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Familial and environmental determinants for wheezing and asthma in a case-control study of school children in Palestine

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Summary

Background Our prevalence study on Palestinian school children aged 6–12 years showed lower rates for asthma and asthma symptoms than economically developed and industrialized countries. Reasons for such differences are largely unknown, and could possibly be related to different environmental and lifestyle factors.

Objective To investigate familial, early life exposures and indoor environmental determinants for asthma in children in Palestine.

Methods From the population of our previous study, a group of 273 children with wheeze in the past 12 months (of whom 99 children had physician-diagnosed asthma) were matched with an equal number of non-wheezing controls. This case-control study involved a parental questionnaire; skin prick testing (SPT) with mixed house dust mites, cat and dog dander, mixed grass, mixed trees pollen, *Alternaria tenuis,* olive tree and cockroach extracts; and serum for total and specific IgE for the same eight allergens.

Results Paternal asthma and maternal hayfever significantly tripled the risk for their children to have wheezing. Previous diagnoses of bronchial allergy, bronchitis, pneumonia, or whooping cough, and positive SPT for house dust mites and cockroaches were significantly more likely among wheezing and asthmatic children than controls. Specific IgE levels for house dust mites and cat allergens showed significantly higher risk for reported wheezing. After adjustment for several environmental and sociodemographic factors using multivariate logistic regression analysis, paternal asthma, maternal hayfever, damp houses, cat and cockroach SPT positivity proved to be strong predictors for wheezing symptoms.

Conclusion Our study confirmed that familial 'atopic' diseases are significant predictors of childhood asthma in Palestinian children. Moreover, indoor environment such as presence of cats and domestic moulds also appear to play a role. Our findings are consistent with studies in Canada, New Zealand, Estonia and Sweden, and show promise to explore further gene–environment interaction in the genesis of asthma.

Keywords asthma, children, environment, epidemiology, family, Palestine
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Introduction

Asthma is multifactorial in origin and has different phenotypes which could be modulated by different genetic, environmental, or lifestyle factors in various ways [1–3]. Because the environmental factors are believed to be the most likely primary determinants of asthma expression [4], the widely accepted paradigm for asthma development is that one must be genetically predisposed to respond to environmental influences [5].

Asthma is known to be associated with atopy, as measured by serum IgE or skin test reactivity to aeroallergens [6, 7]. Children of atopic parents are at greater risk of developing atopy and asthma than are children of non-atopic parents [2]. In addition, children with a positive family history of allergy, i.e. allergic symptoms in first-degree relatives [3], required fewer environmental exposures during infancy [8] to develop sensitization than those with a negative family history [4, 8, 9]. Such exposures include early life experiences and factors such as childhood infections and diseases [10], family size [11–13], day care attendance [14, 15], indoor pollutants such as allergens of domestic pets [16], cockroaches and house dust mite allergens [9, 17, 18], use of gas for heating and cooking [19], parental tobacco smoking [16, 20, 21], outdoor air pollution [22, 23] and factors associated with parental socioeconomic status [3, 11, 24, 25].

In our previous study in Ramallah district, we have shown that the crude prevalence rate for '12 months wheezing' in children aged 6–12 years was 8.9%, while crude prevalence rates of 'wheezing ever' and 'physician-diagnosed asthma' were 17.1% and 9.4%, respectively [26]. These relatively low asthma

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prevalence rates ranked Palestine with countries such as South Korea, Poland and Algeria, but still higher than other countries such as Romania, China, Indonesia, Greece and Ethiopia, and much lower than many other economically developed and industrialized countries [27]. Furthermore, refugee camps had higher prevalence rates for '12 months wheezing' than cities and villages (12.6%, 7.2% and 8.2%, respectively), whereas 'primitive' villages had the lowest rate (5.9%) [26]. Nested in this prevalence survey, we carried out a case-control study.

The aim of this study was to assess the potential 'risk' or 'protective' factors (and/or confounders) for asthma and wheezing in Palestinian children. The objectives were to investigate and explore the role of several lifestyle and environmental factors in determining asthma and wheezing symptoms in children. In this paper, we focused on early life experiences as derived from a parental questionnaire, i.e. previous diseases and infections, family history of atopy and reported indoor environmental exposures. In addition, we analysed and discussed the potential linkage with wheezing and asthma of the objective measure of atopy, as assessed by skin prick testing (SPT) and total and specific IgE.

Materials and methods

Study population

From our previous prevalence study [26], 299 out of 3382 children, aged 6–12 years had a history of wheeze in the previous 12 months as reported by their parents on a standardized questionnaire. The parents of 273 of these 'cases' (91%), and an equal number of controls (never wheeze, i.e. neither in the previous 12 months nor ever) matched by school location, class and gender, consented to have their child participate in a further questionnaire; thus yielding a potential of 546 children. This risk assessment questionnaire was filled out by 489 of these 546 children (285 males, 204 females, 16% living in cities, 38% in refugee camps and 46% in villages). Among those, 420 children (77%) had their parents/guardian approval to participate in the full case-control study. Eventually, the study comprised 191 wheezing children (response rate 70%, male : female ratio = 1.5 : 1) and 184 non-wheezing children (response rate 67%, male : female ratio = 1.3 : 1). Children who were not tested ($n = 45$) were either absent on days we visited their schools and/or they refused to co-operate. The study was conducted between December 2000 and April 2001 with all examinations being carried out between 09:00 and 12:00 h. This study is part of the International Study for Asthma and Allergy in Childhood (ISAAC) phase II, and several of the following protocols were based on study protocols defined by ISAAC [28].

