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Prevention of asthma in genetically susceptible children: A multifaceted intervention trial focussed on feasibility in general practice

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Abstract

Background: Although the effectiveness of the multifaceted allergen-reducing interventions for the prevention of asthma in susceptible children was showed to be proven, the feasibility was not clear.

Methods: The research question of the PREvention of asthma in susceptible children (PREVASC) trial was focused on the assessment of the effectiveness and feasibility of a multifaceted intervention on the prevention of allergic asthma in general practice. The effectiveness and feasibility of an intervention aimed at the simultaneous reduction in the environmental exposures to inhalant- and food allergens in susceptible children was investigated. A total of 476 children susceptible for developing asthma were initially included during pregnancy and were randomly divided over an intervention group of $n = 222$ children whose parents were offered a multifaceted environmental exposure-reducing intervention. Controls ($n = 221$) received usual care. The main outcome was 'diagnosis of allergic asthma at age 6'.

Results: A significant reduction in inhalant allergen exposure levels of house dust mite [(Der p1), $p = 0.043$], cat [(Fel d1), $p = 0.037$], and dog [(Can f1), $p = 0.012$] was reached. Significantly more intervention group children started using cow's milk and solids after the age of 6 months ($p \leq 0.001$). No statistical difference, however, was reached between groups on the duration of breast-feeding ($p = 0.635$) and the reduction in smoke exposure ($p = 0.829$). At age 6, the intervention had no influence on the development of main outcome allergic asthma (OR = 1.010 (CI 0.580–1.758)).

Conclusion: Other primary preventive asthma-reducing interventions were shown to be effective in reducing the occurrence of asthma for at least the first 7–8 yr of life. The multifaceted PREVASC allergic asthma primary preventive intervention was effective in reducing the exposure to inhalant and food allergens, but was not feasible for the parents. A lack of sufficient room for improvement focus on stimulating adherence seemed to be involved. It is suggested that a multifaceted environmental exposure-reducing intervention may have to be adapted to the personal circumstances of patients at baseline.

Abbreviations

Der p1, European house dust mite allergen; Can f1, Dog allergen; Fel d1, Cat allergen; GP, General practitioner; IG, Intervention group; CG, Control group; FeNO, Fractional concentration of exhaled nitric oxide; FEV₁, Forced expiratory volume in one-second; FVC, Forced vital capacity; PC₂₀, Bronchial hyper-reactivity; no, number; PREVASC, PREvention of asthma in susceptible children; Asymp. sign., Asymptotic significance; CI, Confidence interval; s.d., Standard deviation.

The prevalence of allergic asthma in children increased substantially since the eighties (1, 2). Asthma development is the result of gene-environment interaction (3). Although the effectiveness of the multifaceted allergen-reducing interventions for the prevention of allergic asthma in susceptible children, as opposed to its mono-faceted counterparts, was showed to be proven, the feasibility was not clear (4–20).

The PREvention of asthma in susceptible children (PREVASC) study, the trial we currently describe, is a multifaceted intervention study focused on the simultaneous reduction in environmental exposures to (inhalant and food) allergens and cigarette smoke in genetically susceptible children. This intervention was set up to be easy to implement in a primary care setting and therefore not time-consuming and feasible for both parents and general practitioners. Children at high risk of developing allergic asthma were included during prenatal life. The effects of the intervention on the children at the age of 2 yr were reported before and demonstrated less asthma-like symptoms but no significant effect on allergic sensitization (17).

In the present study, we report on the effect of the intervention on allergic asthma at age 6 as well as on the feasibility of the intervention for families to adhere to the advices. So far, multifaceted intervention studies on primary prevention of allergic asthma focused on an intervention duration of approximately 1 yr for food allergen reduction and 2–3 yr for inhalant allergen reduction (6, 13, 17). The optimal intervention duration was never described up until now. Additional follow-up of the PREVASC cohort of children allowed assessment of different intervention duration (2 vs. 6 yr). For this purpose, after 2 yr, the intervention group was randomized in an extended intervention and a short-term intervention.

The research questions of the PREVASC study are as follows:

1 What is the clinical effectiveness of an asthma-reducing multifaceted intervention that is designed to be implemented in general practice and started during prenatal life in genetically susceptible children at 6 yr of age?

2 What is the influence of the duration of the intervention (2 vs. 6 yr)?

Methods

The PREVASC study is a multifaceted randomized controlled trial aimed at the prevention of allergic asthma in susceptible children by a simultaneous reduction in the exposure to inhalant and food allergens and passive smoking; an intervention set-up to be easy to implement in general practice and therefore not too time-consuming and feasible for both parents and general practitioners (16, 21). The rationale behind the PREVASC study and the design were previously published (14, 16). A figure of the PREVASC study design and population is presented in Fig. 1.

This study was approved by the National Ethics Committee and registered in the national trial register (trialregister.nl, no NTR371).

From January 1997 until January 2001, in the south of the Netherlands, eligible children were included during prenatal life, with the help of general practitioners and midwives. These children were born in families in which minimally one parent or sibling was diagnosed with allergic asthma.

