

Age of entry to day nursery and allergy in later childhood

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Summary

Background Infections in early childhood may prevent allergies in later life. If this hypothesis is true, early exposure to childcare outside the home would protect against atopy by promotion of cross infections. We investigated whether children who attend a nursery at a young age have a lower rate of atopy and fewer allergies than children who attend from an older age.

Methods In a cross-sectional study carried out in 1992–93, we examined 2471 children in three age-groups (5–7, 8–10, and 11–14 years) from the towns of Bitterfeld, Hettstedt, and Zerbst in eastern Germany. The children's parents answered a questionnaire about allergies and symptoms, attendance at day care, and related factors. Sensitisation was assessed by skin-prick tests and measurement of allergen-specific IgE antibodies in serum.

Findings In 669 children from small families (up to three people), the prevalence of atopy was higher among children who started to attend day nursery at an older age than in those who started to attend at a younger age ($p < 0.05$). Compared with children who first attended at age 6–11 months, the adjusted odds ratios for a positive skin-prick test were 1.99 (95% CI 1.08–3.66) for children who attended at age 12–23 months and 2.72 (1.37–5.40) for those who attended at age 24 months and older. In 1761 children from large families (more than three people), age of entry to day nursery had no effect on atopy.

Interpretation Our findings accord with the hypothesis that early infection may protect against allergies in later life.

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Introduction

The prevalence of childhood allergies has increased during the past decades.¹ One hypothesis is that a decline in exposure to infections early in life may be partly responsible for this trend.^{2–4} An inverse relation has been shown between some childhood infections and atopy in later life.^{5–7} Stimulation of Th1 lymphocytes by infections that may inhibit the expansion of allergen-specific Th2 lymphocytes at a critical time during early childhood could explain these results,^{8,9} although lack of effect of early vaccination on the development of atopy is puzzling.¹⁰ Indirect evidence of an inverse relation between early childhood infections and allergies in later life comes from studies that reported an inverse relation between the number of siblings and allergic sensitisation.^{7,11,12} Siblings promote cross infections and this effect also takes place in day-care centres. Children who attend day nursery have more infections,^{13–16} especially infections of the respiratory tract,^{17–19} than children who do not attend day nursery. If this infection hypothesis is true, children who attended day nursery should have fewer allergies in later life than children who did not. Comparisons between the two groups showed no differences in allergies or allergic sensitisation in schoolage children²⁰ or in young adults.¹² Why preschool nursery attendance does not seem to reduce the rate of atopy in later life is not known.²¹

An increase in the risk of respiratory illness associated with attendance at day nursery is most pronounced or even detectable if a child has no older siblings.²² Marbury and colleagues¹⁸ reported that the effect of day-care attendance on respiratory illness is stronger in firstborns than in those not born first. Therefore, a reduction in atopy associated with preschool nursery attendance might be detectable only in firstborns or in families with only one child.

We aimed to investigate the association between preschool attendance at day nursery and atopy in later life in a cross-sectional survey of children aged 5–14 years from eastern Germany.

Methods

Participants

Between September, 1992, and August, 1993, 2773 children from the towns of Zerbst, Bitterfeld, and Hettstedt in southern Sachsen-Anhalt, eastern Germany, were selected to take part in the study.²³ There were three age-groups: 5–7 years (school entrants), 8–10 years (third grade), and 11–14 years (sixth grade). In Zerbst and Hettstedt, we enrolled all children in the three age-groups. In Bitterfeld, a random sample that represented a third of all schools and kindergartens (for school entrants) in the region formed the population base used to recruit study participants.

Study design

To keep variability between observers to a minimum, physical examinations and functional tests were done in the three towns by the same team of one physician and one nurse who used standard methods. To exclude seasonal influences, the team

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moved from town to town every 2 weeks. The study protocol was assessed and approved by the appropriate ethics committee and all parents gave their informed consent. A questionnaire was sent to the parents with a letter of invitation. The questionnaire was completed at home and collected by school teachers or leaders of the kindergartens together with the parents' written consent. After one reminder letter, 2471 (89.1%) of the 2773 questionnaires were returned. 302 questionnaires were not filled in because of refusal or non-compliance with study protocol. The response rate in the three towns was similar.