Questionnaire

The parental risk assessment questionnaire was adapted from the ISAAC phase II questionnaire [28], the Alex study questionnaire [29], the Saudi Arabia Childhood Asthma and Nutrition survey questionnaire [30] and the First Palestinian National Health and Nutrition Survey questionnaire [31], with some specific questions added to fit with the Palestinian community and environment as needed. It included questions related to the child's early life experiences and disease, family members' history of atopy, family's indoor exposures and domestic pollutants, farming lifestyle and indicators, and a food frequency questionnaire for the index child.

Sensitization to common allergens

SPTs were performed according to the standardized ISAAC phase II protocol [28], using the ISAAC panel of six aeroallergens: house dust mites (mixed *Dermatophagoides pteronyssinus and D. farinae*), *Alternaria tenuis*, mixed tree pollen (*Betula verrucosa, Alnus glutinosa, Corylus avellana*), mixed grass pollen (*Dactylis glomerata*, *Lolium perenniae*, *Festuca pratensis*, *Poa pratensis*, *Phleum pratense*, *Avena eliator*), cat and dog dander. In addition, extracts of olive tree pollen and cockroach were used. Standardized extracts and controls (negative control and histamine 10 mg/mL as the positive control) were provided by ALK (Soluprick SQ, ALK, Hørsholm, Denmark) [28]. One field worker performed a series of tests with histamine before the onset of the study, until the coefficient of variation was less than 20%. Fifteen minutes after application on the volar side of the forearm, a mean of weal diameter of 3 mm or more was regarded as a positive reaction (in the absence of a reaction to the negative control solution) according to the position paper on SPT of the European Academy of Allergy and Clinical Immunology [32]. Atopy in this study was defined as any positive SPT to the above panel of allergens.

Venous blood was obtained from 187 wheezing children and 180 non-wheezing children (eight children refused venipuncture). Total and specific serum IgE measurements were carried out using enzyme immunoassay using the enzyme-linked fluorescent assay (ELFA) technique (Vidas, bioMérieux, S.A., Lyon, France) for the same allergens as used by the SPT, except mixed trees. All determinations were performed in one central laboratory (Arab Health Center, Jerusalem, Palestine). The lower detection limit was 0.5 kIU/L for total IgE and 0.20 kIU/L for the specific allergens. Coefficients of variations for total IgE controls (Vidas kits controls, 200 kIU/L) and specific IgE controls (Stallergy Vidas kits, average 4.5 kIU/L, SD 0.17) were 5.0% and 3.7%, respectively. Total IgE values below 120 kIU/L were considered normal, as recommended by Vidas kits, although several studies have used different cut-off points, mainly around 100 kIU/L [33]. Specific IgE was considered elevated if its value was 0.35 kIU/L or more. For logistic reasons, we were able to measure specific IgE only in a randomly selected subgroup, which varied for the different allergens.

Pulmonary function testing, including bronchial reactivity measurements, was done. Environmental samples (dust and fungi) were collected from the homes of a subsample of 120 children. However, results concerning pulmonary function and the domestic environment will be reported separately.

Data analyses

Data entry and analysis were done using EPI-INFO version 6.04 (Centers for Disease Control and Prevention, CDC, Atlanta, GA, USA) and SPSS software packages (Statistical Package for the Social Sciences, Inc., Chicago, IL, USA). Four non-wheezing children with a reported physician-diagnosed asthma were removed from the control group. Univariate analysis was first done to compare variables between cases and controls to obtain crude odds ratios (OR) and 95% confidence intervals (95% CI). However, a stricter case definition was also used by restricting the cases to those wheezing children who also

had 'physician-diagnosed asthma' according to the prevalence study questionnaire. Moreover, another stringent definition for cases and controls was also used in the analysis, i.e. comparing those children having wheezing symptoms and atopy (i.e. any SPT positivity) with non-wheezing non-atopic controls.

For questions related to recent lifestyle factors and exposures, missing answers did not exceed 5%, and for questions related to the first year of the child's life the figure was not more than 8%. The distribution of the missing answers did not differ significantly between cases and controls. For specific IgE measurements, missing data varied from 1.6% to 28% (1.6% for cat allergen, 5% for dog, 10% for cockroach, 10% for *D. pteronyssinus*, 13.6% for *D. farinae*, 11% for grass, 15% for *A. tenuis* and 28% for olive allergens). In the statistical analysis, the replacement method for the missing data depended on the individual results of total IgE. Children were divided into groups according to their total IgE values. Missing specific IgE measurements per each total IgE group were replaced by the average of each specific IgE in that particular total IgE group. Using this method, the change in specific IgE means did not exceed 5% (0% change for cockroach, dog and cat, 0.2% for grass, 2% for *D. pteronyssinus*, 4% for *D. farinae* and olives and 5% for *A. tenuis*) after replacement, but no change in medians occurred. Variables significantly related to wheezing in the univariate analysis were then examined in two multivariate conditional logistic regression models (model-1, model-2) to test the association between 12 months' wheezing and the combination of parental history, environmental factors and IgE and SPT. The child's own previous disorders were not included in the regression model. In model-1, a forward stepwise method was used and variables in the model were: addition of food before age 4 months; parents' asthma, eczema, or hayfever; paternal, maternal and post-natal smoking; recent presence of damp spots and mould on walls and ceiling; presence of dog, cat, furry pets recently or in the first year of life; and total IgE as a continuous variable. In model-2, specific IgE and SPT results were added to the same variables as those of model-1. In the second model, due to the addition of specific IgE results, data of many children were not included if these tests were not available for them. So we used the data replacement method as described above in order to keep these children's data in the model-2, to be able to compare it to model-1. The same model but with asthma as an outcome was also done (model-3).

Ethical issues

Ethical approval was obtained from the Palestinian Ministries of Education and Health, the UNRWA School Education Department and individual schools. The study was approved by the institutional review board of the deanship of research at Al Quds University, Palestine. A written parental informed consent was obtained for each element of the study.

