

The primary prevention of asthma in children study: Design of a multifaceted prevention program

Kuiper S, Maas T, van Schayck CP, Muris JWM, Schönberger HJAM, Dompeling E, Gijsbers B, van Weel C, André Knottnerus J on behalf of the PREVASC group. The primary prevention of asthma in children study: Design of a multifaceted prevention program.

Pediatr Allergy Immunol 2005; 16: 321–331. © 2005 Blackwell Munksgaard

The PREVASC study addresses the primary prevention of asthma in infants and small children. The objective of this study is to investigate whether a multifaceted prenatally started intervention strategy in high-risk infants leads to a decrease in the occurrence of (severe) asthma and whether a refinement of the prevention strategy leads to an increase in the adherence to the prevention program. The primary prevention program includes house dust mite impermeable bed coverings, education on breast feeding, hypoallergenic feeding, timing of introduction of solid food and smoking cessation. A total of 888 infants were prenatally included. By the time of inclusion the mothers were 3–7 months pregnant. About 27 infants were excluded from the study and 18 dropped out. Of the remaining 843 infants 535 had a first-degree familial predisposition of asthma (high-risk group), whereas a reference group of 308 (162 boys) infants was not predisposed for asthma in the first-degree (low-risk group). To evaluate the (cost-)effectiveness of the preventive intervention, 222 (118 boys) infants of the high-risk group allocated to the intervention group and 221 (112 boys) allocated to a control group are followed up. The low-risk infants served as controls to evaluate the predictive value of high risk (first-degree familial predisposition of asthma). The infants are followed from the prenatal stage until they reach the age of 6 yr. The remaining 92 high-risk infants were included in an optimized randomized-clinical adherence trial (RCAT). Of these 92 infants, 45 (20 boys) were allocated to an intervention group and 47 (24 boys) to a control group. Until now all infants have been followed for at least 1 yr.

**Sandra Kuiper¹, Tanja Maas¹,
Constant P. van Schayck¹,
Jean W. M. Muris¹,
Huub J. A. M. Schönberger¹,
Edward Dompeling²,
Barbara Gijsbers¹, Chris van Weel³
and J. André Knottnerus¹ on behalf of
the PREVASC group**

¹Department of General Practice, Care and Public Health Research Institute, University of Maastricht, Maastricht, ²Department of Pediatrics, Care and Public Health Research Institute, University Hospital Maastricht, Maastricht, ³Department of General Practice, University Medical Centre Nijmegen, Nijmegen, The Netherlands

Key words: asthma; allergen avoidance; infants; house dust mite; multifaceted primary prevention; randomized-controlled trial

Sandra Kuiper, Department of General Practice, Care and Public Health Research Institute, University of Maastricht, PO Box 616, 6200 MD Maastricht, The Netherlands
Tel.: +31 43 388 21 84
Fax: +31 43 361 93 44
E-mail: sandra.kuiper@hag.unimaas.nl

Accepted 21 February 2005

Childhood asthma, a chronic disease of the airways, is predominantly newly diagnosed in infants and small children. Asthma is the main cause of school absence (1, 2), involves high costs and is known to reduce the quality of life of children and their parents. During the last decades there has been a substantial increase in the prevalence of asthma worldwide (3, 4), which emphasizes the need to prevent its development. It is generally thought that genetic as well as environmental factors are involved in the development of asthma (5, 6). Because it is not yet

possible to influence the genetic factors, prevention programs should focus on influencing the environmental factors. There are reasons to believe that the first signs of sensitization occur already in the prenatal stage by the interaction between the maternal environment and the foetus (7). Therefore, it is important to start intervention in the prenatal stage. Several primary prevention studies are being performed, and are still in progress. In most primary prevention studies only one (8–10) intervention was tested whereas in others two single interventions with or

without a factorial design were tested (11–13), which may lead to underestimation of the effect of prevention. To our knowledge there are three multifaceted primary prevention studies (14–16), in which several interventions are combined into one program and compared with one other modality, like usual care.

We report on the objectives and the design of the prevention of asthma in children (PREVASC) a research program focussed on primary prevention of asthma in children. The objectives of this program are to estimate the predictive value of a positive family history of asthma assessed in the prenatal period by the general practitioner (GP) for the development of childhood asthma and, to assess the effectiveness of a prenatally started multifaceted primary prevention program focused on reducing the exposure to indoor and food allergens and environmental tobacco smoke (ETS) in children at high risk of developing asthma. Furthermore, it will be assessed whether the duration of the prevention program has any effect on the development of asthma as measured at 6 yr of age and whether optimizing the intervention leads to increased adherence. Finally, the health-economic benefits of high-risk identification and primary prevention of asthma will be assessed.

Research plan

General design

Our study comprises three parts, one observational cohort and two intervention studies.