Families were randomly assigned to an intervention group or a control group (1:1). All participating families gave written informed consent before taking part in the study. Information on inclusion and exclusion criteria as well as study design and baseline characteristics were previously published by Schönberger et al. and Kuiper et al. in 2005 (14, 16). In Fig. 1, the information on the study population is presented.

During home visits, the intervention group was offered an intervention from pregnancy onward. All advices were given

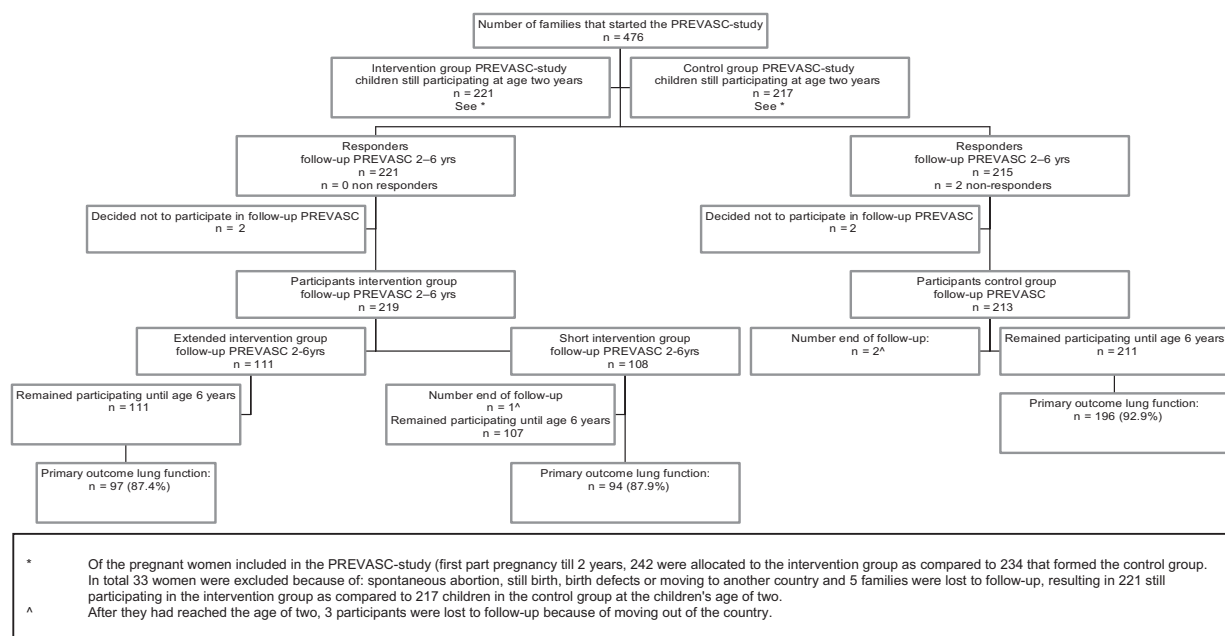


Figure 1 Design and participants' flowchart of PREvention of asthma in susceptible children (PREVASC) at 2–6 yr.

verbally and in writing during the whole study period. The content of the advices given is published by Kuiper et al. (14) A small summary of the intervention: Prevention of the child (pre- and postnatal) from exposure to tobacco smoke, hairy pets, solid foods, and cow's milk before the age of 6 months. Hairy pets, if present, were advised to keep outdoors, exclusive breast-feeding for 6 months was stimulated but, if this showed to be impossible, hypo-allergenic bottle feeding was advised and could be supplied by the researchers for the price of regular formula. For the tobacco smoke-reducing part of the intervention, parents were coached to quit smoking using the minimal intervention strategy (MIS) developed by the Dutch organization STIVORO (22). In addition, parents were advised to keep their child away from smoking areas.

To evaluate the adherence of parents to and the success of the allergen-reducing advices and to correlate the intensity of exposure to allergens with respiratory complaints, dust samples were collected from the children's mattresses during home visits in the prenatal period, at 7–9 months postnatally and at 2 and 4 yr. The allergen levels measured concerned the house dust mite allergen Derp1, the cat allergen Feld1, and the dog allergen Canf1. Dust samples were collected by vacuuming floor dust sample per square meter in a standardized manner as described earlier (14, 23). These samples were kept in the freezer until they were analyzed at the laboratories of the University of Groningen (first two samples) and Allergoconsult Eindhoven. Yearly questionnaires on the allergen exposure-reducing measures (use of bedding encasings, washing $\geq 60^\circ\text{C}$, keeping hairy pets outside, airing and ventilating) were used to monitor the adherence to the allergen-reducing procedure. Adherence of the smoking intervention was measured by carbon monoxide (CO) measurement in exhaled air of the parent(s) during every home visit. In yearly questionnaires on the smoking exposure of the children, adherence to smoking cessation intervention was evaluated.