Results

Univariate analysis

Child's own history of 'atopy' and other diseases Table 1 shows that, as expected, previous diagnoses of bronchitis and pneumonia had an additional risk for a child to have wheezing and asthma, and this risk was doubled with having more frequent bronchitis. Measles also appeared to be a risk factor for asthma, with a fourfold increased risk compared to controls, particularly in the case of having had measles before 3 years of age. Whooping cough proved to be an important determinant for both wheezing and asthma, regardless of the child's age.

Cases were reported to have had more allergic rhinoconjunctivitis and itchy rash than controls; physician-diagnosed hayfever increased the risk of reporting asthma diagnoses by 12-fold, and that of wheezing by fivefold. With atopy defined as having at least one positive SPT [34], 20% of the wheezing children were considered atopic, compared to 8.7% of the controls (Table 2).

However, having just one positive SPT reaction was not significantly different between controls and wheezing-cases, but cases had significantly more positive SPTs (up to seven positive reactions) than controls (see Fig. 1). Thus, skin allergy to house dust mites and cockroach tripled the risk for children to report wheezing, and only wheezing children had positive reactions to dog and *A. tenuis* extracts (Table 2). Atopic children showed a higher arithmetic mean (AM) or geometric mean (GM) for total IgE (AM 427 kIU/L, GM 131 kIU/L) than non-atopic children (AM 378 kIU/L, GM 104 kIU/L). Atopic children with wheezing symptoms had higher total IgE values (AM 447 kIU/L, GM 158 kIU/L) than atopic non-wheezing (AM 387 kIU/L, GM 91 kIU/L), non-atopic wheezing (AM 348 kIU/L, GM 117 kIU/L) or non-atopic non-wheezing children (AM 252 kIU/L, GM 91 kIU/L). Moreover, 52% of the cases had total IgE levels greater than 120 kIU/L compared to 38% of controls, and this was associated with an almost doubling of the risk for wheezing or asthma (OR 1.73, 1.77, respectively; Table 2).

Results of specific IgE showed some differences when compared to SPT results. House dust mites IgE, in particular *D. pteronyssinus*, was also a strong determinant for both wheezing and asthma, but cat IgE was a strong determinant for wheezing only, although this was not the case by SPT. *A. tenuis* and grass IgE results showed an increased risk, but this risk was non-significant (Table 2). Comparing SPT for every allergen with its specific IgE results, SPT and specific IgE were highly associated for *A. tenuis* (OR 43.0, 95% CI 2.44–761), *D. pteronyssinus* (OR 7.05, 95% CI 3.32–14.9), *D. farinae* (OR 5.97, 95% CI 2.54–14.0), but not for grass (OR 3.8, 95% CI 0.24–61.0), cockroach (OR 2.64, 95% CI 0.90–7.77), cat (OR 1.59, 95% CI 0.19–13.4), dog (OR 0.72, 95% CI 0.087–6.00) and olives (OR 0.63, 95% CI 0.76–5.26).

Family history and early life experiences

Table 1 shows the importance of family history in determining wheezing and asthma. Different ORs were seen for a family history of asthma, rhinitis and eczema, and these estimated risks were higher for the physician-diagnosed asthma cases. Having both parents with asthma increased the risk of wheezing by 10-fold (OR 9.9, 95% CI 1.25–79), and that of asthma by 19-fold (OR 19, 95% CI 2.32–157). Also, sibling atopy doubled the risk for wheezing (OR 1.99, 95% CI 1.28–3.08) and asthma diagnosis (2.69, 95% CI 1.58–4.59), especially if any of the siblings had eczema (OR 4.88, 95% CI 1.81–13.0 and 6.24, 95% CI 2.11–18.0, respectively). Moreover, having any family member with asthma or 'atopy' increased the risk for wheezing (OR 1.57, 95% CI 1.04–2.36 and OR 1.57, 95% CI 1.22–2.51, respectively) and doubled the risk for asthma (OR 2.49, 95% CI

Table 1. Child's previous diseases and infections, as reported by their parents, and parental history of asthma, rhinitis and eczema as determinants for wheezing and asthma in school children in Ramallah in year 2000–01