To assess the clinical effectiveness of the PREVASC prevention program, a randomized-clinical prevention trial (RCPT) was started in a group of prenatally selected high-risk infants. Additionally a cohort of prenatally selected low-risk infants was composed of a natural history study, to assess the clinical course of asthma and allergies in high- and low-risk children and to assess the predictive value of 'high-risk'. To be able to identify whether (the parents of) the infants were compliant to the prevention program, the adherence to the intervention was evaluated. In addition, to get a better insight into the determinants of adherence and to improve the preventive program, a 'focus' group approach was applied in a subgroup of trial participants. In addition, an 'optimized randomized-clinical adherence trial' (RCAT) was evaluated in a newly recruited group of prenatally selected infants with a family history of asthma. Cost-effectiveness of the prevention program will be studied on the basis of the RCPT, taking

adherence aspects and validity of screening into account.

In the participants section a general description will be given of how the participants were included in the study. In the section concerning the intervention studies and the natural history study the outline of both intervention studies and the natural history study will be described.

Participants

The infants were recruited prenatally when their mothers were in their first two trimesters of pregnancy. The community-based recruitment started in January 1997 and continued until February 2002. For the RCPT this was performed by the primary caregivers (GP and midwives) and by advertisements. For the natural history study recruitment was exclusively performed by the GP, whereas for the optimized RCAT recruitment was performed by midwives and by advertisements. These complementary ways of recruitment were necessary to include 888 participants.

'High-risk' was defined as 'at least one first-degree family member (i.e. the pregnant woman, the biological father of the unborn child or a sibling) suffering from GP registered asthma', whereas 'low-risk' was defined as 'absence of GP registered asthma in first-degree family members'. Asthma was defined according to the International Classification of Primary Care (ICPC) (17) as recurrent episodes of reversible acute bronchial obstruction with wheeze and/or dry cough. This was checked by the GP and screening questionnaires.

For the RCPT, the natural history study and the RCAT, a family was excluded from the study when there was intrauterine or neonatal death, major language problems, serious birth defects (illness or malformation) and moving abroad.

Intervention studies

In the following specific elements of the various study parts are described. Thereafter aspects that relate to all the three study parts are presented together.

Randomized-clinical prevention trial

The goal of this study was to assess the effectiveness of (the duration of) a prenatally started multifaceted primary prevention program in children at high risk for development of asthma. The study was designed to follow the high-risk children until they reach the age of 6. By that time lung function measurement can reliably be

performed which makes an objective diagnosis of asthma possible.

Recruitment

In the first part of the study (the period from the prenatal stage until the age of 2) 476 pregnant women were included (Fig. 1) and after randomization equally divided over two study groups: an intervention group and a control group. About 443 of the descendants could be followed up, 222 (118 boys) of the intervention group and 221 (112 boys) of the control group.

Intervention first part

The intervention started prenatally in order to reach a low house dust mite (HDM) and pet allergen exposure level at the time the child was born. In addition, the intervention focussed on avoidance of prenatal and postnatal passive smoking and on avoidance of food allergens postnatal.

House dust mite reduction intervention started before the month 7 of pregnancy. This intervention consisted of advice on ventilation and cleaning as well as application of HDM impermeable covers on the parents and children's bed. To prevent exposure to pet allergens, the advice was given to keep pets outdoors from the month 6 of pregnancy. Smoking intervention consisted of advice on smoking cessation of the mother as early as possible in pregnancy and no smoking of the father as well as the mother in the presence of the baby postnatal. Dietary intervention contained advice on exclusively breast feeding (or hypoallergen formula feeding) for at least 6 months and postponing introduction of solid food until 6 months after birth. The high-risk control group received usual care, according to the Guidelines of the Dutch College of GPs that include criteria-based diagnosis and an initial treatment with short acting bronchodilators and when no adequate asthma

