

The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study: Design and first results

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The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study was initiated in 1996. Children born to allergic mothers were enrolled in a double-blind placebo-controlled trial for evaluating the use of mite-impermeable mattress and pillow covers. Children born to allergic and non-allergic mothers were enrolled in a 'natural history' study to assess the role of environmental and dietary risk factors for the development of allergic disease in childhood.

Recruitment started by distributing a validated screening questionnaire among >10,000 pregnant women during their first visit to a prenatal health clinic. Allergic mothers-to-be were invited to participate in the intervention study. Allergic, and a random sample of non-allergic, mothers-to-be were invited to participate in the 'natural history' arm of the study. In the intervention study, homes were visited before birth, 3 months after birth, and 12 months after birth for the collection of dust samples from floors and mattresses. In addition, the homes of about one-third of the children in the 'natural history' part of the study were visited for dust collection when the children were 3 months of age. The intervention study started with 855 participants and the 'natural history' study with 3,291 participants. Follow-up at 3 years of age has now been completed with satisfactory compliance (>90%). A medical investigation and home visit at 4 years of age are nearing completion. Preliminary results show that mite-allergen levels were lower than found in previous Dutch studies, and that the intervention measure had a significant effect on mite-allergen levels, without important clinical benefits up to age 2 years old. The allergic families lived in homes with fewer 'triggers' such as pets, smoking and carpets than the non-allergic families, regardless of the intervention. The ongoing PIAMA cohort study will probably reveal useful information concerning effects of allergen load and reduction in the setting of a relatively low mite-allergen exposure, as well as other variables on the development of allergic manifestations and asthma.

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Childhood asthma and allergy are prevalent conditions in the western world, associated with significant morbidity, reduced quality of life, and high healthcare costs. Despite decades of research, relatively little is known about which factors are the main determinants of the high prevalence and of the large worldwide variation

in prevalence (1). In epidemiology, prospective studies and placebo-controlled studies are considered to be the most valid study designs for investigating causality. However, relatively few prospective cohort studies and placebo-controlled trials have been performed regarding the development of allergic disease. At present, well over

10 prospective birth cohort studies are being conducted, most of them in Europe. Two international workshops were held in Germany, in 1996 and in 2001, to discuss the progress of many of these studies. In this report, we describe the background and design of the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study, which was started in the Netherlands in 1996.

Background of the PIAMA study

In 1992, the Public Health Council of the Netherlands issued a report entitled 'Indoor Allergens, Allergy, and the Development of Chronic Respiratory Diseases'. The report was written on request from the Minister of Housing, Physical Planning and Environment, and from the Minister of Health, Welfare and Cultural Affairs. The report discusses whether reduction of exposure to indoor allergens early in life would prevent or delay the development of inhalant allergies and asthma in children. The report concluded that while there is good evidence that allergen-avoidance measures are useful for improving the clinical condition of allergic patients, it is not yet clear whether similar measures would also help to prevent or delay the process of sensitization and the subsequent development of allergy and asthma in children. The Council recommended that a prospective study should be set up to evaluate the effectiveness of measures to reduce early post-natal exposure to indoor allergens, with the aim of preventing or delaying the development of inhalant allergy and asthma. The Council suggested that an intervention trial should be set up among children genetically predisposed to develop allergy. The proposal was to randomly allocate such children to an intervention group and to a control group without intervention measures. The control group was to be sufficiently large to serve as an independent cohort in which various questions still surrounding the 'natural history' of the development of inhalant allergy and asthma could be investigated. The necessary length of follow-up was suggested to be between 5 and 10 years, because it takes several years for sensitization and asthma to develop.

Mite-allergen intervention studies

Although several clinical trials among mite-allergic patients have been conducted, there are few examples of trials aimed at evaluating the preventive potential of mite-allergen reduction. One example is the Isle of Wight study, which combined mite-allergen reduction with a dietary

intervention (3). Another is the Manchester Asthma and Allergy Study (MAAS) (4), which implements a very detailed allergen-avoidance programme in homes of high-risk children. Results from the Isle of Wight study suggest that the intervention programme which was applied was effective in reducing asthma and allergy at age 4 (5). The MAAS study has not yet published clinical results.