		Cases					
	Controls Non-wheezing	12 months wheezing			Physician-diagnosed asthma		
	$N = 252$† *n*	$N = 237$† *n*	OR*	95% CI	$N = 99$† *n*	OR*	95% CI
Bronchial allergy diagnosis							
Once	11	25	**3.31**	(1.58–6.92)	13	**5.66**	(2.39–13.0)
Several times	4	46	**16.70**	(5.91–47.0)	36	**43.00**	(15.0–126)
Bronchitis diagnosis							
Once	26	43	**3.22**	(1.87–5.56)	22	**7.0**	(3.44–14.0)
Several times	27	89	**6.42**	(3.92–11.0)	53	**16.0**	(8.65–30.0)
Pneumonia diagnosis							
Once	8	25	**4.05**	(1.78–1.19)	19	**9.0**	(3.76–21.0)
Several times	10	32	**4.14**	(1.98–8.66)	20	**7.59**	(3.37–17.0)
Ever had measles	31	41	1.49	(0.90–2.47)	29	**3.0**	(1.69–5.34)
Age having measles							
$=3$ years	16	17	1.20	(0.59–2.44)	13	**4.10**	(1.72–9.77)
>3 years	10	18	1.88	(0.90–3.94)	13	**2.57**	(1.18–5.59)
Ever had whooping cough	10	26	**3.01**	(1.42–6.39)	14	**4.13**	(1.76–9.67)
Child's ever having							
Itchy rash	31	89	**4.25**	(2.69–6.72)	44	**5.56**	(3.27–9.76)
Allergic rhinoconjunctivitis	52	145	**6.17**	(4.12–9.24)	70	**9.47**	(5.55–16.2)
Child's previous 12 months							
Itchy rash	22	60	**3.63**	(2.14–6.13)	32	**5.08**	(2.76–9.34)
Allergic rhinoconjunctivitis	37	113	**5.52**	(3.57–8.54)	56	**7.87**	(4.61–13.5)
Child's physician-diagnosed:							
Eczema	12	30	**3.04**	(1.52–6.11)	19	**5.03**	(2.33–10.8)
Hayfever	15	57	**5.46**	(2.98–9.99)	40	**11.90**	(6.13–23.3)
Symptoms triggers‡	101	179	**4.61**	(3.13–6.81)	82	**8.40**	(4.57–15.4)
Maternal							
Asthma	12	22	2.06	(1.00–4.26)	13	**3.00**	(1.32–6.82)
Eczema	14	20	1.59	(0.78–3.23)	13	**2.61**	(1.18–5.78)
Hayfever	14	36	**3.07**	(1.61–5.85)	21	**4.66**	(2.26–9.61)
Any of the above	36	62	**2.13**	(1.34–3.36)	37	**3.58**	(2.09–6.14)
Paternal							
Asthma	11	28	**2.98**	(1.45–6.13)	16	**4.26**	(1.90–9.55)
Eczema	8	17	**2.41**	(1.02–5.70)	6	2.03	(0.68–6.00)
Hayfever	16	25	1.77	(0.92–3.41)	13	**2.27**	(1.05–4.92)
Any of the above	34	54	**1.89**	(1.18–3.03)	27	**2.40**	(1.36–4.26)
Either parents							
Asthma	22	41	**2.21**	(1.27–3.84)	22	**2.97**	(1.56–5.67)
Eczema	22	34	**1.79**	(1.01–3.16)	19	**2.56**	(1.31–4.98)
Hayfever	26	53	**2.52**	(1.52–4.20)	28	**3.50**	(1.92–6.35)
Any of the above	63	94	**1.97**	(1.34–2.90)	51	**3.19**	(1.96–5.19)

The reference category for each risk factor is absence of the risk factor. *OR, odds ratio – unadjusted and significant OR are in bold. †In the results, the actual denominator may be somewhat lower, as subjects with missing answers were excluded. ‡Reported causes or triggers for breathing problems: At least one trigger: colds, emotions, dust, pollens, weather and physical exercise.

1.51–4.11 and OR 2.77, 95% CI 1.71–4.48, respectively). Furthermore, hayfever in a grandparent was shown to be a strong factor in determining both wheezing and asthma in children (OR 4.98, 95% CI 1.84–13.0 and OR 7.06, 95% CI 2.41–21.0, respectively).

Figure 2(a) shows that some suspected protective factors against asthma and wheezing [11–13], i.e. having older siblings, being exclusively breast-fed, or attending day care centre, did not differ significantly between cases and controls. However, no exclusive breast-feeding (i.e. addition of food before 4 months of age) showed a risk (OR 1.48) to have wheezing, but not asthma. Furthermore, having more than four siblings showed to be a protective factor against wheezing, but only in case the child was not atopic (OR 0.33; Fig. 2a). Other early life experiences such as having parasitic infections showed an increased risk (OR 1.43, 95% CI 0.93–2.22), particularly in the

Table 2. Skin prick test, and total and specific IgE as determinants for wheezing and asthmatic children in Ramallah in year 2000–01

		Cases					
	Controls Non-wheezing	12 months wheezing			Physician-diagnosed asthma		
Number of tested children	$N = 184$† %	$N = 191$† %	OR*	95% CI	$N = 84$† %	OR*	95% CI
SPT-positive reaction to:							
Cat	1.1	3.8	3.56	(0.73–17.0)	2.4	1.43	(0.24–8.73)
Dog	0.0	3.8	–	–	3.6	–	–
Cockroach	2.7	8.1	**3.14**	(1.12–8.83)	12.0	**7.93**	(2.12–29.6)
A. tenuis	0.0	1.1	–	–	1.2	–	–
Olives	0.5	4.3	**8.22**	(1.02–66.0)	2.4	2.16	(0.30–15.6)
D. pteronyssinus & *D. farinae*	4.9	14.0	**3.16**	(1.44–6.94)	9.5	1.34	(0.54–3.38)
Any SPT positive	8.7	19.5	**2.52**	(1.34–4.72)	16.7	1.94	(0.93–4.07)
Total IgE > 120 kIU/L	38.0	52.0	**1.73**	(1.14–2.63)	52.0	**1.77**	(1.05–2.99)
Specific IgE							
Cat	5.1	11.3	**2.38**	(1.06–5.34)	8.2	1.68	(0.60–4.66)
Dog	14.9	16.9	1.16	(0.66–2.06)	14.6	0.98	(0.47–2.05)
Cockroach	14.7	12.1	0.80	(0.43–1.47)	9.4	0.60	(0.26–1.40)
A. tenuis	1.3	3.7	2.81	(0.56–14.1)	5.3	4.11	(0.74–22.9)
D. pteronyssinus	12.4	24.2	**2.25**	(1.28–3.94)	23.5	**2.17**	(1.11–4.24)
D. farinae	12.9	19.5	1.64	(0.89–3.01)	18.4	1.52	(0.72–3.22)
Olives	18.3	17.8	0.97	(0.52–1.81)	23.2	1.34	(0.65–2.78)
Mixed grass	17.3	25.3	1.62	(0.95–2.77)	25.6	1.65	(0.86–3.17)

The reference category for each risk factor is absence of the risk factor. *OR, odds ratios – unadjusted and significant OR are in bold. †In the results, the actual denominator may be somewhat lower, since subjects with missing answers were excluded.