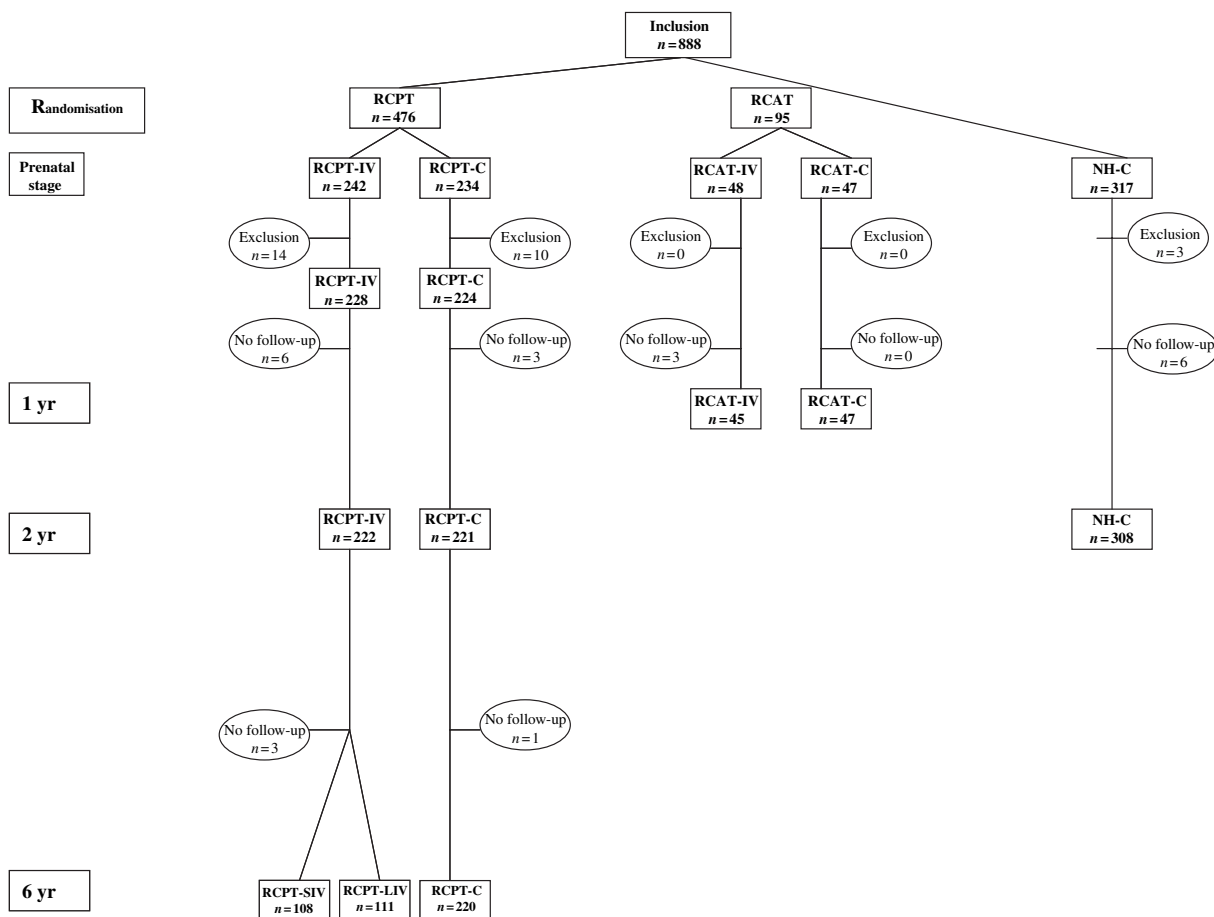


Fig. 1. Schematic representation of the PREVASC studies. RCPT-IV, randomized-clinical prevention trial intervention group; RCPT-C, randomized-clinical prevention trial control group; RCAT-IV, randomized-clinical adherence trial intervention group; RCAT-C, randomized-clinical adherence trial control group; NH-C, natural history control group; RCPT-SIV, RCPT short intervention; RCPT-LIV, RCPT long intervention.

control is achieved with a step-up approach with inhaled corticosteroids in increasing dosage (18).

Intervention second part

In the second part of the study the children are followed from 2 to 6 yr of age. For this part of the study – which is still going on – the children in the original intervention group were randomized again into two groups (Fig. 1). One group was no longer exposed to advice and HDM impermeable mattress covers (short intervention period). The other group still received an intervention program focused on diminishing allergen and irritant exposure and to keep on using HDM impermeable mattress covers (extended intervention period). The children that participated in the control group in the first part continue to participate in the control group in the second part of the study as well and receive usual care.

Randomized-clinical adherence trial

Eighty-one randomly selected families who participated in the intervention group of the RCPT received an invitation letter for a focus-group interview to investigate which determinants influenced the actual adherence behaviour. For these interviews the stepwise guidelines of Van Assema et al. (19) for conducting a focus-group interview were used.

About 43 households (59 participants) were scheduled to meet at times and locations that might be convenient for the participants. Six groups were mixed as to gender and one group was formed containing only fathers, because fathers may have different opinions and thoughts about breast feeding and postponement of solid foods, which might be missed in the presence of women.

The reasons for the 39 non-respondent households were: interested, but date not convenient ($n = 14$), no time ($n = 7$), location of interview not convenient ($n = 3$), on holiday ($n = 2$), unknown ($n = 13$). No significant differences were found between the participation and non-participation group with respect to level of education, feeding behaviour and family history of asthma.

On the basis of the results of the determinant-analysis, a refined prevention educational program was developed.

Recruitment refined intervention program

In this phase, the RCAT study, 92 families expecting a child at high risk of developing asthma were selected. About 45 families received intervention and 47 served as controls (Fig. 1).

Intervention measures

Educational materials and the educational message to be provided orally by research nurses were refined. The effect of the renewed education on the degree of adherence with the advised measures was evaluated in the next phase of this program.

Natural history study

The goal of this study was to assess the clinical course of asthma and allergies in high- and low-risk children and to assess the predictive value of 'high-risk'.

Recruitment

For this study 317 pregnant women, without asthma or asthma in the family, were included. About 308 (162 boys) of the descendants could be followed up (Fig. 1).

Clinical follow up

The clinical course of symptoms of asthma and allergies over the first 2 yr of life in this cohort was compared with the RCPT control group in order to evaluate the predictive value of the family history. The low-risk infants received usual care.

Randomization, withdrawal procedures and blinding

For those women who were recruited by the GP, randomization was done in zipcode clusters on practice level and not on patient level in order to minimize the probability of exchange of information between participants.