Natural history studies

An early example of a cohort study, suggesting that early mite-allergen exposure is related to asthma severity later in life, was conducted in the UK (6). A large birth cohort study from Germany (MAS) has shown that the risk of sensitization to indoor allergens clearly increased with increased exposure to indoor allergens, such as those from mite and cat (7). These exposure-response relationships were already evident at low levels of exposure, suggesting that reduction of exposure to (very) low levels may be needed to avoid sensitization entirely, but also suggesting that any significant reduction in exposure may be associated with a significant reduction in sensitization. However, further follow-up of this cohort has failed to show an association between early exposure to dust-mite allergen and subsequent asthma (8).

Studies from Sweden (9) have shown that sensitization to mite allergen can occur at exposure levels well below 2 µg/g of house dust, supporting the findings of the German study that a fixed threshold level for the risk of developing allergic sensitization may not be appropriate in all climates. Warner et al. (10) have suggested that the sensitization process may even start before birth, which would make measures to avoid allergen exposure necessary during pregnancy.

This evidence supports that sensitization may occur at very low levels of exposure, and may even start before birth. The implications for preventive measures may be that these need to be implemented before birth, and should aim for reduction to very low levels of exposure. However, the existence of an exposure-response relationship (as opposed to a 'threshold' below which no sensitization occurs and above which sensitization is occurring often) implies that any reduction in exposure is also expected to be associated with some reduction in the incidence of atopic disease – although the German MAS study was unable to substantiate a relationship between allergen exposure and atopic disease, despite finding a relationship between allergen exposure and sensitization as well as a relationship between sensitization and atopic disease (8). The European Allergy White

Paper (11) stresses the importance of evaluating an approach for the primary prevention of allergy, and the PIAMA birth cohort study is one attempt to do so.

The PIAMA study

Aims of the PIAMA study

The PIAMA study has two main aims:

- 1 To investigate the effect of mite-allergen avoidance on the incidence of asthma in childhood (Intervention Study); and
- 2 To investigate the incidence of asthma in children from 0 to 8 years of age (Natural History Study).

Design of the PIAMA study

For reasons of efficiency, only high-risk children (born to allergic mothers) were enrolled in the intervention study. In the natural history study, children of allergic, as well as non-allergic, mothers were enrolled. The study was designed to follow-up the study children for 8 years to allow sufficient time for allergic sensitization and clinical manifestations to develop. A validated screening questionnaire (12) was used to identify atopic and non-atopic mothers-to-be in prenatal health clinics. Two groups of 'high-risk' children are therefore being followed up from before birth in a double-blind manner. 'High-risk' was defined on the basis of a screening questionnaire on inhalant allergy administered to the expecting mother. A third group of similarly defined 'high-risk' children is being followed up less intensively, without supplementation of active or placebo cover and without home visit and medical investigation at 1 year of age. Finally, a group of 'low-risk' children is also being followed up, within the 'natural history study'. The 'high-risk' children were randomly allocated to an 'intervention' group, a 'placebo' group, and a second control group, the intervention being application of mite-impermeable mattress covers for the bed of the child and the bed of the parents, and mite-impermeable pillow covers also for the parents. The 'placebo' group was provided with standard cotton covers. No covers for blankets or duvets were provided. Both groups received general advice on the reduction of allergen exposure. The second control group did not receive covers and did not receive advice, but was otherwise similarly at 'high risk'. The active and placebo covers were handed out ≈ 1 –2 months before birth. At that time, samples of floor and mattress dust were taken to determine mite-allergen levels

