19). The study included an intervention part: 416 children (with allergic mother) were given house dust mite-impermeable mattress covers. This intervention had no effect on the incidence of allergy or respiratory symptoms at 4 or 8 years of age (20) nor was it associated with daycare attendance. Therefore, we decided to include these children in the present analysis. The study protocol was approved by the medical ethics committees of the participating hospitals.

Outcome Variables

Parents reported their child's airway symptoms annually at ages 1 to 8 years. Data on shortness of breath and prescription of inhaled steroids were collected yearly after the age of 2 years. We defined the following (dichotomous) outcomes, pertaining to the past 12 months: (1) wheezing: at least one attack of wheezing; (2) inhaled steroid prescription by a medical doctor (after age of 2 yr); (3) asthma symptoms: at least one attack of wheeze and/or at least one attack of shortness of breath and/or a prescription of inhaled steroids (after age of 2 yr); (4) allergic asthma: asthma symptoms plus sensitization to at least one airborne allergen (at age of 8 yr).

Sensitization to airborne allergens at 8 years was defined as specific IgE of 0.70 IU/ml or greater for at least one of the following: house dust mite (*Dermatophagoides pteronyssinus*), cats, dogs, grass pollen (*Dactylis glomerata*), birch, and *Alternaria alternata*. The cutoff was chosen because this was previously shown to be associated with clinical symptoms (21). Frequent respiratory tract infections were defined as parental report of three or more serious infections in the past year. Airway responsiveness was determined according to the protocol of the European Community Respiratory Health Survey (18) and airway hyperresponsiveness (AHR) was defined as a 20% or greater decrease of FEV₁ at a cumulative dose of 0.61 mg methacholine bromide or less.

Exposures and Confounders

Daycare use was assessed yearly and in our final analyses children were divided in three groups: early daycare (first attendance between 0–2 yr), late daycare (first attendance between 2–4 yr), and no daycare. Daycare was defined as at least 4 hours a week in a professional daycare institution, where children were exposed to other children under the age of 12 years. The average group size in professional daycare centers in The Netherlands is 10 children (22). The presence of siblings was defined as having an older sibling at time of birth (dichotomous). As potential confounders we defined: sex, gestational age, birth weight, parental education, ethnicity, mother's age, maternal allergies/asthma, breastfeeding, smoking during pregnancy, tobacco

smoke exposure at home, urbanization, presence of pets, and single parenthood.

Statistical Analyses

Associations of daycare or older siblings with the outcomes at 8 years were analyzed by logistic regression. Generalized estimating equations (GEE) were used to study associations with respiratory outcomes longitudinally, taking into account the correlation between repeated measurements in the same individual. Interaction of exposures and confounders with age was included in the GEE model when significant, allowing associations to vary with age. The analyses were stratified for maternal allergy and sex because these variables were potential effect modifiers. Also interaction between daycare attendance and siblings was tested. Besides a complete case analysis, missing data were multiple times imputed to avoid bias, which may result from complete case analysis (23, 24). The Multivariate Imputation by Chained Equations procedure in the statistical program R version 2.6.2 was used (25, 26). The 10 imputed data sets were analyzed and results combined using PROC MIANALYZE in SAS 9.1 (SAS Institute, Inc., Cary, NC). Data on sensitization and AHR were assessed in a subgroup. Therefore separate multiple imputation procedures were performed for these data, creating multiple imputed data sets for reported airway symptoms ($n = 3,963$), specific IgE ($n = 3,518$), and AHR ($n = 1,554$).

RESULTS

Study Population

Complete data on exposures and confounders was available in 3,643 of the 3,963 children (92%). Table 1 shows baseline characteristics of this group and their association with daycare and older siblings. After 8 years, 92% of the children were still in the study. In 1,445 children (36%) a questionnaire-based outcome was missing for at least 1 year. These children were more likely than children with complete data ($n = 2,518$) to have an atopic mother (39 vs. 27%) or a mother with a low level of education (31 vs. 20%), but less likely to attend daycare before the age of 5 (73 vs. 79%). Data on IgE were obtained in 1,713 children (response rate 49%) and data on airway responsiveness in 938 children (response rate 60%). The response rates were not associated with daycare. To avoid bias resulting from complete case analysis, reported results pertain to the multiple imputed data sets.