The questionnaire was developed with items previously validated in several national and international studies, including the core questions of an earlier version to the International Study of Asthma and Allergies in Childhood²⁴ questionnaire. Our questionnaire contained 78 questions about: lower-respiratory diseases (doctor diagnosed bronchitis ever); allergic diseases and symptoms (doctor diagnosed asthma ever, or hayfever ever, wheezing ever, irritated eyes in previous year); family history of atopy; environmental exposure to tobacco smoke; breastfeeding; preterm birth and intubation at birth; use of medication and surgical history; education of parents; age of entry to day nursery; and outdoor and indoor environmental exposure. We classified age at first entry to day nursery as: 6–11 months, 12–23 months, 24 months and older, and no attendance up to 36 months. We combined the two latter categories to age 24 months or older for first entry to day nursery, because of the small number of children in each of these categories. The outcome variables did not show any significant differences between both categories. Outdoor and indoor environmental exposure was described on the questionnaire as: "smoking of mother during pregnancy"; "heating with fossil fuels"; "damp flat"; "present smoking in flat"; "moulds visible in flat"; "gas use without ventilation"; "age of building"; "frequent contact with animals"; "wall-to-wall carpet in child's bedroom"; and "house located in street with heavy traffic". We obtained information about immunisations from the vaccination card on the day of the physical examination. The only category on the questionnaire with a "do not know" option was the question about wheezing, because in German there is no equivalent word for wheezing. Thus, information on wheezing was missing for 288 children.

We defined family size according to the number of people living together. A small family was classified as fewer than four people living together in the flat. We did not ask about the presence of siblings. We concluded that the child had no siblings if the parents did not answer any of the questions about the health status of the child's brothers and sisters or if they stated that the child had no brothers and sisters. Of the 732 children who had no siblings, 571 (78%) were from small families according to our definition. Of the 1698 respondents who answered any of the questions, 1545 (91%) children came from large families. We included this sibling variable in the analysis to check the stability of our results when we used this variable instead of the family size variable.

Allergy tests

In accordance with the protocol of the European Community Respiratory Health Survey,²⁵ we used skin-prick tests (Allergopharma Reinbeck, Germany) to assess sensitisation to 12 common allergens—*Dermatophagoides pteronyssinus* allergen Der p1, *D farinae* allergen Der f1, *Aspergillus fumigatus*, *Alternaria alternata*, cat epithelium, local grasses, mugwort, hazel, birch, plantain, milk, and egg. A 1/1000 titre of histamine was used as a positive control and a 0.9% saline solution as a negative control. We defined a positive result to an allergen as a wheal of at least 3 mm diameter. If the reaction to the positive control was less than 3 mm or if that to the negative control was greater than 2 mm, we repeated the test the next day. Participants with abnormal reactions to positive or negative controls at the second test were excluded from the analysis. Skin-prick tests were not done in children with acute eczema on both forearms. Valid skin-prick tests were available from 2188 (89%) of the 2471 children whose parents completed the questionnaire.

We measured specific IgE antibodies against birch pollen (t3), grass pollen (g6), cladosporium (m2), ascaris (p1), house-dust mite (*D pteronyssinus* d1), and cat (e1) by enzyme immunoassay with the radioallergosorbent test (RAST) system (Pharmacia, Freiburg, Germany). Identical charges of allergens were used throughout the study. A specific IgE measurement was available for 2130 (86%) of the 2471 children. We were unable to measure some specific IgEs in 422 children because an insufficient amount of blood was collected. RAST was judged positive if any of the available specific IgE concentrations were 0.84 µg/L or greater and judged negative if lower than 0.84 µg/L.