To obtain information on the optimal intervention duration, the effects of two different periods of intervention were compared. For this purpose, the children in the intervention group were randomly assigned to two groups with different intervention duration at the age of two. In the *extended intervention group*, the intervention treatment concerning the diminishing of inhalant allergen exposure and reduction in exposure to tobacco smoke was reiterated at age two and four. All intervention families did receive a new set of house dust mite allergen-impermeable bedding encasings for the child's bed that could be used at least for 10 yr ((special soft or placebo), Sanalife, Lelystad, The Netherlands), and the initial covers were returned. In families allocated to the *short intervention group*, the intervention stopped at age two. They received placebo mattress encasings and no additional advice at ages two and four. The families in both intervention groups were kept uninformed as to the group they were allocated to. Both intervention subgroups were aware of the possibility to receive placebo-bedding encasings. Control group families did not receive a study intervention but received the usual medical care.

Symptoms and diagnoses of asthma and allergy were assessed annually by means of the ISAAC questionnaire to

be completed by parents (24). Symptoms, prescribed medication, and diagnoses related to allergy and asthma were prospectively reported by general practitioners (GP) during every consultation by using a standardized (computer) registration form with ICDPC encoding (22).

In Fig. 2, the algorithm used for categorizing children in the separate primary outcome subgroups (no allergic asthma, possible allergic asthma or current allergic asthma) is presented. The separate lung function results, symptoms, and diagnoses as registered by parents, and/or GP were used as secondary outcome.

The lung function testing was performed at the lung function laboratory of the Maastricht University Medical Centre by experienced lung function assistants, blinded for group allocation. Before lung function testing, all short-acting bronchodilators were stopped at least 8 h and long-acting bronchodilators at least 38 h. At first, FeNO was assessed by means of the NIOX, like described before (25).

Second, maximal expiratory flow volume curves (MEFV) were assessed in each child. The highest forced expiratory volume in one-second (FEV_1), forced vital capacity (FVC), FEV_1/FVC , and maximal expiratory flow at 50% FVC (MEF_{50}) of three technically satisfactory MEFV curves were used for analysis. Thereafter, a histamine challenge test was performed. An aerosol of buffered saline was inhaled, followed by aerosols of histamine acid phosphate in doubling

1 NO ALLERGIC ASTHMA

Symptoms questionnaire AND/OR General Practitioners registration 4–6 years:
No symptoms of wheezing, dyspnoea or night time coughing were reported at the child's age of 4 to 6 years. AND

Lung function results at the age of 6 years:

- a) $\text{FEV}_1/\text{FVC} > \% \text{ predicted-2 SDS}$ AND
- b) Reversibility on a beta-2 agonist $< 9\%$ difference between pre and post bronchodilator FEV_1 $\% \text{ predicted}$ AND
- c) $\text{PC}_{20} > 8 \text{ mg/ml histamine}$.

2) CURRENT ALLERGIC ASTHMA

Symptoms questionnaire AND/OR General Practitioners registration 4–6 years:
Minimally one of the symptoms of wheezing, dyspnoea or night time coughing was reported at the child's age of 4 to 6 years.

AND

Lung function results:

- d) $\text{FEV}_1/\text{FVC} (\text{ml}) \leq \% \text{ predicted-2 SDS}$ AND
- e) Reversibility on a beta-2 agonist $\geq 9\%$ difference between pre and postbronchodilator FEV_1 $\% \text{ predicted}$ AND/OR
- f) $\text{PC}_{20} \leq 8 \text{ mg/ml histamine}$.

3) POSSIBLE ALLERGIC ASTHMA

This was defined as either:

- h) Asthma symptoms reported at age of 4 to 6 years (see current asthma)
- AND
- i) No lung function deviations measured (see no asthma);
- OR:
- j) No current asthma symptoms reported at age 4 to 6 years (see no asthma)
- AND
- k) Lung function abnormalities measured (see current asthma)

Figure 2 Criteria used for determining the asthma status at 6 yr [(the PREvention of asthma in susceptible children (PREVASC) asthma algorithm)].

concentrations from 0.03 to 16 mg/ml at 5-min intervals (26). Dynamic spirometry was repeated once after 30 and after 90 sec following each inhalation. The inhalations of histamine were discontinued when there was 20% fall in FEV₁ or when 16 mg/ml histamine had been administered. The results were expressed as the provoking concentration of histamine inducing a 20% fall in FEV₁ (PC₂₀ histamine). Thereafter, 400 µg of salbutamol (Airomir®, Teva Pharma, Haarlem, The Netherlands) was inhaled via the Aero chamber. After 15 min, three MEFV curves were assessed in a comparable way. The change in FEV₁ was expressed as a percentage of the predicted value (14).

Based on the lung function results and the asthma symptoms as registered by GP and/or parents, a child was characterized in one of three groups of the primary outcome allergic asthma, on grounds of the algorithm for the PREVASC lung function outcome (see Fig. 2).

If children showed to be categorized in the 'possible asthma' group but used asthma medication when they were 4–6 yr old, their dossiers were additionally assessed by (pediatric) pulmonologists associated with the research. If the pulmonologists were in the opinion that the child satisfied the criteria for the outcomes 'current allergic asthma' or 'no allergic asthma', this re-categorization was completed.

Statistical aspects

Based on longitudinal study results (27), a minimum number of 194 infants per group was required to be able to detect a reduction in the asthma incidence by at least 30% (type I error of 0.05 and power of 0.80). Pearson Chi-squared tests were carried out for the analyses on differences between the intervention group and the control group and between the separate intervention subgroups as compared to controls. SPSS for Windows version 15 was used.

