Risk of asthma and cost-effectiveness of multifaceted primary prevention of asthma

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The objective of RAKKER2 is to study is, in terms of implementation, to get insight in the question 'to whom' a multifaceted primary prevention program should be offered. Therefore, in this study the predictive value of family history of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Respiratory disorders NEC
Study type	Interventional

Summary

ID

NL-OMON32746

Source
ToetsingOnline

Brief title
Risk identification and multifaceted prevention of asthma

Condition

- Respiratory disorders NEC

Synonym
chronic respiratory disease, lungdisease

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Zon-Mw

Intervention

Keyword: asthma-prevention, children, Cost-effectiveness, Risk-identification

Outcome measures

Primary outcome

Primary study parameters

The main *cost* parameters are the direct-, indirect and intervention costs.

The main primary effectiveness study parameter will be a diagnosis of asthma according to the international GINA guidelines. For the children from the RAKKER2 study this will be the same as for the children from the PREVASC study and will be based on an algorithm that is composed of the results of the ISAAC questionnaire, GP registration and lung function measurements, as well as total and specific immunoglobulin E (IgE) levels. A child will be labelled with *certain asthma* whenever lung function is deviating from the norm$ accompanied by at least one of the following items (ISAAC questionnaire or GP registration):

*ISAAC questionnaire:

• Has your child had any wheezing in the chest from its 5th to its 6th birthday? Answer: Yes.

• How many attacks of wheezing did your child experience during this period? Answer: >= 1.

• How often did your child wake up by wheezing in the chest? Answer: >= 1/week.

• Has your child had any chest tightness from its 5th to its 6th birthday? Answer: Yes.

• How many attacks of chest tightness did your child experience during this

period?

Answer: >=1.

• How often did your child wake up with chest tightness during this period?

Answer: >= 1 night/week.

• How often did your child wake up with coughing, without having a cold or

breast infection? Answer: >= 1 night/week.

*GP registration:

Expiratory wheezing at least registered once.

• Wheezing without exercise, at least registered once.

• Nightly cough more than once registered.

• Shortness of breath without exercise at least registered once.

$Lung function is deviating from the norm:

FEV1/FVC (ml) <= % predicted (*79%, *75%) -2 standard deviations and

reversibility >= 9% and/or PC20 <= 8 mg/ml histamine.

Secondary outcome

Quality of life is a secundary parameter in this study

Study description

Background summary

Asthma, an important chronic disease in childhood, exerts a great burden on the society, is the main cause of school absence (2, 3) and reduces the quality of life of entire families (4, 5). The prevalence of asthma is high. In Dutch children, it amounts to 4% in children aged 4-5 years (6). The number of asthma-related physician contacts and hospitalizations are high, which results in substantial costs of treating asthma, i.e. 24.1% of the total health care

costs, of children aged 1-14 years, are spent on asthma (7).
For a substantial proportion of patients, asthma will be a lifelong condition. Prevention of asthma will therefore result in considerable health gains and reductions in health care resource use (costs).
Asthma is a polygenetic disease, which can be aggravated by exposure to a range of environmental factors. This makes it extremely difficult to prevent the disease by eliminating only one risk factor. In a recently published meta-analysis of our group it was shown that multifaceted intervention studies probably have a much greater chance of being successful than mono-intervention studies (1). Therefore multifaceted primary prevention might be the best possibility to reduce the incidence of (severe) asthma. To be able to give advice as to whether and whom prevention should be offered, more insight is needed into the cost-effectiveness of such programs.
The PREVASC program is a multifaceted intervention program that focuses on primary prevention of asthma in children, who were selected prenatally and followed-up by the general practitioner (8-19). Several other primary prevention studies are being performed and are still in progress. However, in most other programs only one or two single interventions are tested (20-25), which may lead to underestimation of the effect of prevention. The current opinion is that mono-interventions will not reduce asthma morbidity, while multifaceted intervention studies might do (26-28). PREVASC was originally set-up as a typical example of a multifaceted intervention program. To be able to give advice as to whether and whom a prevention program should be offered, information concerning which children bear the highest risk as well as the (cost-) effectiveness of the prevention program is needed. Therefore, as part of the PREVASC program, the RAKKER study was defined. The original scope of RAKKER was to investigate high-risk identification and the cost-effectiveness of the PREVASC intervention strategy.
For the RAKKER study a cohort of prenatally selected children with a negative family history of asthma (i.e. no first-degree family members suffering from GP registered asthma) was added to the program. The RAKKER study comprises two parts. The first part [ZON 2100.0002] covered the prenatal period to the age of two. In the second part (this study) the children will be studied at age six. This second part is of great importance since definite conclusions can only be drawn based on an objective diagnosis of asthma, which is not possible before the age of six. The conclusions from part one are therefore only indicative for whether asthma may occur at later age.
The results of part one show that in the first two years of life the PREVASC program was not cost-effective. The intervention was more expensive than usual care, and in addition, there was only a limited positive effect in this period (appendix 1: fig.1, 2).
As the compliance to preventive measures (e.g. smoking behaviour) turned out to be low and the room for improvement for other measures (e.g. reduction of allergen exposure) was also very low the first results at age six show no clinical effectiveness, in terms of asthma outcome, of the program. However, since the follow-up of the children of the PREVASC program is incomplete (the children with a negative family history of asthma have not been measured yet at