Statistical analysis

We used logistic-regression models to analyse all the data for the 2430 children with information on family size and the exposure variable for age of entry to day nursery. The estimates of the models were transformed to odds ratios (95% CI). Children who started to attend day nursery from age 6–11 months were the reference group and were compared with those whose first attendance was at 12–23 months or 24 months and older. We also did trend tests with the categorical value of age at entry as a continuous variable. A p value of 0.05 or less was judged significant. The core model included sex, age-group, allergy in family, place of residence, and education as fixed covariates. Additional potential confounders were indoor and outdoor environmental exposure. We included these confounders in the final model if they changed one of the odds ratios for age of entry to the day nursery by at least 10%.²⁶ Odds ratios were calculated for only the 2250 children with complete information on all covariates. We tested interactions of age at entry (as continuous variables) with each of the chosen covariates by inclusion of the respective product terms in the logistic-regression model; higher order interactions were not investigated.

Results

Data on family size and the exposure variable for age of entry to day nursery were known for 2430 children, 669 of whom were from small families and 1761 from large families. Table 1 shows the rate of allergy-related variables by age of entry to day nursery and by family size.

Among children from small families, all allergy-related variables showed an upward trend with older age at entry

	Age (months) of entry to day nursery		
	6–11	12–23	≥24
Whole group (n=2430)			
Asthma ever	446 (0.5)	1464 (1.2)	504 (2.4)
Wheezing ever	392 (25.0)	1294 (30.1)	456 (24.3)
Hayfever ever	447 (4.3)	1469 (4.0)	507 (5.1)
Irritated eyes previous year	446 (7.4)	1453 (6.3)	497 (7.0)
Positive skin-prick test	399 (19.1)	1310 (20.2)	447 (23.0)
Positive RAST test	387 (43.9)	1276 (37.7)	440 (43.9)
Bronchitis ever	446 (57.4)	1464 (55.6)	504 (46.6)
Small families (n=669)			
Asthma ever	147 (0.0)	383 (1.0)	134 (3.0)
Wheezing ever	124 (22.6)	338 (27.2)	117 (25.6)
Hayfever ever	148 (2.7)	386 (4.4)	134 (8.2)
Irritated eyes previous year	146 (5.5)	382 (6.8)	134 (10.5)
Positive skin-prick test	134 (15.7)	331 (21.8)	111 (27.0)
Positive RAST test	126 (35.7)	327 (33.9)	112 (45.5)
Bronchitis ever	147 (56.5)	383 (53.5)	134 (47.8)
Large families (n=1761)			
Asthma ever	229 (0.7)	1081 (1.3)	370 (2.2)
Wheezing ever	268 (26.1)	956 (31.2)	339 (23.9)
Hayfever ever	299 (5.0)	1083 (3.8)	373 (4.0)
Irritated eyes previous year	300 (8.3)	1071 (6.2)	363 (5.8)
Positive skin-prick test	263 (20.2)	971 (19.2)	332 (21.4)
Positive RAST test	261 (47.9)	949 (39.0)	328 (43.3)
Bronchitis ever	299 (57.9)	1081 (56.3)	370 (46.2)

Data are number (%).

Table 1: Allergy-related symptoms, diagnoses, and sensitisations by age of entry to day nursery in children aged 5–14 years