Families who were recruited by the GP were screened by the GP. Families who were recruited for the RCPT study by midwives or advertisements completed questionnaires concerning the presence of asthma in their family. Whenever it turned out from the questionnaire that there was no asthma in a 'high-risk' family, the GP was contacted. When the GP confirmed the questionnaire outcome, the family was withdrawn from the study. Families who were recruited by midwives or advertisements for the RCAT study were screened by the GP.

For the RCPT and the RCAT, blinding for group assignment was performed at family level.

Economical evaluation

To assess the efficiency of 'high-risk' identification and the cost-effectiveness of the PREVASC intervention, it will be evaluated whether cost savings [associated with a decrease in (severe) asthma cases and an increase in the quality of

life] outweigh the costs of the prevention program. This will be achieved in two steps, by assessing (i) the cost-effectiveness of the PREVASC intervention among the high-risk group and (ii) the cost-effectiveness of the complete PREVASC RCPT program including the high-risk identification at the population level.

Ad (1)

It will be assessed what the PREVASC preventive intervention with its allied costs yields in terms of health outcome and savings concerning direct and indirect health-related costs in the high-risk group. For this purpose, the clinical course, health outcomes and costs of primary prevention of asthma (PREVASC intervention group) will be compared with the clinical course, health outcomes and costs of usual care (PREVASC control group). To be able to assess the cost-effectiveness, information concerning the direct and indirect medical costs, the costs of the prevention program, and the health status of the children will be collected, using information from questionnaires that will be completed by the parents. By use of these questionnaires the use of medical care and products can be measured. This use will be valued against national recommended prices (20) to be able to determine the costs of care per individual. The health status of the children will be measured using the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire as well as the morbidity registration of the GP. When the children have reached the age of 6 yr asthma will objectively be diagnosed, which makes it possible to express asthma as a dichotomous variable. In this way the costs per asthma case prevented can be determined.

Ad (2)

By connecting the results Ad (1) (the cost-effectiveness of the primary prevention program among the high-risk group) to the predictive value of the 'high-risk' identification, the costs of prenatal high-risk identification, the prevalence of a positive family history, and the observed disease course in the absence of intervention in both the high-risk control group and the low-risk group, the expected cost-effectiveness of the complete PREVASC program at population level will be assessed.

Data collection procedure

Symptoms/diagnosis

First-degree familial predisposition of asthma was determined by the GP and by use of a

questionnaire directly at the inclusion. For the RCPT and the 'natural history' study this was re-evaluated at the age of 2 yr. Information on complaints, diagnosis, laboratory tests and medication concerning respiratory morbidity are prospectively registered by the GP at every consultation. Additionally the parents were asked to complete weekly reports, concerning questions about asthma-related complaints, over-the-counter (OTC) medication and asthma-related costs, during the first 2 yr of the infants' life and to complete the internationally accepted ISAAC questionnaire (21) yearly until the age of 6 (Tables 1–3).

Mite collection and humidity

Dust samples were collected (Table 1) to measure the compliance with the intervention advice in the intervention group (RCPT and RCAT) and to correlate the intensity of exposure to inhalant allergens with respiratory morbidity (RCPT, RCAT and natural history study) and to evaluate the validity of using the low-risk infants as control group. The collection was performed in a standardized manner. Samples were taken, using a vacuum cleaner (Bosch BSA1100 1300 W; Bosch BV, Brussels, Belgium) with a special cassette (ALK Abello, Nieuwegein, The Netherlands) containing a Whatman GF/F 70 mm filter; Whatman, Breda, The Netherlands, from the living room floor ($2 \times 1 \text{ m}^2$), the parents' mattress (1 m^2) and the mattress of the baby (whole mattress). The samples were kept on 4°C until they were analysed for mite, cat and dog allergens by use of enzyme-linked immunosorbent assay (ELISA) (22–24). Humidity was measured by use of a hygrometer in the parents' bedroom and, when in use, the infants' bedroom.

Type of feeding and ETS exposure

The parents completed questionnaires concerning the type of feeding, environmental allergen exposure and ETS exposure.

IgE

Blood samples were collected in the RCPT and natural history group to measure the concentration of total immunoglobulin E (IgE). IgE was analysed using the method of Aalberse et al. (25).

Carbon monoxide

To study the compliance with the smoking advice in the intervention group, to detect spontaneous smoking cessation by the mother during pregnancy in the control groups and to correlate the intensity of exposure to smoke with respiratory

Table 1. Timing schedule of the measurements of environmental exposures and outcome variables in the RCPT