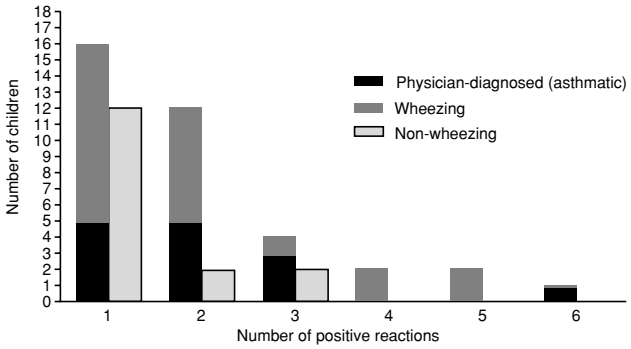

Fig. 1. Frequency of positive SPT among wheezing, asthmatic and non-wheezing children in Ramallah in year 2000–01. Number of children with negative SPT but with physician-diagnosed asthma ($n = 68$); number of children with negative SPT but with wheezing in the previous 12 months ($n = 148$); number of children with negative SPT who were non-wheezing controls ($n = 165$).

case of having had such treatment more than twice (OR 1.58), and this was more important if the child was atopic (OR 1.83).

Domestic environment

Exposure to environmental tobacco smoke (ETS) showed an increased risk for wheezing if the mother was a smoker, i.e. current, past or post-natal smoking mothers (Fig. 2a). Having furry animals (hamsters, sheep, rabbit, goats, cats, or dog) recently indoors showed an increased risk for wheezing or asthma. However, this was not the case for cats and dogs separately, although dog ownership tended to increase the risk for wheezing. Moreover, many families of wheezing and asthmatic children reported the removal of indoor pets, changing the child's pillow and reducing or stopping smoking due to breathing problems among their children. Apart from the presence of furry animals, the only significant difference between the domestic environment of cases and controls was the reported presence of damp spots or fungus on walls or ceiling, which doubled the risk for having asthma (Fig. 2b).

Looking in more detail at the respective roles of cats and dogs, it appears that 19 of 237 wheezing children reported having a dog recently or in infancy in the house. Domestic dog presence recently or in infancy was not associated with SPT positivity to dog allergens and all seven children with positive SPT to dog did not have a dog indoors (data not presented). However, Table 3 shows that the exposure to dog in infancy could be protective against having serum IgE to dog in wheezing children compared to non-wheezing children (OR 0.36), although the association was not significant.

Having a cat indoors recently or in infancy was associated with positive SPT to cat (OR 2.05, 95% CI 0.41–10.2 and OR 1.30, 95% CI 0.16–10.8, respectively), but the association was not significant. Moreover, there was an increased risk for SPT to cat allergen by owing a cat recently in the non-wheezing children (OR 7.85, 95% CI 0.47–130, data not presented), but not in infancy. However, comparing wheezing to non-wheezing children, not owning a cat showed an increased risk of having positive SPT to cat, but not of having positive IgE to cat allergen (see Table 3).

Multivariate logistic regression

Two multivariate logistic regression models were used to ascertain variables predicting wheezing symptoms in those children (Table 4). However, children's own diseases were not