in the 'active' and 'placebo' groups. Three months after birth, the homes were visited again for dust collection, to evaluate the effectiveness of the treatment in reducing mite-allergen levels. Homes of the second control group were also visited at this time-point for dust collection, as was a random sample of ≈ 600 homes of 'low-risk' children. During the first year of their child's life, parents completed a 'diary' to record the weekly occurrence of respiratory and other symptoms indicative of allergic manifestations or respiratory infections. Visits to the doctor, treatment, and medication use were also recorded. At 12 months of age, another home visit was conducted to collect dust samples. At 12 months of age, blood samples were also collected for immunoglobulin E (IgE) determination, and to observe manifestations of atopic dermatitis. At all contacts mentioned above, questionnaires were completed to collect information about family history of allergic disease, nutrition, exposure to environmental tobacco smoke, breast-feeding, home characteristics, day-care use, etc. The planned sample size of the intervention study cohort was 800 (400 in each group). This was based on a power calculation assuming a cumulative incidence of inhalant allergy and/or asthma in the placebo group of 50% over 8 years, and a treatment effect of a 1.5-fold reduction in incidence, i.e. an expected incidence of 33% in the active group. To be able to detect such an effect, at least 200 subjects were required in each group, so that a non-biased drop-out of 50% over 8 years could be absorbed.

Implementation of the PIAMA study

Selection of the birth cohort started in March 1996 and continued until May 1997. Prenatal healthcare clinics (≈ 50 ; 12,000 deliveries annually) participated. A total of 10,819 women completed a screening questionnaire (see below) of which 10,232 were usable. Of these women, 28.8% ($n = 2,949$) fulfilled our criteria for inclusion in the study as being 'atopic' mothers-to-be, which is more than accounted for in the study proposal where it was estimated to be 20%. A total of 1,986 'atopic' pregnant women were asked to participate in the intervention study in which a first home visit was planned before birth. Forty-two per cent ($n = 855$) of the pregnant women were willing to participate, while 800 was the planned number of participants. A total of 965 atopic women were invited to participate in the 'natural history' part of the study, and 472 (49%) agreed. A total of 5,084 non-atopic women were invited to participate, and 2,819 (55%) agreed. The study children were born between the summer of 1996



Fig. 1. The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study areas.

and the late fall of 1997. The study protocol was approved by the Medical Ethical Committees of the participating institutions. All participants gave written, informed consent.

Figure 1 shows the location of the communities that are included in the birth cohort study. Figure 2 shows the results of the recruitment phase, and the allocation of subjects into the five arms of the study. Figure 3 shows the time-frame of the study, including details of the type of

contacts with the study populations in the various phases of the study.

As an example of the compliance with the study protocol so far, Fig. 4 shows details of the follow-up in the 'natural history' part of the study in the first 2 years. It is apparent that the loss to follow-up in this arm of the study was small. Similar figures apply to the intervention part of the study, although the loss to follow-up was somewhat larger, probably owing to the more intensive character of the study.

In the spring of 2001, the 4-year follow-up was almost complete.

Figure 5 shows the results of the allergen levels measured in dust samples collected from the mattresses of the children before birth, when the children were 3 months old, and when the children were 12 months old. Fig. 5 shows that at the start, the *Dermatophagoides* (*Der* 1) load [the sum of *Dermatophagoides pteronyssinus* (*Der* p) and *Dermatophagoides farinae* (*Der* f)] was similar, but different at the 3-month time-point, and even more different at the 12-month time-point. The 'treatment' effect was more pronounced for the parental beds than for the children's mattresses (results not shown).

Figure 6 shows exposure to environmental tobacco smoke, in relation to the allergy status of the parents. The findings are reported in greater detail in Wijga et al. (13). It is clear that children born in families with one or two allergic parents are less exposed to environmental tobacco smoke than children born to non-allergic parents.

Figure 7 shows a similar analysis for some indoor environmental variables. In families with two allergic parents, children are exposed much less to cat and to carpeted floors than in families with non-allergic parents.