	Age (months) of entry to day nursery			p
	6-11	12-23	≥24	
Small families (n=669)				
Sex (female/male)	66/82	199/188	72/62	0.253
Parents with allergy/ total (%)	37/132 (28)	128/366 (35)	40/130 (30.8)	0.303
Age (years)				
5-7	16 (10.8)	205 (53.2)	27 (20.2)	<0.001
8-10	70 (47.3)	78 (20.2)	41 (30.6)	
11-14	62 (41.9)	102 (26.6)	66 (49.3)	
Total for variable	148	387	134	
Town of residence				
Zerbst	50 (33.8)	117 (30.2)	40 (29.9)	0.360
Bitterfeld	42 (28.4)	145 (37.5)	51 (38.1)	
Hettstedt	56 (37.8)	125 (32.3)	43 (32.1)	
Total for variable	148	387	134	
Education of parents (years at school)				
<10 years	10 (6.8)	24 (6.3)	13 (10.0)	0.690
10 years	74 (50.3)	191 (50.1)	60 (46.2)	
>10 years	63 (42.9)	166 (43.6)	57 (43.9)	
Total for variable	147	381	130	
Large families (n=1761)				
Sex (female/male)	134/286	539/549	194/179	0.158
Parents with allergy/ total (%)	79/281 (28.1)	281/1037 (27.1)	78/347 (22.5)	0.180
Age (years)				
5-7	13 (4.3)	409 (37.6)	85 (22.8)	<0.001
8-10	124 (41.3)	347 (31.9)	117 (31.4)	
11-14	163 (54.3)	331 (30.5)	171 (45.8)	
Total for variable	300	1088	373	
Town of residence				
Zerbst	107 (35.7)	386 (35.5)	145 (38.9)	0.753
Bitterfeld	98 (32.7)	337 (31.0)	111 (29.8)	
Hettstedt	95 (31.7)	366 (33.6)	117 (31.4)	
Total for variable	300	1088	373	
Education of parents (years at school)				
<10 years	20 (6.9)	78 (7.3)	44 (12.3)	0.002
10 years	155 (53.3)	501 (47.0)	184 (51.3)	
>10 years	116 (39.9)	487 (45.7)	131 (36.5)	
Total for variable	291	1065	359	

Results are number (%) unless indicated.

Table 2: Health risk factors and lifestyle characteristics by age of entry to the day nursery in children aged 5-14 years

to day nursery. Exclusion of children with insufficient serum samples did not affect the results for sensitisation. The RAST test was positive in 89 (36.0%), 268 (35.5%), and 90 (44.4%) of children who first attended day nursery at age 6-11 months, 12-23 months, and 24 months and older, respectively. For children from large families, age at entry to day nursery had no effect on atopy. For bronchitis, there was a downward trend for older ages of entry to day nursery. Table 2 shows the distribution of characteristics and risk factors for allergies by age of entry to day nursery. Table 3 shows the number of children with allergies by age of entry to day nursery who have complete information on all covariables.

There were significant differences in exposure between the three age-groups. Children aged 5-7 years in 1992 had entered day nursery at an older age than those older than 7 years. The parents of children who entered day nursery at age 24 months and older had lower educational attainment than the parents of children who entered day care before this age. None of the other potentially confounding variables on exposure we tested reached the chosen change-in-estimate criterion. We report the estimates of the core model. Since no child in the reference group of small families had asthma, we calculated p values for trend but not odds ratios for this variable. The results of the logistic regression analysis are shown in table 4.

For small families, the adjusted odds ratios range from 1.11 to 2.29 for allergy-related variables for children who entered day nursery at age 12-23 months compared with

	Number of children by age (months) at entry to day nursery			
	6-11	12-23	≥24	Total
Small families (n=620)				
Asthma ever	0/131	4/357	4/127	615
Wheezing ever	28/110	85/315	30/110	535
Hayfever ever	4/132	16/360	11/127	619
Irritated eyes previous year	5/131	25/357	14/127	615
Positive skin-prick test	17/119	67/308	30/107	534
Positive RAST test	38/112	104/304	50/105	521
Bronchitis ever	74/131	192/357	63/127	615
Large families (n=1630)				
Asthma ever	2/275	13/1012	6/334	1621
Wheezing ever	66/247	282/893	76/306	1446
Hayfever ever	14/274	38/1014	14/337	1625
Irritated eyes previous year	21/275	66/1002	19/330	1607
Positive skin-prick test	50/243	180/914	64/302	1459
Positive RAST test	112/240	349/889	124/296	1425
Bronchitis ever	160/275	576/1012	155/334	1621