age six) and the fact that the total body of knowledge has to be actualised, further analyses are necessary. As shown in the meta-analysis performed by our group (1), multifaceted intervention studies probably have a substantially greater chance of being successful than mono-intervention studies (appendix 2: fig. 3, appendix 3: fig. 4). In terms of implementation, the purpose of the second part of the RAKKER study is therefore to evaluate, at age six with an objective (on lung function measurement based) asthma diagnosis, the value of a *family history of asthma* as predictor for asthma and the influence and the cost-effectiveness of the multifaceted intervention strategies compared to mono-intervention strategies. For this purpose the clinical effectiveness data (i.e. presence or absence of asthma) of the different intervention programs included in the meta-analysis will be used to calculate the overall effectiveness of mono- versus multifaceted interventions. The PREVASC and RAKKER data will be part of these analyses. Information concerning the presence of asthma in the PREVASC children (i.e. children with a positive family history of asthma, which means at least one first-degree family member with GP registered asthma) was collected previously in the OMEGA study (ZonMw OMEGA:2100.0091, NAF OMEGA-PREVASK:3.2.99.38). Information concerning the presence of asthma in the RAKKER children, has to be collected (this application).
In this study a cost-effectiveness analysis from two different viewpoints, a societal viewpoint and a health care viewpoint, will be performed. For the calculation of the cost-effectiveness of the mono- and multifaceted intervention strategies, the clinical effectiveness data from the meta-analyses, including the information of the PREVASC program and information concerning the quality of life (which will be collected in this second part of the RAKKER study will be used in combination with the medical consumption data and the costs of the intervention of the PREVASC program that will be collected in the RAKKER study. Using decision analytic modelling techniques, cost-effectiveness of mono- versus multifaceted intervention strategies will be calculated. Starting point for this model will be both a societal and a health care viewpoint and a six-year time horizon. In addition the discounting principle will be applied. Besides baseline estimates of the cost-effectiveness of mono- versus multifaceted intervention strategies probabilistic sensitivity analysis will be performed. Effectiveness will be expressed as the number of asthma cases at the age of six years. Besides the probabilistic analysis value of information analysis will be performed. The process of modelling will consist of two important steps. First, developing and validating the structure of the model, for which purpose expert sessions will be organised. Based on the validated model the second step will be to bring the relevant data into the model and to perform the analyses. For interpreting the results a second expert session will be organised to validate the model*s outcome.

Study objective

The objective of RAKKER2 is to study is, in terms of implementation, to get insight in the question 'to whom' a multifaceted primary prevention program

should be offered. Therefore, in this study the predictive value of family history of asthma will be evaluated. In addition, the cost-effectiveness of multifaceted primary prevention of asthma compared to mono-faceted primary prevention will be evaluated, in order to decide whether the PREVASC program can be implemented. To be able to perform the cost-effectiveness study the effectiveness of all international available randomised intervention studies in *high-risk* birth cohorts as well as the *low-risk* birth cohort of the PREVASC program, will be used as input for the calculation of the cost-effectiveness of primary prevention of asthma in general.

Research questions
1. What is the value of a *family history of asthma* as predictor for asthma and what is the influence of important co-variables?
2. What is the cost-effectiveness of primary prevention of asthma using multifaceted intervention strategies compared to mono-intervention strategies?