Time-point	Environmental exposures	Outcome measures
3–5 months of pregnancy	Dust (Der p 1, Can f 1, Fel d 1) Humidity CO	
7–8 months of pregnancy (intervention group only)	Humidity CO	
Weekly from birth until 2 yr of age	Type of feeding Day care attendance	Asthma-related complaints Health-care consumption Absent from work
Around 4 wk after birth (intervention group only)	Humidity CO	
3–5 days after birth 6 months after birth	Type of feeding	Total IgE Amount of wheezing episodes in the last 6 months Nightly wheezing in the last 6 months Nocturnal coughing in the last 6 months Doctors diagnosed asthma Constitutional eczema Food allergy Non-viral rhinitis Other upper airway infections Other lower airway infections Dyspnoea
7–9 months after birth (exactly 1 yr after first dust sampling)	Dust (Der p 1, Can f 1, Fel d 1) Humidity CO	
1 yr after birth	Humidity CO ETS Exposure to house dust mite and animal allergens	Amount of wheezing episodes in the last 6 months Nightly wheezing in the last 6 months Nocturnal coughing in the last 6 months Specific IgE (Der p 1, Fel d 1, Can f 1) Doctors diagnosed asthma Total IgE Constitutional eczema Food allergy Non-viral rhinitis Other upper airway infections Other lower airway infections Dyspnoea
2 yr after birth	Humidity CO	Amount of wheezing episodes in the last year Nightly wheezing in the last year Nocturnal coughing in the last year Specific IgE (Der p 1, Fel d 1, Can f 1) Doctors diagnosed asthma Total IgE Constitutional eczema in the last year Food allergy in the last year Non-viral rhinitis in the last year Other upper airway infections Other lower airway infections Dyspnoea
3 yr after birth	ETS Allergen exposure	Amount of wheezing episodes in the last year Nightly wheezing in the last year Nocturnal coughing in the last year Doctors diagnosed asthma Doctors diagnosed cows milk allergy Other food-related allergies diagnosed by a doctor Doctors diagnosed inhalation allergies Non-viral rhinitis in the last year Other upper airway infections in the last year Other lower airway infections in the last year Dyspnoea in the last year

Table 1. Continued

Time-point	Environmental exposures	Outcome measures
4 yr after birth	Dust (Der p 1, Can f 1, Fel d 1) Humidity CO ETS	Tidal airway resistance (microRint) Amount of wheezing episodes in the last year Nightly wheezing in the last year Nocturnal coughing in the last year Specific IgE (Der p 1, Fel d 1, Can f 1) Doctors diagnosed asthma Doctors diagnosed cows milk allergy Other food-related allergies diagnosed by a doctor Doctors diagnosed inhalation allergies Total IgE Non-viral rhinitis in the last year Other upper airway infections in the last year Other lower airway infections in the last year Dyspnoea in the last year
5 yr after birth	ETS Allergen exposure	Amount of wheezing episodes in the last year Nightly wheezing in the last year Nocturnal coughing in the last year Doctors diagnosed asthma Doctors diagnosed cows milk allergy Other food-related allergies diagnosed by a doctor Doctors diagnosed inhalation allergies Non-viral rhinitis in the last year Other upper airway infections in the last year Other lower airway infections in the last year Dyspnoea in the last year
6 yr after birth	ETS Allergen exposure	Asthma Specific IgE (Der p 1, Fel d 1, Can f 1)

CO, carbon monoxide; RCPT, randomized-clinical prevention trial; IgE, immunoglobulin E; ETS, environmental tobacco smoke.

morbidity, carbon monoxide was measured in expired air.

Tidal airway resistance and lung function

To assess the tidal airway resistance by means of an interrupter technique, microRint measurements are performed when the children are 4 and 6 yr of age, while lung function [forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC)], reversibility on β 2-mimetics (change in FEV₁ after 400 μ g salbutamol through a spacer) and bronchial responsiveness to increasing doses of histamine (PC20) will be assessed when the children reach the age of 6 yr.

Statistical aspects

Power calculation

The power calculation of the RCPT study was based on a study of Saarinen and Kajosaari (26), in which it was shown that breast feeding as preventive measure, in a comparable group of infants as in the RCPT, resulted in a 30% reduction in the development of asthma. This percentage was chosen in the RCPT as the minimum clinically relevant difference. A minimum amount of 194

infants in the intervention as well as in the control group was required to reduce the asthma incidence with at least 30% (taking a type I error of 0.05 and a power of 0.80 into account).

The power calculation of the RCAT was based on the number of parents required to measure the compliance of the parents with the optimized prevention program. Based on literature studies (27) an effect-size of 0.46 was expected. With a minimum of 38 participants in each group a power of 0.80 could be reached (taking a type I error of 0.05 and a drop out of at the most 18% into account).

The power calculation of the natural history study was based on a sample size that would be large enough to show a statistically significant difference, between the high- and low-risk groups, in the development of asthma at 6 yr of age (28). An odds ratio of at least 2 was assumed for the association of a first-degree family history of asthma with the risk to develop asthma in descendants. Taking a cumulative asthma incidence of 10%, a maximum drop out of 10% and a type I error of 0.05 into account a power of 0.80 could be reached with an addition of 308 low-risk infants.