TABLE 1. GENERAL CHARACTERISTICS OF STUDY POPULATION

Characteristic	Baseline Population with Complete Data (<i>n</i> = 3,643)		Population with Early Daycare (<i>n</i> = 1,112)		Population without Early Daycare (<i>n</i> = 2,531)	
	%	<i>n</i>	%		%	
Female sex	48.3	1,760	47.3		48.8	
Born by caesarean section*	8.5	305	9.5		8.0	
Older siblings present†	50.2	1,828	60.2		45.3	
Maternal smoking in pregnancy†	16.8	604	14.3		17.9	
Smoking in house after birth (≥ once per week)*†	27.4	998	23.0		29.3	
Breastfeeding ever given*†	82.7	3,013	87.3		80.7	
Allergic mother	29.9	1,089	30.0		29.8	
Allergic father	30.7	1,119	32.6		29.9	
Single parenthood*†	1.1	42	1.9		0.8	
Pets present at birth†	53.4	1,937	49.7		55.0	
Maternal education level*†						
Low	22.7	825	11.4		27.6	
Intermediate	41.9	1,528	36.6		44.3	
High	35.4	1,290	52.0		28.1	
Daycare attendance‡						
Early daycare, age 0–2 yr	30.5	1,112	100		—	
Late daycare, age 2–4 yr	46.9	1,709	—		67.5	
No daycare before age 4 yr	22.6	822	—		32.5	
Urbanization, addresses/km ² *†						
<1,000	33.0	1,202	25.9		36.1	
1,000–1,500	23.3	847	20.1		24.6	
>1,500	43.7	1,594	54.0		39.3	
	mean	SD	mean		mean	
Maternal age, yr*†	30.4	3.8	31.3		30.0	
Duration of pregnancy, wk†	39.8	1.7	39.8		39.8	
Birth weight child, g†	3,517	544	3,502		3,515	

Significance of associations between characteristics and exposure variables (daycare/siblings) was tested using chi-square test (categorical variables) or analysis of variance (continuous variables). Smoking during pregnancy was considered positive only if mother reported smoking at least 4 weeks after estimated date of conception.

* Association with older siblings significant ($P < 0.05$).

† Association with daycare significant ($P < 0.05$).

‡ Defined as at least 4 hours per week in a daycare center with other children (younger than 12 yr of age) present.

Prevalence of Airway Symptoms and Asthma

Wheezing at least once was reported by 22% at 1 year and showed a linear decline to 8% at 7 years (Figure 2). Shortness of breath showed a similar time trend, with 16% positive at 3 years and 9% at 7 years. Prescription rates for inhaled steroids remained stable over time, between 8 and 9%. At 8 years, 15% of the children had at least one asthma symptom (wheezing, shortness of breath, or the use of inhaled steroids) (Table 2). Of the invited children, 33.6% were sensitized to one or more airborne allergens, and 8.9% had allergic asthma. Forty-six per cent with an allergic mother and 38% with a nonallergic mother had AHR.