Study design

Approach and research population
Within the School for Public Health and Primary Care, the PREVASC research line started in 1997 (7). The scope of this research line is multifaceted primary (prenatally started) prevention of asthma in children. In this respect multifaceted means intervention at several aspects (breastfeeding, mite reduction and smoking cessation) at the same time.
The PREVASC research line consists of different studies. The, in this case, most important studies are the PREVASC and the RAKKER study (table 1). For the randomized PREVASC trial 441 children with a positive family history of asthma (PFH; father, mother, brother and/or sister with asthma) were prenatally selected and randomly assigned to an (multifaceted primary) intervention or a control group (table 1). The intervention started prenatally in order to reach a low house dust mite and pet allergen exposure level at the time the child was born. In addition, the intervention focused on avoidance of prenatal and postnatal passive smoking and on avoidance of food allergens postnatally. House dust mite (HDM) reduction intervention started before the 7th month 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 6th month 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 postnatally. Dietary intervention contained advice on exclusively breastfeeding (or hypo-allergen formula feeding) for at least six months and postponing introduction of solid food until six months after birth.
To answer the questions *to whom multifaceted primary prevention should be offered* and whether multifaceted primary prevention is cost-effective, the RAKKER study was added to the PREVASC research line. For this study, a cohort study, 308 children with a negative family history of asthma (NFH; no asthma in

first-degree family members) was added (table 1).
Both the children from the PREVASC and the RAKKER study were followed prospectively until the age of two in part one of the study. All children were selected in a primary care setting. The RAKKER group as well as the PREVASC control group did not get preventive advices and received usual care (according to the Guideline of the Dutch College of General Practitioners). Information concerning atopy, respiratory tract and asthma related morbidity, serum IgE levels in the PREVASC and RAKKER children as well as house dust mite levels, and information on the direct and indirect costs concerning respiratory morbidity and the costs of the primary prevention program was collected until the children reached the age of two.
To be able to answer the research questions of the first part, different approaches were chosen. For the research question *What is the value of a *family history of asthma* as predictor for asthma and what is the influence of important co-variables?*, the PREVASC control group was compared to the RAKKER group (table 1). For answering the research question whether multifaceted primary prevention is already cost-effective in the first two years of life, the prevalence of a positive family history of asthma and the relative risk of a positive family history in the development of asthma were taken into account.
Follow-up at the age of six years is a necessary next step: a definitive asthma diagnosis has to be assessed with objective criteria. The latter requires two aspects: firstly the children must have reached an age at which there are no more transient wheezers. Small children often have periods of wheezing when they suffer from infections. These periods may have a transient character and will not necessarily lead to the development of asthma. By the age of six the transient character of these wheezing episodes has faded. Secondly the children must have reached an age at which objective lung function testing is possible. Before the age of six, spirometry, reversibility and bronchial responsiveness cannot appropriately be performed.
Therefore in the second part of the PREVASC study, the (PFH) children were followed until they reached the age of six. At this age asthma was diagnosed using the outcomes of spirometry and *asthma related* morbidity. For the children of the RAKKER study (NFH), asthma will be diagnosed in the second part at the age of 6/7, using the same methods and criteria as in the second part of the PREVASC study.
The asthma diagnosis is one of the most important outcome measures for the research questions of the second part of the RAKKER study. To be able to diagnose asthma objectively, the children must have reached an age of at least six years, as mentioned above. This means that the conclusions concerning asthma, from the first part of the study are only indicative for the appearance of asthma at a later stage.
However, in terms of implementation it is also important to have insight in the question *to whom* a multifaceted primary prevention program should be offered. In other words, which children bear the highest risk to develop asthma? Therefore the value of a *family history of asthma* as predictor for asthma and the influence of important co-variables will be studied?
As shown in a meta-analysis of our group (1), in which all available randomised