Post hoc multiple logistic regression analyses were carried out for evaluating the effect of the intervention(s) on the outcome allergic asthma at age 6. The outcome tested was the combined algorithm outcome of 'current allergic asthma or possible allergic asthma' compared with those categorized as having 'no allergic asthma'. The independent variables included in the logistic regression analyses were those that are assumed to be related to the development of allergic asthma (group allocation, exposure variables, and base line characteristics). A backward procedure was followed.

Results

A total of 443/476 children were followed up (Intervention group, IG n = 222, Control group, CG n = 221). A participant's flowchart is presented in Fig. 1.

After 2 yr, the children in the intervention group were additionally randomized into an extended intervention group (n = 111) or a short intervention group (n = 108). Overall, most children could be followed up until age 6 (<10% lost to follow-up, 45/476).

All the results on the exposure to allergens and tobacco smoke are presented in Table 1. Only the results of the

feeding intervention and the allergen-reducing intervention are described in the current section. The feeding intervention (6 months breast-feeding and postponing the introduction of solids and the use of regular formula) showed to be significantly more often practiced by families in the intervention group(s) as compared to the control group ($p < 0.001$). However, the number of weeks children were breast-fed did not differ significantly between groups ($p = 0.635$). The house dust mite-impermeable mattress encasings were used more often in intervention group families as opposed to controls during the whole study period ($p < 0.001$). The mite-impermeable mattress encasing showed to be effective in reducing the allergen exposure levels of house dust mite, cat, and dog in the extended and total intervention group. Placebo encasings, as expected, did not reduce the exposure to inhalant allergens in the short intervention group, as compared with controls. At their children's age of 2–6, the families in the short intervention group showed not to have significantly more often performed allergen avoidance behavior as compared to controls (results not shown).

No statistical significant differences were observed between groups for the adherence to the airing and ventilating procedures that were advised (data not shown).

The intervention had no significant influence on the primary outcome presence of (the algorithm) diagnosis of allergic asthma at age 6 (see Table 2). Moreover, we also found no significant effect of the intervention on the GP diagnosis of asthma or complaints of wheezing, nighttime cough, or dyspnoea separately (Table 2).

There was no influence of the intervention on the secondary outcome 'separate lung function parameters', 'reversibility on a beta-2 agonist', 'bronchial hyper-responsiveness', or 'FeNO' (see Table 3).

The prescribed asthma medication did not differ between groups ($p = 0.929$, data not shown). The general practitioners of 83 children prescribed medication to children included in the PREVASC study for their asthma symptoms of wheezing, coughing, and/or dyspnoea when they were 4–6 yr old (mostly inhaled (6%)/systemic (0.75%) corticosteroids, long-acting (0.5%) or short-acting (5.75%) bronchodilators).

The results of the post hoc multivariate logistic regression analysis seem to show the interventions used in the PREVASC study (overall, short or extended) did not influence the development of asthma significantly. This result is presented in Table 4. Grouping variable A represents the total intervention group as compared to controls (overall study period, combination of short and extended intervention). Grouping variable B indicates the separate randomized intervention duration subgroups, of 2 or 6 yr, as compared to the control group. The only variables that seemed to influence the development of asthma were number of weeks a child was breast-fed and the exposure to the house dust mite allergen Der p1 above or below the group median (0.6606 µg/g of dust). Breast-feeding seems to significantly reduce the development of asthma ($p = 0.026$), whereas a Der p1 exposure level at 4 yr of age below the group median may indicate a protective effect ($p = 0.061$).

Discussion

Although the first results of the PREVASC study showed that the intervention was effective in reducing the development of asthma symptoms at age two, (17) asthma prevalence at age 6 showed not to be influenced by the multifaceted intervention. Even when the primary outcome was re-evaluated, by categorizing all asthma medication-using children in the age of 4–6 yr as having current asthma because the medication could have suppressed lung function problems or symptoms, this did not change the primary results.

The intervention, however, has shown to be reasonably effective in reducing the exposure to inhalant and food allergens. No influence on passive smoking exposure, however, was observed. The post hoc multivariate analysis seemed to indicate that a low Der p1 exposure level and breast-feeding during the first 6 months of life may both be negatively related to the development of allergic asthma. This may indicate that the intervention was directed toward relevant risk factors. Although the inhalant- and food allergen exposure data showed to differ significantly, they were not clinically relevant. These results are not similar to the results of other multifaceted prevention trials.

In a recent meta-analysis, we tested whether single-intervention strategies or multifaceted interventions for reduction in

allergen exposure in children at high risk of developing asthma would be more effective for the primary prevention of asthma (20). It was shown that multifaceted interventions were significantly more effective than mono-faceted interventions.

As compared to the other multifaceted intervention studies, the outcome measure 'allergic asthma' in the PREVASC study was more extensive including not only asthma symptoms and provocation testing but also reversibility. The reversibility testing, however, could not be performed in the conventional manner as all lung function measures were exerted in 1 day reducing the burden for parents and children to cooperate. This seems not to have influenced the study outcome as there were no statistically significant differences between the total intervention and the control group on all parts of the main outcome measure (symptoms and all lung function measurements).