Associations of Daycare and Siblings with Airway Symptoms, Sensitization, and AHR

Children with early daycare were twice as likely to experience wheezing in the first year of life, compared with children without daycare (adjusted odds ratios [aOR] at 1 yr, 1.89; 95% confidence interval [CI], 1.50–2.39). The association changed with increasing age; at 5 years there was a trend for less wheezing in children with early daycare (aOR, 0.83; 95% CI, 0.60–1.14). At 8 years, early daycare was not associated with wheezing. Figure 3 shows the adjusted odds ratios of daycare for wheeze, steroid prescription, and asthma symptoms. The associations of early and late daycare are plotted with no daycare as reference. The outcome “asthma symptoms” was not available at ages 1 and 2 years, but the associations with daycare at later ages followed the same pattern as for wheeze. We found no

protective effect from early daycare on asthma symptoms until 8 years (aOR at 8 yr, 0.96; 95% CI, 0.73–1.29). In the early daycare group a trend for fewer prescriptions of inhaled steroids was observed between the ages of 5 and 7 years, but not at 8 years. A sensitivity analysis in which stricter outcomes were defined as “frequent wheezing (≥ 4 episodes per year)” and “doctors diagnosis of asthma with asthma symptoms past year” led to similar results, without any protective effect of daycare at the age of 8 years. The associations with late daycare were less pronounced and not statistically significant on any outcome. We found the effect of daycare to change gradually with the age of first attendance, without a clear window of opportunity. Also when daycare was defined as “very early daycare” (attendance before the age of 6 mo) we found no protective effect on any respiratory outcome at the age of 8 years.

In the first year of life, children with older siblings had more wheezing than first-born children (aOR, 2.15; 95% CI, 1.81–2.56). The strength of the association with wheezing, steroid prescriptions, and asthma symptoms decreased linearly with age and disappeared at 8 years. The presence of older siblings was not protective for wheeze, inhaled steroid prescriptions, or asthma symptoms at any age.

Table 2 shows the adjusted associations between daycare, older siblings, and the clinical outcomes at 8 years. Neither daycare nor the presence of older siblings was associated with asthma symptoms, sensitization, allergic asthma, or AHR at 8 years.

Of the variables tested for confounding, the following changed the point estimate of either daycare or siblings, and were controlled for in all analyses: sex, birth weight, breastfeed-

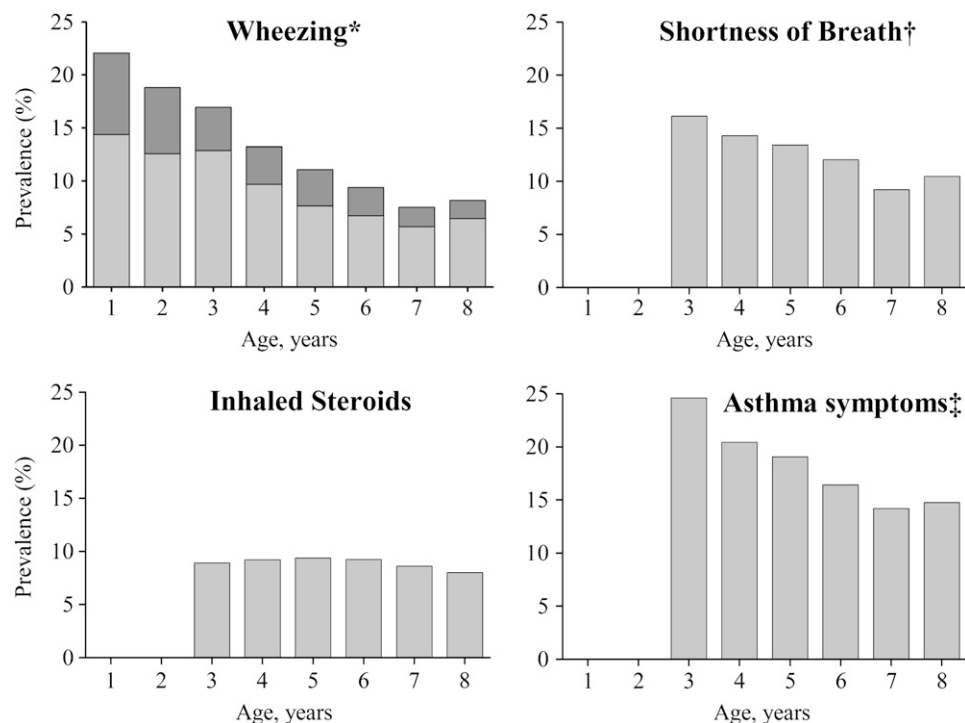


Figure 2. Annual prevalences of wheezing, shortness of breath, inhaled steroid prescriptions, and asthma symptoms up to the age of 8 years ($n = 3,963$). *Bars show infrequent (1–3 times, light gray) and frequent (4 or more times, dark gray) wheezing episodes per year. †At least one attack of shortness of breath in the past year. ‡Defined as at least one attack of wheeze, one attack of shortness of breath, or a prescription of inhaled steroids in the past year.