international intervention studies in birth cohorts with a positive family history were compared, multifaceted primary prevention studies seem to be effective. In addition it seems that multifaceted primary prevention studies have a higher chance to be successful as compared to mono-intervention primary prevention studies.
If this is the case, multifaceted primary prevention might even be more cost-effective compared to mono-intervention. With respect to the possible implementation of multifaceted primary prevention, it is important to know the financial consequences of multifaceted primary prevention of asthma in children. Until now this information is lacking.
Based on the above mentioned results we decided to place the cost-effectiveness research question, for the second part of the RAKKER study, into a broader perspective and study *whether multifaceted primary prevention is cost-effective compared to mono-faceted primary prevention. By use of the data collected already in the first part of the PREVASC and RAKKER studies, as well as in the second part of the PREVASC study, the data from the literature and the data that will be collected in the second part of the RAKKER study this research question can be answered.
The indirect costs were collected prospectively over the first two years, for both the PREVASC and the RAKKER children. At the age of six the indirect costs were collected retrospectively over the past three months for the PREVASC children. For the RAKKER children these costs at age 6/7 will be collected in the same manner. It is however, not expected that there is an important fluctuation in the indirect costs during years 3-6, which was expected in the first two years, the period from which we have prospective data. Concerning the direct costs, information is available for the complete study period (first and second part).
Due to the lack of, part of, the indirect costs and the accompanying uncertainty, the cost-effectiveness analysis will be performed in two ways, based on a society perspective and based on a health care perspective.
To be able to analyse the data adequately and objectively, it is important to include the information concerning the appearance of asthma at age 6/7 of children with a negative family history (NFH; the RAKKER children). This information will be collected in the second part of the RAKKER study.
With the available information we are able to perform a cost-effectiveness study, using interpolation techniques and regression analysis. In addition we are able to perform a *cost-consequence* study. Based on the fact that, in this specific field, there are no economic evaluations yet, we think that our research question is of additional value on the scientific knowledge and societal applicability in this field.
Another important aspect is the fact that these kind of studies are very time consuming and costly. Currently we have the availability of information concerning morbidity and costs over the first six years of children with a positive family history asthma. To be able to perform the second part of the RAKKER study we only have to add the information of children with a negative family history of asthma (the RAKKER children).

Time frame
December 2008 - January 2009: Sending questionnaires
February 2009-December 2010 Blood sampling and lung function, bronchial responsiveness
Start: data-entry, data-cleaning
Preparation publications
Developing and validating the cost-effectiveness model

November 2009 - December 2010-October 2011: Data-entry, data-cleaning, statistical analyses
Populating the cost-effectiveness model and running the model analyses
Writing publications/thesis

Table 1: PREVASC research line (PREVASC and RAKKER studies)
PREVASC researchline
TRIAL COHORT
PFH(1) NFH(2)
Randomisation

Intervention (n=222) Control (n=221) (n=308)
PREVASC
RAKKER
Study
Study
1st part Prenatal Measurement Measurement 1st part Prenatal Measurement
birth Measurement Measurement birth Measurement
1 year Measurement Measurement 1 years Measurement
2 years Measurement Measurement 2 years Measurement
3 years Measurement Measurement
4 years Measurement Measurement
5 years Measurement Measurement
6 years Measurement Measurement 6-7 years Measurement

(1)PFH: children with a positive family history of asthma
(2)NFH: children with a negative family history of asthma

Intervention

In this study a lungfunctionmeasurement will be performed, in young children, to diagnose possible asthma. In advance to measurement of FEV1 and FVC a reversibility test with salbutamol will be performed. Those children who report 'asthma related' morbidity, but turn out not to be reversible, will be invited to visit the Academic Hospital Maastricht, to undergo a histamin provocation test. It is expected that about 10% of all the children (n=30) will be invited to undergo a histamin provocation test.

In IgE measurement will be performed in all children. By use of a fingerprick a small amount of blood will be collected for the measurement of IgE (total and specific against house dust mite, cat and dog allergens).

Study burden and risks

It is not expected that the study is painfull or very aggravating for the child. The risks of the study will be minimal, since all measurements are save and will have, under normal circumstances, no negative consequences. The child can get short of breath during the histamin provocation testing. Whenever this happens, the test will be stopped immidiately and the child will receive a bronchodilator. The measurements will be performed by trained and experienced people.
Whenever it turns out that any test is too aggravating for the child, the test will be stopped immediately.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Children (2-11 years)

Inclusion criteria

Only those children will be invited who have participated in the first part (the period before birth untill the age of two) of the study. In the first part the main inclusion criterium was: a negative family history of asthma (i.e. no biological father, mother, brothers and/or sisters with asthma).

Exclusion criteria

In the first part of the study, the exclusion criteria were 'spontaneous abortion, miscarriage, language problems, serious health problems in the child at birth for which hospitalization is necessary. In this second part there will be no exta exclusion criteria, except that when children are not able to undergo a lungfunction measurement because of serious (co-) morbidity, the will be excluded from the study.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-02-2009
Enrollment:	308
Type:	Actual

Ethics review

Approved WMO

Date:	05-02-2009
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL26143.000.08