Table 2. Timing schedule of the measurements of environmental exposures and outcome variables in the natural history study

Time-point	Environmental exposures	Outcome measures
Weekly from birth until 2 yr of age	Day-care attendance	Asthma-related complaints Health-care consumption Absent from work
3–5 days after birth 6 months after birth	Type of feeding	Total IgE Amount of wheezing episodes in the last 6 months Nightly wheezing in the last 6 months Nocturnal coughing in the last 6 months Doctors diagnosed asthma Constitutional eczema in the last 6 months Food allergy in the last 6 months Non-viral rhinitis in the last 6 months Other upper airway infections Other lower airway infections Dyspnoea
7–9 months after birth 1 yr after birth	Dust (Der p 1, Can f 1, Fel d 1) ETS Exposure to house dust mite and animal allergens	Amount of wheezing episodes in the last 6 months Nightly wheezing in the last 6 months Nocturnal coughing in the last 6 months Doctors diagnosed asthma Constitutional eczema in the last 6 months Food allergy in the last 6 months Non-viral rhinitis in the last 6 months Other upper airway infections Other lower airway infections Dyspnoea
2 yr after birth		Amount of wheezing episodes in the last year Nightly wheezing in the last year Nocturnal coughing in the last year Doctors diagnosed asthma Constitutional eczema in the last year Food allergy in the last year Non-viral rhinitis in the last year Other upper airway infections Other lower airway infections Dyspnoea

ETS, environmental tobacco smoke.

Data analysis

In the RCPT compliance will be evaluated in terms of reduced exposure to HDM, cat and dog allergens as well as reduced smoking and increased breast feeding.

Differences in proportions between groups in bivariate analyses will be tested with the chi-square test. Differences in mean values for continuous normally distributed variables are analysed using the Student's *t*-test. Multiple logistic and linear regression techniques are used for multivariate analyses with a fixed follow-up time, while Cox proportion hazard analyses will be performed when the follow-up time is variable.

Concerning the cost-effectiveness one-way sensitivity analyses regarding important assumptions will be performed. In addition, statistical uncertainty regarding the cost-effectiveness estimates will be assessed using non-parametric bootstrap re-sample methods. By means of the analysis of effect modification it will be evaluated

whether the effect differs between subgroups. For most analyses a p-value smaller than 0.05 is considered as significant.

Statistical analyses are performed using the Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) version 10.0.

Ethics approval and informed consent

Ethical approval for this study was obtained from the ethics committees of the participating institutes. All participants gave written, informed consent.

Preliminary results of the RCPT

Preliminary results indicate that infants in the intervention group were significantly more breast-fed ($p = 0.001$) and/or received significantly more hypoallergenic formula feeding than infants in the control group. The first intake of solid food was significantly more often

Table 3. Timing schedule of the measurements of environmental exposures and outcome variables in the RCAT

Time-point	Environmental exposures	Primary and secondary outcome measures
Month 3 of pregnancy	Dust (derp1) Humidity CO	
Month 7 of pregnancy	Humidity CO	
2–3 wk after birth	Humidity CO	Compliance with dietary advices
6 months after birth	Dust (derp1) Humidity CO	Compliance with dietary advices Amount of wheezing episodes in the last 6 months Nightly wheezing in the last 6 months Nocturnal coughing in the last 6 months Doctors diagnosed asthma Constitutional eczema in the last 6 months Non-viral rhinitis in the last 6 months Other upper airway infections Other lower airway infections
1 yr after birth	Humidity CO	Amount of wheezing episodes in the last 6 months Nightly wheezing in the last 6 months Nocturnal coughing in the last 6 months Doctors diagnosed asthma Constitutional eczema in the last 6 months Non-viral rhinitis in the last 6 months Other upper airway infections Other lower airway infections

RCAT, randomized-clinical adherence trial.

postponed to the age of 6 months in the intervention group compared with the control group ($p = 0.001$). No difference was found in the intervention compared with the control group concerning the exposure to tobacco smoke. Measurement of environmental exposure to HDM, cat and dog allergens was performed during pregnancy (baseline) and exactly 1 yr later. One year after baseline measurements the concentration of HDM, cat and dog allergens, measured at the living room floor (except for dog allergens), the mattress of the parents and the mattress of the baby, were statistically significant decreased in the intervention group, but not in the control group (29).

Discussion

The PREVASC study is a longitudinal prospective birth cohort study with its focus on the development of a primary prevention program for asthma in children. The main goal of the PREVASC study is to assess the effectiveness of (the duration of) an intervention program focussed on reducing the exposure to indoor and food allergens and ETS in children at high risk of developing asthma. This is investigated in a RCPT. To be able to define to what extent first-degree familial predisposition for asthma is predictive for the development of asthma, a natural history study was started

with children with a high- or low-risk of developing asthma.

Whether the participants are compliant to the prevention program and whether optimizing the intervention leads to an increase in adherence is investigated in a RCAT. The health-economic benefits of 'high-risk' identification and primary prevention of asthma will be assessed on the basis of the RCPT, taking compliance aspects and validity of screening into account.

There are few prospective birth cohort studies in which the effect of primary prevention of asthma is studied (8–16). Most of these studies focus on one or two preventive measures (8–13). To our knowledge there are three multifaceted intervention studies, the study of Halken et al. (14), the CAAP (15) study and SPACE (16) study. The PREVASC study differs from these studies in several aspects. In contrast to these studies a low-risk group was included in the PREVASC study, which enables an estimation of the high-risk prediction and in addition facilitates the evaluation of the external validity of the primary prevention study. In the PREVASC study, 'high-risk' was defined as presence of asthma in first-degree family members. This definition was chosen because asthma in first-degree family members is expected to be the most predictive risk factor for the development of asthma in descendants (30) although this is often based on retrospective and cross-sectional data.