At least two explanations seem to be possible for the discrepancy with the other published multifaceted studies: (i) little room for improvement and (ii) low adherence to the multifaceted intervention program.

Room for improvement

The mite allergen exposure level in the Netherlands, as measured in PREVASC and another Dutch intervention study

Table 1 The exposure to allergens and parental indoor smoking in the intervention and control groups

no	Variables	Control group no/Total (%), median	Intervention group (IG) no/Total (%), Median Asymp. sig. 2-sided	Extended IG no/Total (%), Median Asymp. sig. 2-sided	Short IG no/Total (%), Median Asymp. sig. 2-sided
Food allergen exposure					
1	Breast-feeding and/or hypo-allergenic formula feeding 6 months and introduction of solids >6 months	25/221 (12.0)	84/222 (37.8) <0.001	48/111 (43.2) <0.001	36/108 (33.3) <0.001
2	Breast-feeding (no weeks)	13 (2–26)	12 (2–24) 0.635	14 (3–25.0) 0.932	10 (2–23) 0.318
3	Hypo-allergenic formula ever	66/221 (29.9)	193/222 (86.9) <0.001	96/111 (86.5) <0.001	97/108 (89.8) <0.001
4	Introduction of solids >6 months	58/221 (26.2)	142/222 (63.7) <0.001	76/111 (68.5) <0.001	66/108 (61.1) <0.001
Inhalant allergen exposure					
5	Hairy pets at home (no years, 0–6 yr)	0.00 (0–4)	0.00 (0–2) 0.015	0.00 (0–3) 0.017	0.00 (0–2) 0.089
6	Use of house dust mite-impermeable mattress covers (no years)	0 (0–0)	2 (2–4) <0.001	4 (2–5) <0.001	2 (2) <0.001
7	Der p1 ng/m ² 2–6 yr	124.36 (1.93–155.27)	82.62 (0.13–37.42) 0.043	65.79 (0.08–16.90) 0.007	119.98 (1.18–57.79) 0.558
8	Fel d1 ng/m ² 2–6 yr	21.67 (5.04–51.89)	13.48 (5.04–51.89) 0.037	6.21 (1.53–25.82) <0.001	21.53 (8.07–60.61) 0.692
9	Can f1 ng/m ² 2–6 yr	88.88 (23.58–283.10)	48.83 (23.58–383.10) 0.012	37.65 (9.88–103.48) 0.002	87.19 (15.38–320.95) 0.307
Smoke exposure					
10	Indoor smoking by parents (no years, 0–6 yr)	1.00 (0–2.00)	0.50 (0–2.00) 0.829	0.00 (0–2.00) 0.121	1.00 (0–4.00) 0.176

Numbers with percentages or median values with interquartile ranges are demonstrated. Pearson Chi-squared tests were carried out for outcomes 1–4, and the Mann–Whitney U-tests for the outcomes 5–10. Of the results presented in bold, the differences between groups showed to be statistically significant.

Table 2 The allergic asthma diagnosis at 6 yr (according to the PREVASC algorithm), the GP diagnosis of allergic asthma, and the separate symptoms of wheezing, nighttime cough, and dyspnoea (according to the GP and/or parents) in the various study groups with control group as reference

	Control group n of total (%)	Intervention group (IG) n of total (%) Asymp. sig. 2-sided	Extended IG n of total (%) Asymp. sig. 2-sided	Short IG n of total (%) Asymp. sig. 2-sided
Current allergic asthma (PREVASC algorithm)	44/221 (19.9%)	51/222 (23.0%) 0.432	23/111 (20.7%) 0.836	28/108 (25.9%) 0.229
Possible allergic asthma (PREVASC algorithm)	86/221 (38.9%)	80/222 (36.0%) 0.532	43/111 (38.7%) 0.862	37/108 (34.3%) 0.224
No current allergic asthma (PREVASC algorithm)	40/221 (18.1%)	41/222 (18.5%) 0.632	20/111 (18.0%) 0.891	21/108 (18.5%) 0.874
GP allergic asthma diagnosis at 4–6 yr	18/221 (8.1%)	12/222 (5.4%) 0.208	8/111 (7.2%) 0.557	4/108 (3.7%) 0.138
Reported wheezing (parents/GP)	28/221 (21.7%)	45/222 (20.3%) 0.493	18/111 (16.2%) <i>0.085</i>	27/108 (25.0%) 0.486
Reported nighttime coughing (parents/GP)	135/221 (61.1%)	127/222 (57.2%) 0.283	60/111 (54.1%) <i>0.060</i>	67/108 (62.0%) 0.842
Reported dyspnoea (parents/GP)	51/221 (23.1%)	57/222 (25.7%) 0.666	27/111 (24.3%) 0.883	30/108 (27.8%) 0.300

GP, General practitioner; PREVASC, PREvention of asthma in susceptible children.

Pearson Chi-squared tests are carried out for all outcomes.

Italic results imply that a statistical trend was pragmatic.