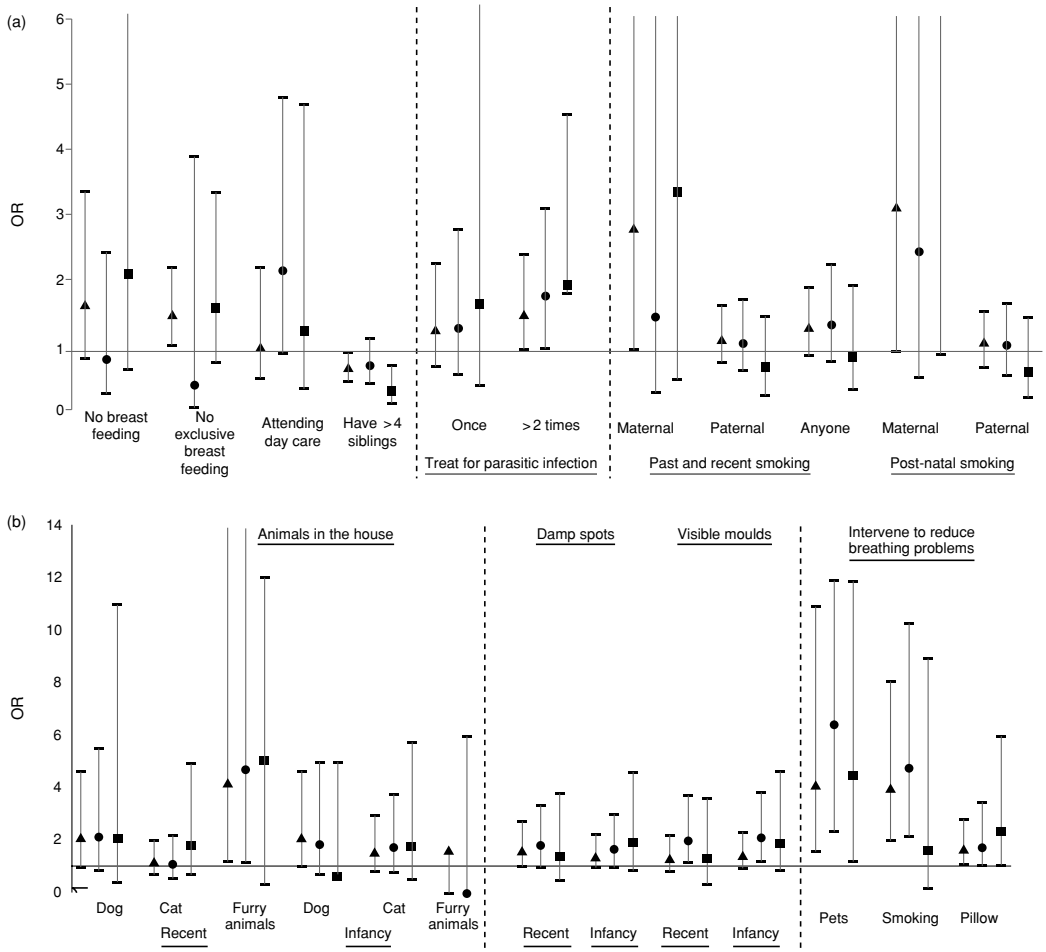

Fig. 2. (a) Early days exposures and environmental tobacco exposure (ETS) as determinants for wheezing or asthma in children in Ramallah in year 2000–01. (b) Indoor pollutants, animal presence, house conditions as determinants for wheezing or asthma in children and interventions done by families to reduce breathing problems among their children in Ramallah, in year 2000–01. ▲, unadjusted OR for wheezing children compared to non-wheezing children; ●, unadjusted OR for physician-diagnosed asthma compared to non-wheezing children; ■, unadjusted OR for wheezing atopic children compared to non-wheezing children.

included as these could mainly be other expressions of the same disease.

In the first model, which included total IgE as a variable, no exclusive breast-feeding showed to be a strong early life determinant for wheezing. Paternal asthma and maternal hayfever were shown to be strong family determinants for wheezing. Moreover, indoor environmental factors, i.e. living in a damp house and having furry pets, were also important risk factors for reporting wheezing (Table 4). In model-2, in which SPT and specific IgE were added to model-1, family history showed almost the same association with wheezing, but cockroach allergen was shown to increase the probability of having wheezing by threefold. Model-3, in which physician-diagnosed asthma was the outcome, did not show much differences compared to model-1 or model-2.

Discussion

Our case-control of wheezing and asthma study in Palestine yields similar results to children in Canada [19, 35], Sweden and Estonia [36], New Zealand [37] and Costa Rica [38]. It confirms the importance of a family history of atopy as a risk for wheezing and asthma. Moreover, results showed that mouldy houses, presence of furry animals and cockroaches indoors are important determinants for asthma in Palestinian children. These findings give support for a 'gene–environment' interaction [39] and only a limited support to the 'hygiene hypothesis' [40].

This was a case-control study nested in a cross-sectional survey. Selection bias could not be excluded from such studies. For example, several parents refused blood drawing or SPT in their asthmatic children, particularly those chronic and/or severe cases. Other parents, who were aware of, knew and/or care more about allergy, were more likely to participate in the study. Another bias could be in the reporting and recall bias. Parents of allergic children or allergic families, consciously or unconsciously, might tend to give more 'desirable' answers about their lifestyle behaviour than those of non-allergic children from non-allergic families. Others, especially parents of older children, had a problem in recalling their child's first year of life exposures.

Child's atopy and diseases

Atopy as a risk factor for asthma and wheezing is still argued [33], but recurrent wheezing is still considered one of the atopy

Table 3. Skin prick testing to cat and dog allergens, specific IgE to dogs and cats as determined by the presence of domestic cats or dogs recently or in infancy among wheezing, asthma-diagnosed children and controls in Ramallah in year 2000–01

			Cases					
			12 months wheezing			Physician-diagnosed asthma		
		Non-wheezing Positive/no. controls	Positive/no. cases	OR*	95% CI	Positive/no. cases	OR*	95% CI
SPT cats		SPT+/no. controls	SPT+/no. cases			SPT+/no. cases		
Domestic cats								
Recently:	Yes	2/20	1/24	0.39	(0.03–4.67)	0/11	–	–
	No	1/159	6/163	3.98	(0.44–25.0)	2/73	0.98	(0.94–1.02)
Infancy	Yes	1/12	2/22	1.10	(0.09–13.5)	1/12	1.00	(0.06–18.1)
	No	2/167	3/165	1.53	(0.25–9.26)	2/68	0.98	(0.94–1.02)
Cat-specific	IgE > 0.35 kIU/L	IgE > 0.35/no. controls	IgE > 0.35/no. cases			IgE > 0.35/no. case		
Domestic cats								
Recently	Yes	0/19	2/24	–	–	1/11	–	–
	No	9/158	19/162	0.94	(0.88–1.00)	6/74	0.97	(0.90–1.05)
Infancy	Yes	0/13	2/22	–	–	1/12	–	–
	No	9/164	19/164	0.94	(0.88–1.00)	6/73	0.97	(0.90–1.05)
Dog-specific	IgE > 0.35 kIU/L							
Domestic dog								
Recently	Yes	1/6	3/15	1.25	(0.10–15.2)	1/7	0.83	(0.04–16.9)
	No	25/168	27/162	1.14	(0.63–2.07)	11/75	0.98	(0.46–2.1)
Infancy	Yes	3/9	2/13	0.36	(0.05–2.82)	0/5	–	–
	No	23/165	18/164	1.27	(0.70–2.32)	12/77	0.98	(0.88–1.10)

*OR, unadjusted odds ratios for positive SPT test. SPT for dogs were positive in seven children, none of them having reported exposure to dog.

phenotypes in childhood [3]. Several studies concluded that usually less than half of the asthma proportion could be attributed to atopy [33]. Our questionnaire results clearly showed that a child's atopic disorders symptoms had an important role in having asthma symptoms, and wheezing children showed an increased risk of fivefold if they had allergic rhinoconjunctivitis or hayfever, and by threefold if they had had eczema or itchy rash in the previous 12 months [34, 41]. Our findings support other recently published studies in Canada, Sweden, New Zealand and Estonia [35, 42].