ing, urbanization, mother's age, mother's education, and maternal allergy. We found the associations with airway symptoms in the imputed data to be weaker than in the complete case data. However, the overall pattern did not change on any outcome. Results on sensitization and AHR were not affected by the multiple imputation analysis.

Interactions between Daycare and Sex, Atopy, or Siblings

Stratified analyses were performed to investigate effect modification by sex or maternal atopy. The effects of daycare and siblings did not differ between boys and girls or between children with and without an allergic mother. We found a significant interaction between siblings and daycare for wheeze ($P < 0.001$). In Figure 4 the occurrence of frequent respiratory infections, wheeze, and asthma symptoms are shown for children with early daycare and older siblings ($n = 486$), with early daycare but no older siblings ($n = 714$), and without daycare and siblings ($n = 330$). Children with older siblings and

early daycare had a more than fourfold higher risk of frequent respiratory infections and a more than twofold higher risk of wheezing in the first year compared with children without older siblings and daycare. After the age of 4 years children with early daycare and no older siblings were less likely to wheeze (significant at 5 yr), to use inhaled steroids (significant at 6 yr), and to have asthma symptoms (significant at age 5 to 7 yr) as compared with those without daycare. At the age of 8 years these associations had disappeared. Importantly, children exposed to both early daycare and older siblings experienced most infections and symptoms in early childhood, without a protective effect on wheeze, inhaled steroid prescription, or asthma symptoms until the age of 8 years. Interaction between daycare and older siblings was also significant for the outcomes sensitization and allergic asthma. In models allowing for this interaction, the associations of daycare and siblings with these outcomes remained not significant (Table 3).

TABLE 2. PREVALENCES OF OUTCOMES AT 8 YEARS AND ASSOCIATIONS WITH DAYCARE AND OLDER SIBLINGS

	Asthma Symptoms*		Sensitization†		Allergic Asthma‡		AHR§	
Overall prevalence	14.7%	$n = 429¶$	33.6%	$n = 473¶$	8.9%	$n = 147¶$	43.0%	$n = 402¶$
aOR** Older siblings††	aOR	95% CI	aOR	95% CI	aOR	95% CI	aOR	95% CI
aOR Early daycare‡‡	1.14	(0.92–1.42)	0.89	(0.73–1.09)	0.98	(0.69–1.40)	1.09	(0.81–1.45)
aOR Late daycare‡‡	0.99	(0.74–1.32)	0.86	(0.63–1.18)	0.77	(0.53–1.13)	0.80	(0.57–1.14)
	0.94	(0.72–1.23)	0.83	(0.65–1.05)	0.82	(0.60–1.14)	1.01	(0.82–1.45)

Definition of abbreviations: AHR = airway hyperresponsiveness; aOR = adjusted odds ratio; CI = confidence interval.

* Defined as at least one attack of wheeze, one attack of shortness of breath, or a prescription of inhaled steroids in the past year.

† Defined as a specific IgE concentration ≥ 0.70 IU/ml for at least one of the tested airborne allergens.

‡ Defined as positive score on both asthma symptoms and sensitization.

§ Defined as a decrease $\geq 20\%$ in FEV_1 at a cumulative dose of 0.61 mg methacholine.

|| Percentage of cases based on imputed data sets.

¶ Absolute number of cases based on complete data set (not imputed).