Table 3 Lung function parameters, FeNO, and bronchial hyper-responsiveness in the different study groups (control group is reference)

	Control group Median inter-quartile range	Intervention group Median inter-quartile range	Extended Intervention Median inter-quartile range	Short Intervention Median inter-quartile range
FEV ₁ % predicted	107.74 98.70–117.08	109.09 100.15–119.00	108.90 99.85–118.25	109.28 98.70–117.08
FVC % predicted	99.80 91.00–109.50	100.80 93.80–109.45	100.70 93.98–110.80	102.00 91.00–109.50
Reversibility (%)	3.6 –2.60–13.17	4.57 –2.45–15.08	5.71 –3.36–16.19	3.54 –1.71–12.28
FEV ₁ /FVC ratio	93.26 87.11–98.43	93.29 87.77–97.35	93.18 86.58–96.97	93.54 87.11–98.43
FeNO (ppb)	11.80 7.7–17.3	10.80 7.55–16.90	10.80 8.60–16.68	10.90 7.70–17.30
PC ₂₀ histamine (mg/ml)	4.56 2.70–7.82	4.11 2.50–7.46	4.07 2.31–6.37	4.42 2.70–7.94

FVC, forced vital capacity.

(PIAMA), was shown to be low, indicating a reasonably healthy allergen exposure environment in the Netherlands (7). The mite allergen exposure levels in the Canadian, but even more so in the Isle of Wight study, were shown to be much higher at baseline (Canadian study baseline 1.5 µg/g of dust, Isle of Wight 25 µg/g, and PREVASC 0.7 µg/g) (13, 19). The reduction levels of mite allergen exposure in the intervention group as compared to controls (therefore) were much higher in these studies when compared to the PREVASC trial.

Also the room for improvement in the tobacco smoke exposure level in the current trial showed to be low. The Canadian Study appeared to have the same problem of little

room for improvement and lack of success for the smoke-reducing intervention (13). It is possible that in a multifaceted intervention program, parents choose to adhere to the easiest parts of the intervention. It is evident that stopping passive smoking exposure is not easy to accomplish. The lack of sufficient adherence to the smoke-reducing intervention, however, cannot be the cause of the lack of effectiveness as the Isle of Wight intervention, effective in reducing allergic asthma in children, did not use a smoke-reducing intervention.

Although the intervention showed to be reasonably effective in reducing the exposure to allergens, the adherence to the total package of advices to use house dust mite-

Table 4 Results of the logistic regression analysis of the effect of the intervention, of Der p1 exposure, and of breast-feeding on the outcome of allergic asthma at 6 yr. Only the results of the intervention and of variables with a $p \leq 0.100$ are presented. Both the effects of the total intervention (A) and of the extended and short intervention (B) are given.

	Odds ratio	95% CI lower	95% CI upper	Asymp. sig. 2-sided
A. Intervention group vs. controls (total group, irrespective of duration)	1.010	0.580	1.758	0.973
B. Intervention duration groups vs. controls				0.999
Short intervention (2 yr)	0.992	0.452	2.178	0.985
Extended intervention (6 yr)	0.987	0.496	1.964	0.969
Der p 1 exposure (above/below median value of 0.6606 $\mu\text{g/g}$ of dust)	1.706	0.976	2.980	<i>0.061</i>
Breast-feeding, quartiles no weeks (reference 0 weeks)				0.026
1–11 wk	0.385	0.145	1.003	<i>0.058</i>
12–25 wk	0.247	0.093	0.655	0.005
Minimally 26 wk	0.523	0.187	1.458	0.275

Results presented in bold imply that a statistically significant difference was observed.

Results presented in italic imply that a statistical trend was observed.

impermeable bedding encasings and to solely breast-feed the children until they reached the age of 6 months was low.

Families were shown not to have consistently used the (house dust mite impermeable) bedding encasings they received. In the study period from pregnancy until 2 yr, the adherence to the house dust mite allergen-reducing intervention was nearly 100%, resulting in statistically significant allergen reduction in the total intervention group. One of the reasons for the low adherence in the follow-up period might have been that, unlike the first 2 yr of the trial, there was a chance to receive placebo encasings. The second randomization, however, cannot be the reason for the difference in outcome between the separate multifaceted studies as in the Isle of Wight trial, no covers were used at all and impermeable bedding encasings were only supplied for the baby mattress in the Canadian study. It is more plausible that the low exposure level at base line seems to be the cause of the lack of clinical effect of the inhalant allergen-reducing intervention. The Dutch inhalant allergen exposure level in asthmatic families showed to be too low to be able to reach clinical relevance.

The cow's milk avoidance advices used in the PREVASC research were successful although the breast-feeding part of the food allergen-reducing intervention did not result in significant differences between groups. Breast-feeding seems to be of significant importance in the prevention of allergic asthma, and hypo-allergenic formula, an advice that was complied with significantly more often in the intervention group as compared to controls, showed not to have the same effect as breast-feeding. Reason for the difference in effect of hypo-allergenic formula and breast-feeding may be that breast-feeding does not only reduce exposure of infants to cow's milk as it also provides the child with important components that may strengthen both their immune and digestive system, such as secretory immune globulin A, cytokines, poly-unsaturated fatty acids, pre-biotics, and lysozyme (28).