Table 3: Number of children with information on all covariates by age (months) at entry to day nursery

the reference group. The odds ratio for a positive skin-prick test is significantly higher than 1.0. For children who entered day nursery at age 24 months or older, the odds ratios ranged from 1.12 to 3.63, and are significantly greater than 1.0 for all variables apart from wheezing. Similarly, all allergy-related variables apart from wheezing showed a positive trend with older age at entry to day nursery (as continuous variable) significantly greater than zero. These findings did not change when we analysed the data for the 621 children with no siblings who have information on all covariates. With the exception of wheezing, all trends for an increase in atopy with older age at entry to day nursery were positive for these 621 children. The adjusted p values for trend are 0.06 for asthma, less than 0.01 for hayfever, 0.03 for irritated eyes, less than 0.01 for positive skin-prick test, and 0.06 for positive RAST. The adjusted effects are stronger than the unadjusted ones. There were no such effects for children from large families. For bronchitis, the odds ratios were lower than 1.0. We found no significant interaction of age at entry to day nursery with age-group or with educational attainment of the parents. Of all other tested interactions, the only significant interaction was of parental allergy with age of entry to day

	n	Odds ratio (95% CI) by age (months) of first entry to day nursery		p for positive trend
		12-23	≥24	
Small families (n=620)				
Asthma ever	615			0.03
Wheezing ever	535	1.11 (0.66-1.85)	1.12 (0.61-2.04)	0.36
Hayfever ever	619	1.80 (0.56-5.75)	3.63 (1.09-12.09)	0.03
Irritated eyes previous year	615	2.29 (0.84-6.24)	3.23 (1.11-9.38)	0.03
Positive skin-prick test	534	1.99 (1.08-3.66)	2.72 (1.37-5.40)	<0.01
Positive RAST test	521	1.26 (0.78-2.05)	2.03 (1.15-3.59)	<0.01
Bronchitis ever	615	0.86 (0.56-1.32)	0.77 (0.47-1.27)	NT
Large families (n=1630)				
Asthma ever	1621	1.76 (0.38-8.22)	2.77 (0.54-14.14)	0.09
Wheezing ever	1446	1.09 (0.78-1.52)	0.89 (0.60-1.33)	NT
Hayfever ever	1625	0.90 (0.47-1.72)	0.98 (0.46-2.12)	NT
Irritated eyes previous year	1607	0.86 (0.50-1.46)	0.78 (0.41-1.47)	NT
Positive skin-prick test	1459	0.98 (0.67-1.42)	1.16 (0.75-1.77)	NT
Positive RAST test	1425	0.81 (0.60-1.09)	0.89 (0.63-1.27)	NT
Bronchitis ever	1621	0.90 (0.68-1.19)	0.63 (0.45-0.87)	NT

NT=trend was negative, so no p values.

*Reference category age 6-11 months at first entry to day nursery.

†Adjusted for parental allergy (bronchitis not), parental education, gender, age group, and place of residence.

Table 4: Effect of age of entry to day nursery on allergy-related variables in children aged 5-14 years with information on all covariates

nursery. There was a positive trend of hayfever with older age of entry to day nursery in only those children whose parents have an allergy.

Discussion

Our findings show that in children aged 5–14 years from small families who entered day nursery at age 6–11 months, the prevalence of atopy was lower than in children who entered day nursery at an older age. There was no such association in children from large families.

Selection bias cannot explain these results. Even if the response to the study were associated with atopy, it is unlikely that this association would vary with age of entry to day nursery. Recall bias may have a role; parents who did not want their child to enter the day nursery at the usual age of 1 year, but let, for example, a grandmother care for the child, might also deviate in the recollection of diagnoses and the perception of symptoms. Parents who sent their child to the day nursery at a very young age might not have detected some illnesses, but this factor would not explain the association with positive skin-prick tests or specific IgE values. Because of the cross-sectional nature of our data, we cannot rule out that older age of entry to day nursery reflects a bad health status. However, three points can be made against this argument: first, this explanation is not valid for bronchitis for which the trend goes in the opposite direction; second, hay fever and related symptoms mostly start after age 3 years; and, third, such an effect should also have been seen in large families.