** Associations are adjusted for sex, birth weight, breastfeeding, urbanization, age and education of mother, history of allergies in mother.

†† No older siblings at birth is reference group.

‡‡ No daycare before the age of 4 years is reference group.

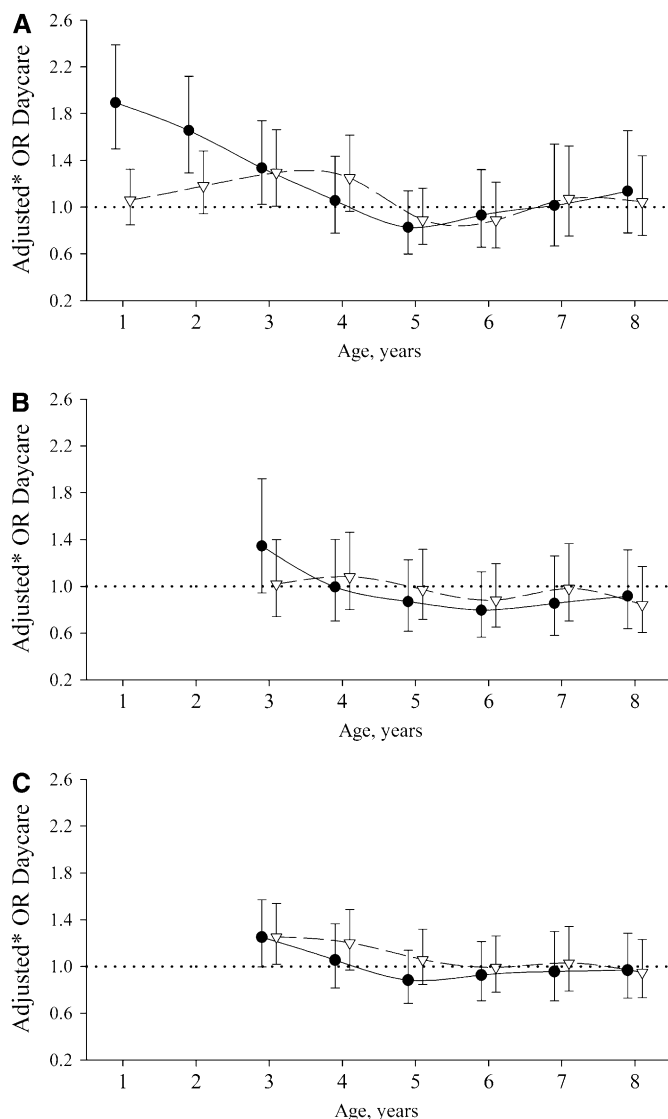


Figure 3. Adjusted odds ratios for longitudinal outcomes of wheezing at least once, inhaled steroid prescription, and asthma symptoms. Odds ratios and confidence intervals for early daycare and late daycare (no daycare is reference) for all outcomes, from longitudinal generalized estimating equations model. *Estimates adjusted for sex, birth weight, breastfeeding, urbanization, age, and education of mother, history of allergies in mother. (A) Wheezing at least once. (B) Steroid prescription by doctor. (C) Asthma symptoms. Circles = early daycare; triangles = late daycare; dotted line = no daycare (reference).

DISCUSSION

We found no evidence for a protective or harmful effect of daycare on the development of asthma symptoms, allergic sensitization, or airway hyperresponsiveness at the age of 8 years. Early daycare was associated with more airway symptoms until the age of 4 years and, only in children without older siblings, with a transient decrease in symptoms between 4 and 8 years. Children with early daycare and older siblings had the highest prevalence of respiratory symptoms in early childhood, but no decreased prevalence of asthma symptoms at any time point.