While the study was ongoing, the intervention was evaluated by Gijsbers et al. This evaluation already revealed that the breast-feeding intervention was not enough tailor-made for the mothers to be strengthened to stand up to the difficulties they encountered (29). Tailoring the breast-feeding part of the intervention in a new group of women in the research of Gijsbers et al. indeed showed to significantly double the adherence, indicating that the intervention was not enough focussed on stimulating parents to adhere to the breast-feeding advices given (30). Higher breast-feeding rates were reported for other asthma prevention studies, assumingly being a plausible explanation for the discrepancy in outcome between PREVASC and the other multifaceted asthma prevention trials (4, 5).

All intervention parts, but the smoke-reducing and breast-feeding-promoting interventions, showed to be possible to adhere to in the first 2 yr of the study. It may be true that the intervention would have been more effective if the parents were more often contacted concerning the performance of the intervention measures as was carried out in the other multifaceted asthma prevention studies. In the PREVASC study, however, we aimed at educating parents using a feasible method easy to implement in daily general practice. Additional effort to improve adherence would have been too time-consuming and therefore not in accordance with daily care.

Intervention's duration

As far as the authors know, the present study is the only study in which two multifaceted interventions of different duration were compared. The extended intervention showed to be more effective in reducing the inhalant allergen exposure but this did not result in group differences in primary outcome, seemingly because of the low allergen levels in asthmatic families in the Netherlands. The symptoms

wheezing and nighttime coughing seem to have been negatively influenced by the extended intervention only, but this effect was not consistent between the symptom reports of parents and general practitioners. It seems that parents not always consult a doctor for their child's symptoms as no differences were observed in the general practitioner's registration of asthma symptoms (data not shown) or that the symptoms parents reported to their general practitioner were classified as being the result of 'happy wheezing' or a 'common cold'.

Strengths of the PREVASC asthma preventive intervention

- 1 The PREVASC research was a large prospective randomized controlled trial in which a multifaceted asthma preventive intervention was tested in high-risk children. PREVASC was designed for researching the effectiveness as well as the feasibility of an asthma preventive intervention. This simultaneous focus on effectiveness and feasibility gave the opportunity to investigate implementation in real-life circumstances.
- 2 Because the design of the PREVASC study took the busy schedules of general practitioners into account, the intervention, if effective, can be implemented in daily care immediately.
- 3 The close cooperation with first-line health care workers as well as the personal contact of researcher and assistants with the families may both have positively influenced the cooperation and continuation of parents in the research resulting in a low drop out rate.

Weaknesses of the PREVASC asthma preventive intervention

- 1 The intervention could have been more tailor-made and therefore more effective;
- 2 Although the focus of the research was to test a hypothesis that was easy to implement in usual care of general practitioners and parents, additional contact moments with the parents after the questionnaires were received could have increased the adherence to the intervention measures.

References

1. Warner JA, Jones AC, Miles EA, Colwell BM, Warner JO. Prenatal origins of asthma and allergy. *Ciba Found Symp* 1997; **206**: 220–8; discussion 8–32.
2. Mommers M, Gielkens-Sijstermans C, Swaen GM, Van Schayck CP. Trends in the prevalence of respiratory symptoms and treatment in Dutch children over a 12 year period: results of the fourth consecutive survey. *Thorax* 2005; **60**: 97–9.
3. Marino DJ, Prescott SL. Silent mysteries: epigenetic paradigms could hold the key to conquering the epidemic of allergy and immune disease. *Allergy* 2010; **65**: 7–15.
4. Arshad SH, Matthews S, Gant C, Hide DW. Effect of allergen avoidance on development of allergic disorders in infancy. *Lancet* 1992; **339**: 1493–7.
5. Chan-Yeung M, Manfreda J, Dimich-Ward H, Ferguson A, Watson W, Becker A. A randomized controlled study on the effectiveness of a multifaceted intervention program in the primary prevention of asthma in high-risk infants. *Arch Pediatr Adolesc Med* 2000; **154**: 657–63.
6. Arshad SH, Bateman B, Sadeghnejad A, Gant C, Matthews SM. Prevention of allergic disease during childhood by allergen avoidance: the Isle of Wight prevention study. *J Allergy Clin Immunol* 2007; **119**: 307–13.
7. Brunekreef B, Smit J, De Jongste J, et al. The prevention and incidence of asthma and mite allergy (PIAMA) birth cohort study: design and first results. *Pediatr Allergy Immunol* 2002; **13** (Suppl 15): 55–60.
8. Custovic A, Simpson BM, Simpson A, Kissen P, Woodcock A. Effect of environmental manipulation in pregnancy and early life on respiratory symptoms and atopy during first year of life: a randomised trial. *Lancet* 2001; **358**: 188–93.
9. Koopman LP, Van Strien RT, Kerkhof M, et al. Placebo-controlled trial of house dust mite-impermeable mattress covers: effect on symptoms in early childhood. *Am J Respir Crit Care Med* 2002; **166**: 307–13.
10. Mallet E, Henocq A. Long-term prevention of allergic diseases by using protein

Conclusions

Other primary preventive asthma-reducing interventions were shown to be effective in reducing the occurrence of asthma in the first 7 (13) or 8 yr of life (6). The PREVASC intervention, although effective in reducing the exposure to inhalant and food allergens, was not effective for the prevention of the development of allergic asthma. This lack of effectiveness seems to be partially caused by too little room for improvement and too little focus on stimulating adherence to measures taken by the parents. It might be possible that a multifaceted environmental exposure-reducing intervention may have to be adapted to the personal circumstances of the families concerned.