Two objective methods have been used in the literature to define atopy: SPT or total or specific IgE measurements. SPT has been used in population studies as a convenient test for atopy [33], although atopy is characterized by the production of specific IgE in response to environmental allergens [43]. In this study we used the SPT definition, and this gave a proportion of atopy of 20% in our wheezing children. This percentage is still lower than rates seen in the Swedish (58%) and Estonian children (26%) [36], and other economically developed and industrialized countries (range 25–58%) [33]. Using a different definition for atopy, i.e. any positive SPT or any specific IgE greater than 0.35 kIU/L, resulted in 57% of wheezing children being atopic, with an OR 1.54 (95% CI 1.1–2.33). However, only 26% of those children having positive SPT had high levels of specific IgE levels, with an OR 9.1 (95% CI 4–20). Likewise, using a different definition for atopy by using allergen-specific sensitization, i.e. any specific IgE results greater than or equal to 0.35 kIU/L, the prevalence of atopy increased to 39% versus 14% by SPT-definition. Using a higher cut-off point for specific IgE positivity, such as 0.70 kIU/L, led to a decreased prevalence of 19%. Our results showed strong associations between several specific IgE results and SPT of the same allergen. Despite the factors or the combination of numerous variables that could affect SPT, such as extract potency, skill of tester, accuracy of interpretation and influence of medications on test results, *in vitro* testing might not be an alternative to SPT but a complementary tool to define such subjects [44, 45]. The aeroallergens we used in this survey showed an increased risk for developing wheezing in our children, particularly cockroaches and house dust mites' allergens, which was linked to increased morbidity from asthma in some studies [46]. These allergens, i.e. house dust mites, cat and cockroach, were suggested to be direct causes for allergic sensitization, while others such as grass pollens and moulds may cause sensitization in an indirect way [47]. *A. tenuis* was shown to be associated with an increased risk of death from asthma [46]. A recent study in New South Wales and Australia showed that atopy, particularly present at the age of 8–10 years, predicts the subsequent onset of wheeze [48].

Several published studies had defined atopy as high total IgE, with different cut-off points [7, 33]. This survey showed that 52% of wheezing children had total serum IgE levels greater than 120 kIU/L, which might reflect an estimate of the allergic component of asthma [3]. Total IgE level was found to be lower among allergic Arabs living in Israel (35%) compared to Israeli Jewish (50–60%) [49]. However, the tendency to have high levels of total IgE is only one factor related to the inheritance of the likelihood of developing asthma [50], and it is independent of specific IgE levels [43]. Also, total IgE depends on a variety of genetic and environmental factors, including sex and age, and is associated with viral, fungal, or parasitic infections [51–53]. This was clearly demonstrated by our results, where wheezing and asthmatic children reported to have more parasitic infections than controls, and the risk increased when the child had been treated more than once.

Table 4. Crude and adjusted odds ratios (Wheezing children, and asthmatic vs. controls) for familial and indoor environmental risk factors in children in Ramallah in year 2000–01

	Wheezing in the previous 12 months					Physician-diagnosed asthma	
	Crude OR*	Model-1 Adjusted OR*	95% CI	Model-2 Adjusted OR*	95% CI	Model-3 Adjusted OR*	95% CI
No exclusive breast-feeding before age 4 months	**1.48**	**1.55**	(1.01–2.39)	–	–	–	–
Family and child history							
Paternal asthma	**2.98**	**2.64**	(1.15–6.03)	**4.30**	(1.68–11.0)	**2.64**	(1.15–6.07)
Maternal hayfever	**3.07**	**2.94**	(1.40–6.19)	**5.22**	(2.23–12.2)	**2.86**	(1.34–6.09)
Paternal eczema	**2.41**	–	–	–	–	**3.18**	(1.08–9.34)
Environmental factors							
Recent presence of damp spots in the house	**1.69**	**1.87**	(1.06–3.32)	**1.80**	(1.01–3.22)	–	–
Having furry animals recently in the house	**4.19**	**5.71**	(1.23–26.6)	**10.5**	(1.97–56.7)	**5.27**	(1.10–25.3)
Having dog recently in the house	2.09	–	–	–	–	**3.24**	(1.09–9.56)
Having cat in the child's first year of age	1.57	–	–	**3.10**	(1.22–7.86)	–	–
Cockroach SPT-positive >3 mm	**3.14**	–	–	**4.74**	(1.07–14.9)	**5.92**	(1.65–21.3)

Model-1: variables related to family history, environmental factors, and total IgE were included. Model-2: model-1 with adding the continuous variables of specific IgE for each allergen and SPT categories (>3 mm in diameter) for every allergen. Model-3: equal to model-2 but with physician-diagnosed asthma as response variable. The reference category for each risk factor is absence of the risk factor. *Significant adjusted odds ratios are in bold.

Family history of atopy

The univariate analysis showed that familial 'atopic' diseases are significant predictors of childhood asthma, with parental and grandparental hayfever being a very strong determinant for asthma in Palestine. The demographic indicators in Palestine show a young population (47% under 15 years of age) with relatively high life expectancy (71 years), which means that the same household could have three generations living together at the same time. So answers related to grandparents' atopy are probably valid. Sandford and others showed that a strong familial aggregation of asthma and allergy has been established, although familial concordance is at least partly due to a shared environment, as well as shared genes [50, 54]. In a longitudinal family and birth-cohort study in Boston, USA, the risk for childhood asthma increased with the number of parents with asthma, and was six times greater in families with two asthmatic parents; this risk increased further by parental history of inhalant allergy other than asthma [2].

The issue of whether the outcome depends more on the father or the mother being asthmatic is still debated. Our data showed that maternal and paternal asthma were both strong determinants for wheezing, but after adjustment only maternal hayfever continued to be a very strong predictor (adjusted OR 2.61) compared with paternal asthma. Paternal atopy was more important than maternal atopy in German school children [55], whereas in Canadian [35] and New Zealand [37] children, maternal asthma was more important and was a stronger predictor of newborn IgE levels than paternal history [56]. However, children in the United Arab Emirates showed an equal risk by paternal and maternal asthma (OR was 2.67 and 2.85, respectively) [42]. These results are comparable with the hypothesis suggested by Augusto et al. that 'maternal conditions might exert a stronger effect early in the life of the child, whereas the paternal condition may be involved in the development of asthma in later life' [2]. Further investigations are needed into the relative importance of genetic factors and *in utero* and postnatal exposures in determining the differential effects of maternal and paternal asthma on the development of childhood asthma.