Since the postulation of the “hygiene hypothesis” by Strachan (1), many studies have focused on the relation between daycare and the development of asthma. Studies investigating the association between reported respiratory infections in early life and

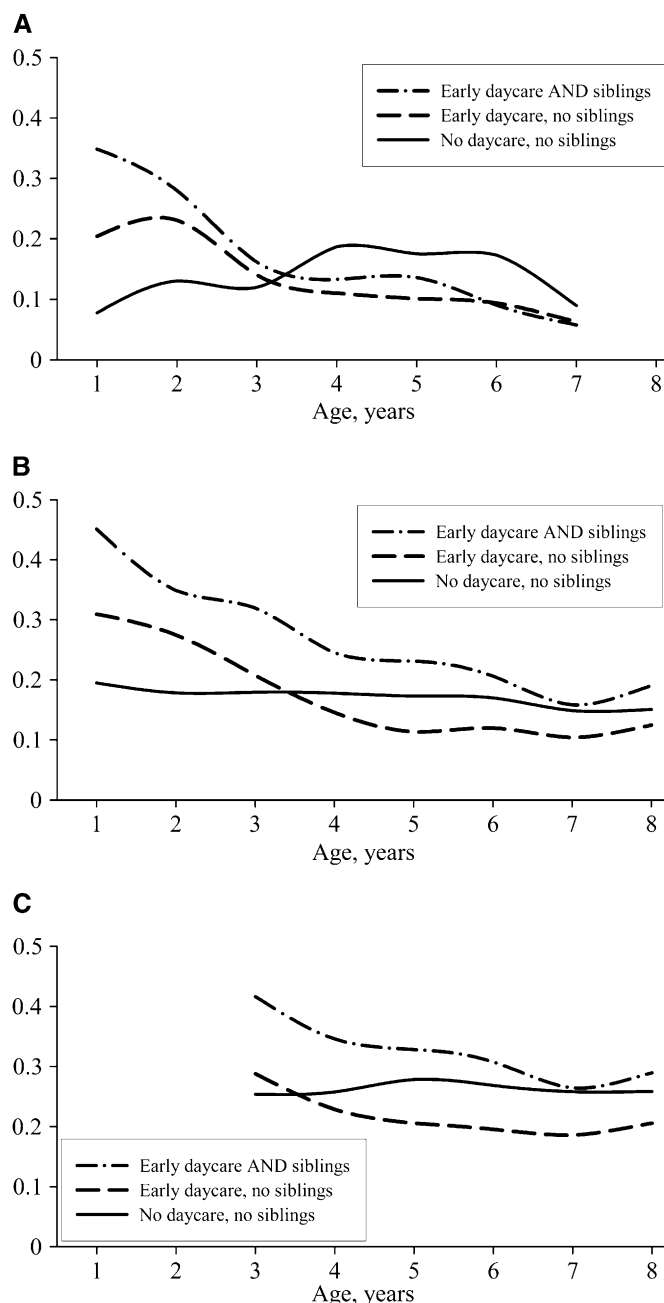


Figure 4. Predicted probabilities for longitudinal outcomes frequent respiratory infections, wheezing at least once, and asthma symptoms. (A) Predicted probability of frequent respiratory infections. (B) Predicted probability of wheezing at least once. (C) Predicted probability of asthma symptoms. Three lines represent children with: (1) early daycare and older siblings, (2) early daycare but no older siblings, and (3) no daycare and no older siblings. Predicted probabilities are calculated for children with: male sex, a nonallergic mother, breastfeeding ever given, and average values for gestational age, birth weight, urbanization, and age and education of mother.

development of asthma consistently found no protective effect on asthma (5, 10–15, 27). We studied the effect of daycare, which is a proxy for infections (2–5). Studying daycare has two important advantages compared with reported infections. First, the relation between daycare and asthma is unlikely to be influenced by reverse causation. This is a problem with reported infections because young children with an asthmatic constitution may be

TABLE 3. ASSOCIATIONS OF ASTHMA SYMPTOMS AND SENSITIZATION AT 8 YEARS WITH EARLY DAYCARE ATTENDANCE, ALLOWING INTERACTION BY PRESENCE OF OLDER SIBLINGS