Recruitment

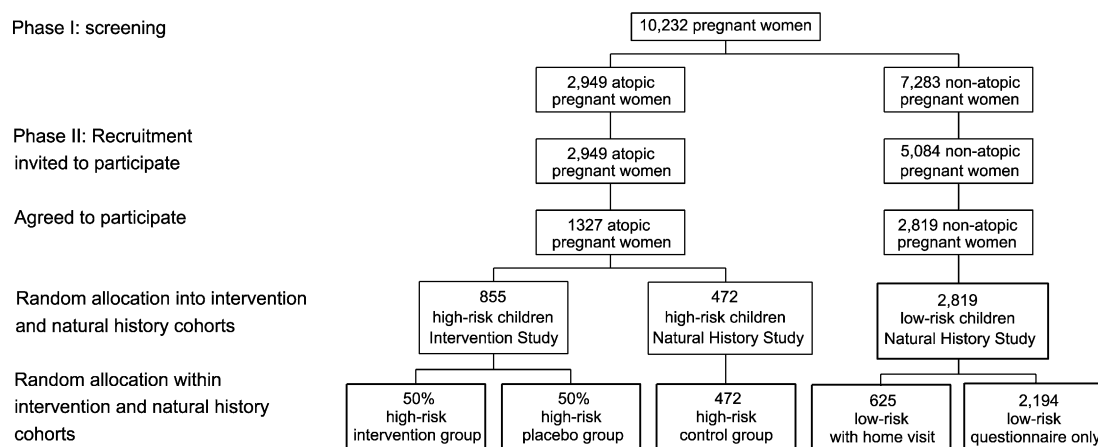


Fig. 2. The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) recruitment scheme.