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Conflicts of interest

Dr Tanja Maas, Dr Edward Dompeling, Dr Jean Muris, Dr Geertjan Wesseling, Prof Dr André Knottnerus, and Prof Dr Onno van Schayck state not to have any conflicts of interest.

- hydrolysate formula in at-risk infants. *J Pediatr* 1992; **2**: S95–100.
11. Marks GB, Mahrshahi S, Kemp AS, et al. Prevention of asthma during the first 5 years of life: a randomized controlled trial. *J Allergy Clin Immunol* 2006; **118**: 53–61.
 12. Woodcock A, Lowe LA, Murray CS, et al. Early life environmental control: effect on symptoms, sensitization, and lung function at age 3 years. *Am J Respir Crit Care Med* 2004; **170**: 433–9.
 13. Chan-Yeung M, Ferguson A, Watson W, et al. The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age. *J Allergy Clin Immunol* 2005; **116**: 49–55.
 14. Kuiper S, Maas T, Van Schayck CP, et al. The primary prevention of asthma in children study: design of a multifaceted prevention program. *Pediatr Allergy Immunol* 2005; **16**: 321–31.
 15. Peat JK, Mahrshahi S, Kemp AS, et al. Three-year outcomes of dietary fatty acid modification and house dust mite reduction in the Childhood Asthma Prevention Study. *J Allergy Clin Immunol* 2004; **114**: 807–13.
 16. Schönberger H, Schayck Cv. Prevention of asthma in genetically predisposed children in primary care-from clinical efficacy to a feasible intervention programme. *Clin Exp Allergy* 1998; **28**: 1325–31.
 17. Schonberger HJ, Dompeling E, Knottnerus JA, et al. The PREVASC study: the clinical effect of a multifaceted educational intervention to prevent childhood asthma. *Eur Respir J* 2005; **25**: 660–70.
 18. Zeiger RS, Heller S. The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. *J Allergy Clin Immunol* 1995; **95**: 1179–90.
 19. Arshad SH, Bateman B, Matthews SM. Primary prevention of asthma and atopy during childhood by allergen avoidance in infancy: a randomised controlled study. *Thorax* 2003; **58**: 489–93.
 20. Maas T, Kaper J, Sheikh A, et al. Mono and multifaceted inhalant and/or food allergen reduction interventions for preventing asthma in children at high risk of developing asthma. *Cochrane Database Syst Rev* 2009; **3**: CD006480.
 21. Bindels P, Van Der Wouden J, Ponsioen B, et al. NHG guideline asthma in children. *Huisarts Wet* 2006; **49**: 557–72.
 22. Van Deursen J. Nurses can point out to parents the adverse effects for young children. Campaign against passive smoking. *Tvz* 1997; **107**: 551–2.
 23. Maas T, Rovers JJ, Schonberger HJ, Schayck CP. Distribution of house dust mite allergen: comparing house dust mite allergen levels in dust samples collected from different sites on living room floors with smooth coverings. *Allergy* 2003; **58**: 500–2.
 24. Committee Is. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC). *Lancet* 1998; **351**: 1225–32.
 25. Robroeks CM, Van De Kant KD, Jobsis Q, et al. Exhaled nitric oxide and biomarkers in exhaled breath condensate indicate the presence, severity and control of childhood asthma. *Clin Exp Allergy* 2007; **37**: 1303–11.
 26. Cheung D, Wever AM, Goeij JA, Graaff CS, Steen H, Sterk PJ. Effects of theophylline on tolerance to the bronchoprotective actions of salmeterol in asthmatics in vivo. *Am J Respir Crit Care Med* 1998; **158**: 792–6.
 27. Saarinen UM, Kajosaari M. Breastfeeding as prophylaxis against atopic disease: prospective follow-up study until 17 years old [see comments]. *Lancet* 1995; **346**: 1065–9.
 28. Penders J, Thijs C, Vink C, et al. Factors influencing the composition of the intestinal microbiota in early infancy. *Pediatrics* 2006; **118**: 511–21.
 29. Gijsbers B, Mesters I, Knottnerus JA, Legtenberg AHG, Schayck Van CP. Factors influencing breastfeeding practices and postponement of solid food to prevent allergic disease in high-risk children: results from an explorative study. *Patient Educ Couns* 2005; **57**: 15–21.
 30. Gijsbers B, Mesters I, Knottnerus J, Kester A, Schayck Van CP. The success of an Educational Program to Promote Exclusive Breastfeeding for 6 Months in Families with a History of Asthma: A Randomized Controlled Trial. *Pediatr Allergy Immunol* 2006; **19**: 214–22.