Exposures*		Asthma Symptoms†		Sensitization‡		Allergic Asthma§	
Early daycare	Siblings	aOR	95% CI	aOR	95% CI	aOR	95% CI
Yes	Yes	1.32	(0.95–1.83)	0.97	(0.68–1.37)	1.06	(0.66–1.68)
Yes	No	0.83	(0.61–1.12)	0.86	(0.66–1.13)	0.64	(0.43–0.96)
No	Yes	0.99	(0.76–1.29)	0.82	(0.66–1.02)	0.81	(0.54–1.22)
No	No	1.00	<i>P</i> = 0.10¶	1.00	<i>P</i> = 0.36¶	1.00	<i>P</i> = 0.18¶

Definition of abbreviations: aOR = adjusted odds ratio; CI = confidence interval.

* No older siblings at birth in combination with no early daycare reference category.

† Defined as at least one attack of wheeze, one attack of shortness of breath or a prescription of inhaled steroids in the past year.

‡ Defined as a specific IgE concentration ≥ 0.70 IU/ml for at least one of the tested airborne allergens.

§ Defined as positive score on both asthma symptoms and sensitization.

¶ Significance of F-test for combined variable (siblings $\times$ early daycare).

|| Odds ratios are adjusted for sex, birth weight, breastfeeding, urbanization, age and education of mother, history of allergies in mother.

more likely to experience symptoms during respiratory infections and to get a doctors' diagnosis of infection. Second, daycare is a feasible target for prevention.

Previous studies investigating the effects of daycare on the risk of asthma were mostly cross-sectional and the results differed. Discrepancies can be explained by considering the results according to age. In early childhood, daycare has been consistently associated with more respiratory infections and wheezing (2–4, 28, 29). Between 3 and 5 years no association was found between daycare and asthma (29, 30). Between the ages of 4 and 14 years, a cross-sectional study reported less wheezing and asthma in children who attended daycare (6). A recent longitudinal study ($n = 922$) also reported a reduced risk of wheezing at 5 years in children with daycare (31). Our data cover a wide age range and show a pattern of an early increase in airway symptoms followed by a later reduction. Similar results were found in the Tucson Children's Respiratory Study ($n = 1,035$) and in the Home Allergens and Asthma Study ($n = 505$) (7, 32). We observed a reduction in airway symptoms associated with early daycare only in children without older siblings, in line with earlier reports of interaction between daycare and siblings (3, 4, 6).

The relationship between daycare and asthma later in childhood is less clear. We found no decreased prevalence of asthma symptoms at the age of 8 years in children who attended daycare. Similarly, Nafstad and colleagues reported no association between daycare and asthma at the age of 10 years in the Oslo birth cohort ($n = 2,540$) (10). A retrospective study in adults aged 20 to 44 years reported an increased risk of asthma associated with daycare attendance (9). In contrast, the Tucson study reported a preventive effect of daycare on the development of asthma lasting up to the age of 13 years (7). In this study, exposure was defined as daycare before the age of 6 months and information was collected retrospectively around the age of 7 years, introducing the possibility of recall bias (7). Furthermore, a significant effect on asthma was only reported for the combined effects of older siblings and daycare. To our knowledge, no prospective study has reproduced these findings.

This is the first prospective study to report on the relation between daycare and AHR. We found no significant decrease in AHR in children exposed to daycare or older siblings in early childhood. The high prevalence of AHR could imply that the cutoff at a cumulative dose of 0.61 mg or less of methacholine bromide was not strict enough for our population. However, in a separate sensitivity analysis where responsiveness was defined as the dose-response slope (% change in FEV₁ in response to total methacholine bromide dose), a continuous variable, we found no significant association with early daycare. AHR is a feature of

asthma (33) and has strong predictive value for the long-term prognosis (34, 35). The findings that daycare was not associated with asthma symptoms at 8 years and did not affect AHR strongly support our conclusion that early daycare does not prevent asthma.