Risk versus protective factors

In 1989, Strachan proposed the 'hygiene hypothesis' as an explanation for the principal epidemiological features of hayfever and the apparent rise in the prevalence of allergic diseases [40]. However, recently he suggested that a modifying effect of household structure, including birth order, sibling gender and parental ages, needs more clarification [12]. There are still hot debates on the protective role of infections against asthma and other allergies [12], and reported findings must be interpreted with caution [57, 58].

In our sample, 93% of children had been breast-fed. Consequently, we could not see the effect of never breast-feeding, although the risk of adding food before 4 months on wheezing was significant, even after adjustment. Studies have suggested that breast-feeding could be a protective factor, but addition of food before 4 months might be a risk factor for wheezing [59], which was also seen in our study [37, 60–62]. In the PIAMA study, breast-feeding was also a risk factor in case both parents were allergic [63].

Our results showed that children attending day care centres before 3 years of age are at greater risk of reporting asthma than controls, but this association was not significantly associated with wheezing in the previous 12 months. These findings are consistent with some published studies [64, 65] but not with others that showed a protective role of infections through attending day care centres [66]. However, Strachan concluded that the balance of evidence does not therefore suggest a relationship between allergy and early child contacts outside the home, which is difficult to reconcile with the 'hygiene hypothesis' [12]. In addition, this case-control study did not show any significant effect of domestic crowding (and older siblings) on wheezing, but ORs suggested a protective role. However, the protective effect against wheezing by the number of siblings could be seen if the child was atopic. Several studies showed a protective role of having siblings on hayfever but not on asthma [67], and others showed that membership of large sibship confers some protection against atopic diseases [68]. Other socioeconomic differences among the different locations, such as poverty and deprivation, could modify or confound the association between the different factors and asthma inception and/or exacerbation.

Wheezing children in this study were reported to have had more respiratory diseases such as bronchial allergy (probably synonymous for asthma), bronchitis, pneumonia and whooping cough. A birth-cohort study in Germany, the MAS study, showed that repeated viral infections like herpes and running nose before 1-year-old, may reduce the risk of asthma up to school age, but showed a positive association with repeated lower respiratory tract infections in the first year of life [10].

Several studies showed that immunization, and the fall in common infections such as measles and hepatitis A [69], are unlikely to explain the rise in atopic disease [68]. In Palestine, a successful immunization programme (95% coverage) using the WHO criteria (diphtheria, pertussis, tetanus, polio, measles and tuberculosis as well as German measles, hepatitis B and mumps) has been operating [70]. However, measles was shown to be a strong risk factor for wheezing in our study. This might reflect an over- and/or misclassification in reporting measles or confusion with other childhood diseases. Our findings are consistent with studies in Canada [35, 71], New Zealand [37] and Sweden and Estonia [36].

Indoor environmental exposures

In our study, maternal smoking, either currently or previously and/or post-natally, was a strong determinant for wheezing, but paternal smoking was not. This is consistent with several studies that showed the negative role of smoking, especially maternal smoking [21], as a provoking factor and possibly a causal factor [62] for asthma and other respiratory diseases. A study in Israel that compared maternal smoking between Arab and Jewish children showed a strong effect of smoking on asthma among Jewish but not in Arab children [72]. The MAS study found that an increased risk for sensitization was found in children whose mothers smoked up to the end of pregnancy and continued to smoke after birth [3].

Ownership of a cat, either recently or in infancy, was shown to be a potential risk factor for developing atopy. Moreover, having a cat in infancy showed risk for wheezing in our study, which could be seen clearly in the regression model. Demonstration of an association between exposure to cats and the development of asthma has been complicated by the fact that sensitized individuals often removed cats from their homes [73, 74], so acquiring a cat recently could not be discerned. There is conflicting evidence in the literature regarding the role of indoor pets such as cats and dogs as well as house dust mites on asthma development in the different environments [75]. Our findings are supported by several studies, but not others [75–77]. For instance, in the UK, an independent association with severe wheeze was seen for current ownership of furry pets in children and ownership at birth [78]. In the PIAMA study, 53% of allergic parents considered their allergy when they furnished their homes, and their homes were free of cats and free of cigarette smoke, there were smooth floors in the babies' bedrooms, and the introduction of fruits and vegetables was postponed until the age of 26 weeks [63].

Several studies showed the role of domestic moulds on asthma prevalence, incidence and/or symptoms exacerbation. Our findings show the reported presence of mould as a strong risk factor for asthma, and having damp spots in the house continued to be a strong determinant after adjustment for other familial and environmental factors. Our findings are consistent with several studies in Canada and New Zealand [37], Estonia and Sweden [36]. Similarly, studies on allergen exposure and allergic symptoms always consider the possibility that low allergen levels may be more prevalent in homes of genetically high-risk children [63]

Conclusion

Our study has shown that some environmental and familial factors are more important than others for predicting wheezing, but failed to demonstrate a consistent relationship between domestic environment and asthma. Other factors not yet examined, for instance diet, infections, outdoor environment and other domestic environmental factors, could also determine asthma. In addition, other socioeconomic and psychosocial factors might also be important factors. Another part of this survey, in which the impact of a farming environment, dietary factors and environmental indoor samples are assessed, will be subject of future publications. The specific questions related to the Palestinian situation are: Are Palestinians adopting a more 'Westernized lifestyle' than expected, or does the interaction between familial factors and lifestyle changes result in changes in asthma, atopy and other allergic diseases prevalences? Prospective studies are needed to shed further light on several determinants for asthma and other allergies.

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