We expect the strongest effect of the intervention program in children with a first-degree hereditary predisposition of asthma. Concerning the intervention program, in the PREVASC study the dietary advices for the baby were exclusively breast feeding for at least 6 months as well as delay of solid food until 6 months of age. The mother was not advised to follow a diet. As the goal of the prevention program was that it should be easy to implement into practice, prevention was based on easily applicable intervention measures. Recruitment was performed predominantly by the GP. The Dutch health care system is organized in such a way that the GP keeps complete medical records all registered families which makes the GP the most appropriate health care worker to assess whether an unborn child is at high risk of developing future asthma.

There are however, some limitations to our study. Although there is a well-defined cleaning regimen some exposure could not be avoided. However, by keeping the cleaning regimen close to daily practice, the HDM reduction that will be reached is realistic and can easily be obtained. In general, we expect that people will better adhere to the intervention program when the intervention is as close to daily practice as possible. In studying a multifaceted intervention strategy it is impossible to directly investigate the effectiveness of all single intervention measures in all possible combinations (like would be done in a factorial design), as this should result in a sample size that is far too large for in one trial. Moreover, synergistic effects can be missed in comparing single interventions only, while the most pronounced clinical effect possible should be expected from a combined intervention. Finally, the GP and the parents could not be blinded to the intervention, which might result into classification bias and reporting bias with respect to medical records and questionnaires in relation to health outcome. Therefore, it is important to follow the cohort until the children have reached the age of 6 yr, at which age lung function measurement can be performed.

Acknowledgments

The PREVASC study was financially supported by the Dutch Asthma Foundation, the Prevention Fund (ZON-MW), the Royal Academy of Science (KNAW), Astra-Zeneca. The study was a joint project of the Departments of General Practice of the University of Maastricht and the Radboud University Nijmegen. Authors would like to thank the general practitioners and practice assistants allied to these departments and the participating midwives for recruiting eligible families. Authors are grateful to all families for their participation in the study. Also thank the

research assistants: Kittie Coolen, Ilse van Beerendonck, Kitty van der Meer, Frieda Waasdorp, Bernadette Zinzen, Anita Legtenberg, Kirsten Ritter, Maaïke Jilderda, Manon Langhoor; the data manager: Jacqueline Pisters; the statistician: Jildou Sijbrandij; the nurses who visited the participating families and sampled data: Cindy Brink, Twanny Jeijnsman, Marjorie Rovers, Elly de Vree, Ineke Schaap, Marjan Terhaar, Gertie van Driel, Mariken Dorsemagen, Mieke Witte, the PREVASC secretaries: Annemarie Spaninks and Angelique Lefebure and the secretary of Care and Public Health Research Institute (CAPHRI): Annemarie Korsten; and finally thank all other people who were scientifically involved in the PREVASC study: Hans Severens, Geertjan Wesseling, Mariëlle Goossens, Guido van den Boom, Ilse Mesters, Lisette van den Bemt, Annemiek Nijholt, Karin Manders, Alfons Schrooten, Ruud Schmeitz, Han Hendriks, Rein Jobsis, Bart Thoonen, Willem van Gerwen, Wil van den Bosch and Job Metsemakers.

References

1. AUSTIN JB, SELVARAJ S, RUSSELL G. Childhood asthma in the highlands of Scotland – morbidity and school absence. *Scott Med J* 2004; 49: 18–21.
2. VERMEIRE PA, RABE KF, SORAIANO JB, MAIER WC. Asthma control and differences in management practices across seven European countries. *Respir Med* 2002; 96: 142–9.
3. PEAT JK, van den BERG RH, GREEN WF, MELLIS CM, LEEDER SR, WOOLCOCK AJ. Changing prevalence of asthma in Australian children. *BMJ* 1994; 308: 1591–6.
4. RONA RJ, CHIN S, BURNEY PG. Trends in the prevalence of asthma in Scottish and English primary school children 1982–92. *Thorax* 1995; 50: 992–3.
5. HEINZMANN A, DEICHMANN KA. Genes for atopy and asthma. *Curr Opin Allergy Clin Immunol* 2001; 1: 387–92.
6. VON MUTIUS E. The environmental predictors of allergic disease. *J Allergy Clin Immunol* 2000; 105: 9–19.
7. WARNER JA, JONES CA, JONES AC, WARNER JO. Prenatal origins of allergic disease. *J Allergy Clin Immunol* 2000; 105: S493–6.
8. ZEIGER RS, HELLER S, MELLON MH. Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: a randomized study. *J Allergy Clin Immunol* 1989; 84: 72–89.
9. CUSTOVIC A, SIMPSON BM, MURRAY CS, LOWE L, WOODCOCK A. The national asthma campaign Manchester asthma and allergy study. *J Allergy Clin Immunol* 2000; 105: 252–8.
10. BRUNEKREEFF B, SMIT J, de JONGSTE J, et al. The prevention and incidence of asthma and mite allergy (PI-AMA) birth cohort study: design and first results. *Pediatr Allergy Immunol* 2002; 13 (Suppl. 15): 55–60.
11. ARSHAD SH, MATTHEWS S, GANT C, HIDE DW. Effect of allergen avoidance on allergic disorders in infancy. *Lancet* 1992; 339: 1439–97.
12. MARINI A, AGOSTI M, MOTTA G, MOSCA F. Effects of a dietary and environmental prevention program on the incidence of allergic symptoms in high atopic risk infants: three years' follow-up. *Acta Paediatr Suppl* 1996; 414: 1–21.
13. MIHRSAHI S, PEAT JK, WEBB K, et al. The Childhood Asthma Prevention Study (CAPS): design and research protocol of a randomised trial for the primary prevention of asthma. *Control Clin Trials* 2001; 22: 333–54.