The relationship between daycare attendance and atopy remains unclear despite earlier studies. Several studies reported a lower prevalence of sensitization in children with daycare, as measured by skin prick test reactivity (7, 14, 30) or specific IgE (14, 28). Other studies found no significant association (9, 10, 36, 37), or even increased sensitization, after daycare (31, 38). These studies vary in methodology: some investigated skin tests, others specific IgE, and different allergies were assessed. Furthermore, the definition of daycare and the age at which outcomes were assessed varied. We found no significant effect of daycare or siblings on sensitization measured by the presence of specific IgE. We found a trend of less asthma with sensitization in children with early daycare and without siblings. Likewise, Krämer and colleagues reported lower rates of sensitization and asthma associated with early daycare in a cross-sectional study in Eastern Germany, in a subgroup of children without siblings (6). Possibly children with older siblings are already exposed to more infections early in life, reducing any additional effects of daycare. However, if infections would protect, one would expect a dose-response relationship with the largest protection in children with the highest microbial burden at an early age. Our results show that children with older siblings and early daycare indeed experienced most infections in infancy but did not develop less asthma or sensitization, thus arguing against a causal relationship.

Strong points of our study are the large cohort with a prospective design, long follow-up with very good compliance, and collection of objective data, including AHR and specific IgE. Because the study population is a fairly random representation of the Dutch population, our results can be generalized. However, in the population invited for AHR measurement there was an overrepresentation of children with an allergic mother. Because we found no interaction by allergy of the mother on the association between daycare and AHR, this does not compromise generalizability of our findings. There is evidence that the age of entry into daycare may influence the natural course of asthma (6, 31). It has been suggested that a window of opportunity exists earlier in life (e.g., in the first 6 mo of life) (7). We found no support for this in our data. Early daycare was defined as attendance before the age of 2 years, but the majority of these children (59%) visited daycare before the age of 6 months. Also, when the definition was limited to attendance before the age of 6 months there was no significant association with any of the studied outcomes at 8 years.

Some limitations should be considered in the interpretation of our results. First, in the absence of a gold standard, the definition for asthma remains arbitrary. Apart from the sensitive definition "asthma symptoms" we performed sensitivity analyses with outcomes "frequent wheezing (≥ 4 times/yr)" and "doctors' diagnosis of asthma with asthma symptoms past year." Early daycare was associated with higher prevalence of all these outcomes in the first years of life, but there was no association at the age of 8 years. Second, airway symptoms were based on parental reports. Especially at early ages this may have led to some misclassification. Most likely any misclassification would be independent of the exposure to daycare (i.e., nondifferential), causing underestimation of the effect. Because we found strong correlations especially in the first years of life, we consider it unlikely that our results have been biased by misclassification of early symptoms. Parents with an atopic history may report wheeze more accurately and this could influence our results. However, we found that atopy of the mother had no confounding effect nor did it modify the effect of daycare on any of the outcomes. Furthermore it should be realized that apart from early infections, multiple other pathways might explain a relation between daycare and later asthma symptoms. Finally, children were followed up to the age of 8 years. Strictly, we can therefore not exclude a protective effect of early daycare on symptoms at later ages. Our data are not suggestive of such an effect.

What are the practical implications of our findings? We found that early daycare is associated with a transient decrease in wheezing after the age of 4 years, but not with the development of allergic sensitization, AHR, or asthma symptoms at 8 years. Apparently, the incidence of asthma cannot be reduced by promoting early daycare attendance. Early daycare merely seems to shift the burden of respiratory morbidity to an earlier age, where it is more troublesome than at a later age. Hence, early daycare should not be promoted for reasons of preventing asthma and allergy.

Conclusion

Early daycare is associated with an increase in airway symptoms until the age of 4 years, and fewer symptoms between 4 and 8 years. We found no protection against asthma symptoms, hyperresponsiveness, or allergic sensitization at the age of 8 years.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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