Our analysis of whether missing values for the variables wheezing, and positive skin-prick test, or positive RAST were associated with any of the included covariates showed that none of the variables were associated with age of entry to day nursery. Missing data for wheezing were mostly for boys and for children whose parents had low educational attainment. Missing values for the sensitisations were most common for parents without allergies. Since the effect of age of entry on allergy was not modified by these covariates, we do not believe that this selection biased our results.

Our finding that children aged 5–7 years entered day nursery later than children older than 7 years is explained by a change in law in 1986 (*Gesetzesblatt der Deutschen Demokratischen Republik vom April 24, 1986*), just before the children aged 5–7 years were born. From that time on, mothers with a firstborn could get 1 year of paid maternity leave and mothers with more children had longer leave. Before 1986, mothers of a firstborn child were entitled to only 6 months of paid leave. Thus, the crude rates given in table 1 underestimate the true effect of age at entry to day nursery and atopy, and the adjusted odds ratios show a stronger association than the unadjusted ones. Most of the other factors associated with age of entry to day nursery act in the same direction—ie, bias the unadjusted odds ratio towards null. The parents of children who entered day nursery at an older age had low educational attainment and girls entered day nursery at an older age than boys. These factors are associated with a low rate of atopy.²⁷ Since we did not know the child's position in the sequence of siblings in the large families, we cannot adjust for the fact that children who entered day nursery at age 6–11 months could be firstborns, which has been associated with an increased risk of atopy.¹² Therefore, the missing

effect in larger families could reflect missing data.

Family size correlated to the sibling variable and our results did not change when we used the sibling variables instead of the family size variables.

The similarity of effects across the age-group is unexpected since there were dramatic changes in environmental conditions after the political changes in Germany in 1989. This finding hints at a true effect of early infections. The result that the effect for hayfever is present only in children whose parents have allergies could be an artefact caused, for example, by a better ability to recognise hayfever in parents who have allergies or by a true effect.

Previous studies have reported differences in the cognitive development,²⁸ and in the number of injuries between children who attended day care and those who did not,²⁹ which cannot explain our findings. The fact that day-care children have more infections—diarrhoea, hepatitis A, otitis media, respiratory-tract infections, and haemophilus influenza type B, especially after first attendance at day care, is well documented.^{13–19,22,30} Comparison of our results with those of other studies in developed countries is not appropriate since the type of childcare in the former German Democratic Republic differed from that in most western societies. For example, the Indoor Air and Children's Health Study in the USA found that 5% of children had child care in the home, 37% in day-care homes, 10% in day-care centres, and 48% did not have day care.¹⁸ In the former German Democratic Republic about 80% of children attended day-care centres. The risk of cross infections might be stronger in these centres. The US study reported a positive association for lower-respiratory-tract infection and wheezing with day-care attendance. Marbury and colleagues¹⁸ concluded that if wheezing represents early-onset asthma then the increasing use of childcare might be one reason for this increase in asthma. Our data confirm the association between day-care attendance and lower respiratory illnesses. Children who entered day care at a younger age had bronchitis more frequently than those who entered at an older age, but we were not able to confirm the hypothesis that day-care attendance may lead to an increase in asthma. Our results point towards the hypothesis that early infection may protect against allergies in later life. This hypothesis was not supported by our findings for wheezing, which is understandable given the heterogeneous nature of wheezing in early life which is mostly not atopic. Our results accord with those of Hurwitz and colleagues²² on the risk of respiratory illness associated with age and number of siblings in a nationwide study in the USA. We showed that children from small families (usually one-child families) who entered a day nursery early in life have less atopy, and less hayfever and irritated eyes later in life than children who first attend day care at an older age.

Contributors

Joachim Heinrich and Heinz-Erich Wichmann contributed to the grant application and to the implementation of the fieldwork, and Joachim Heinrich organised and supervised the fieldwork. Matthias Wjst and Joachim Heinrich organised the data management. Ursula Krämer did the data analyses and prepared the paper. All investigators contributed to the discussion of the results and the writing of the paper.

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