14. HALKEN S, HOST A, HANSEN LG, OSTERBALLE O. Effect of an allergy prevention program on incidence of atopic symptoms in infancy. A prospective study of 159 'high-risk' infants. *Allergy* 1992; 47: 545–53.
15. CHAN-YEUNG M, MANFREDA J, KIMICH-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.
16. HALMERBAUER G, GARTNER C, SCHIERL M, et al. Study on the Prevention of Allergy in Children in Europe (SPACE): allergic sensitization in children at 1 year of age in a controlled trial of allergen avoidance from birth. *Pediatr Allergy Immunol* 2002; 13 (Suppl. 15): 47–54.
17. The WONCA Classification Committee. ICPC-2. International Classification of Primary Care. Oxford, UK: Oxford University Press, 1998.
18. DIRKSEN WJ, GEIJER RMM, de HAAN M, de KONING G, FLIKWEERT S, KOLNAAR BGM. Astma bij kinderen. NHG-Standaard. *Huisarts Wet* 1998; 41: 130–43.
19. VAN ASSEMA P, MESTERS I, KOK G. Het focusgroep-interview: een stappenplan (The focus group interview: stepwise guidelines). *Tijdschr Soc Gezondheidsz* 1992; 70: 431–7.
20. OOSTENBRINK JB, KOOPMANSCHAP MA, RUTTEN FFH. Handleiding voor kostenonderzoek. Methoden en richtlijnrijzen voor economische evaluaties in de gezondheidszorg. Amstelveen: College voor zorgverzekeringen, 2000.
21. ASHER MI, KEIL U, ANDERSON HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; 8: 483–91.
22. VAN DER HEIDE S, van AALDEREN WM, KAUMAN HF, DUBOIS AE, de MONCHY JG. Clinical effects of air cleaners in homes of asthmatic children sensitized to pet allergens. *J Allergy Clin Immunol* 1999; 104 (2 Pt 1): 447–51.
23. LUCZYNSKA CM, ARRUDA LK, PLATTS-MILLS TA, MILLER JD, LOPEZ M, CHAPMAN MD. A two-site monoclonal antibody ELISA for the quantification of the major *Dermatophagoides* spp. allergens, Der p I and Der f I. *J Immunol Methods* 1989; 118: 227–35.
24. INGRAM JM, SPORIK R, ROSE G, HONSINGER R, CHAPMAN MD, PLATTS-MILLS TA. Quantitative assessment of exposure to dog (Can f 1) and cat (Fel d 1) allergens: relation to sensitization and asthma among children living in Los Alamos, New Mexico. *J Allergy Clin Immunol* 1995; 96: 449–56.
25. AALBERSE RC, KOSHTÉ V, CLEMENS JG. Immunoglobulin E antibodies that crossreact with vegetable foods, pollen en hymenoptera venom. *J Allergy Clin Immunol* 1981; 68: 356–64.
26. SAARINEN UM, KAJOSAARI M. Breastfeeding as prophylaxis against atopic disease: prospective follow-up study until 17 years old. *Lancet* 1995; 346: 1065–9.
27. KOK G, van den BORNE B, MULLEN PD. Effectiveness of health education and health promotion: meta-analyses of effect studies and determinants of effectiveness. *Patient Education Counseling* 1997; 30: 19–27.
28. MARTINEZ FD, WRIGHT AL, TAUSSIG LM, HOLBERG CJ, HALONEN M, MORGAN WJ. Asthma and wheezing in the first six years of life. *New Engl J Med* 1995; 332: 133–8.
29. SCHÖNBERGER HJAM, MAAS T, DOMPELING E, KNOTTNERUS JA, van WEEL C, van SCHAYCK CP. Compliance of asthmatic families with a primary prevention program of asthma and effectiveness of measures to reduce inhalant allergens – a randomised trial. *Clin Exp Allergy* 2004; 34: 1024–31.
30. BURKE W, FESINMEYER M, REED K, HAMPSON L, CARLSTEN Ch. Family history as a predictor of asthma risk. *Am J Prev Med* 2003; 24: 160–9.