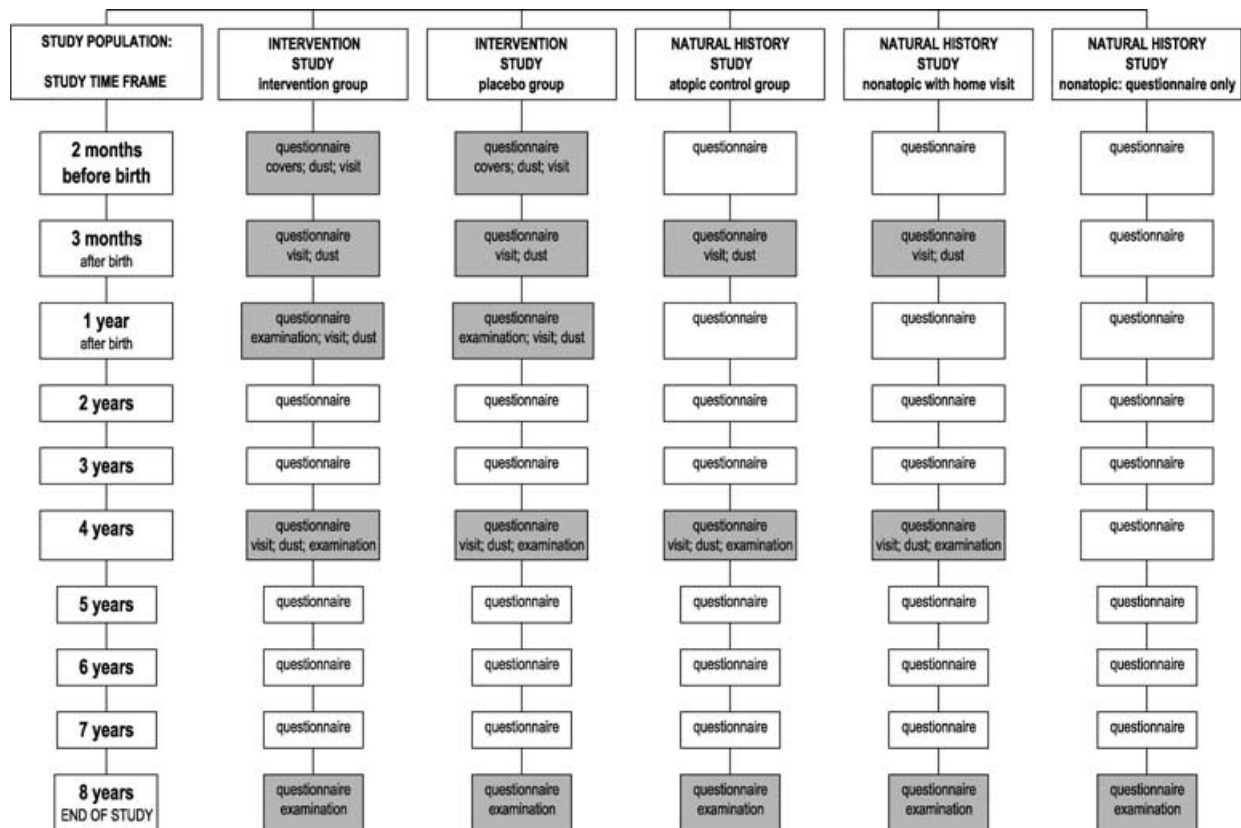


Fig. 3. The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) observation scheme.

- Recruited: 3291
- entry questionnaire: 3289
- 3 months q sent: 3283
- 3 months q rec'd: 3174
- 1 yr q sent: 3243
- 1 yr q received: 3029
- 2 yr q sent: 3167
- 2 yr q received: 3053
- definitely lost: 8
- definitely lost: 40 (+8=48)
- definitely lost: 76 (+48=124)

Fig. 4. Loss to follow-up in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) 'natural history' cohort.

Discussion

The PIAMA birth cohort study is a large longitudinal study combining a classical, placebo-controlled intervention trial with a 'natural history' study. The study was initiated more than 5 years ago, and is now fully developed. A cohort of $\approx 4,000$ newborns was enrolled, who have now been followed up for ≈ 4 years. Loss to follow-up has, to date, been small. Response rates in the initial phase have been slightly below (intervention study) or above (natural history study) 50%. There is the potential therefore that the study population is not representative of the population of newborns in the study areas, in general. As the

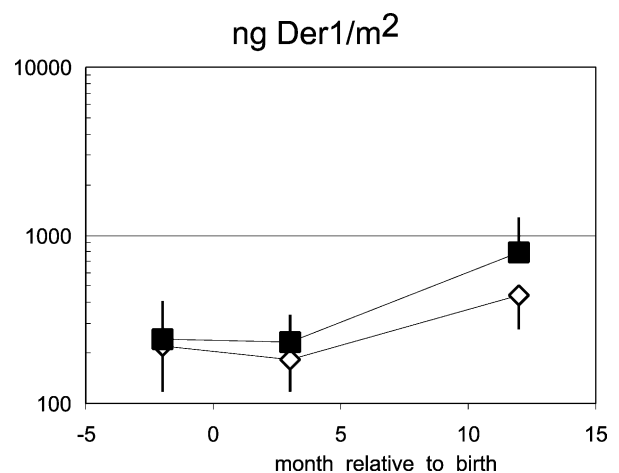


Fig. 5. *Dermatophagoides* (Der 1) concentrations in dust from the child's mattress before intervention and 3 and 12 months after intervention. Concentrations and 95% confidence intervals are shown for active (open symbols) and placebo (closed symbols) groups separately, and are adjusted for the season of sampling.

study primarily aims to find intervention effects (intervention study), and associations between risk factors and allergy and asthma incidence (natural history study), respectively, we maintain that valid conclusions can still be reached despite the moderate response magnitude. In studies of

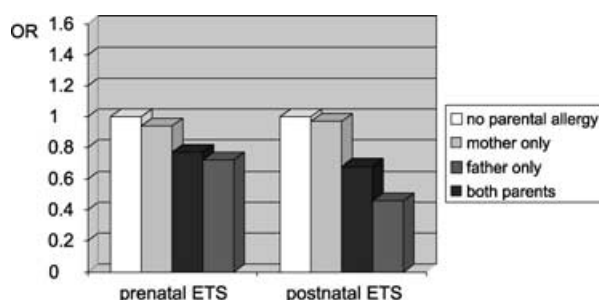


Fig. 6. ETS exposure and parental allergy (13).

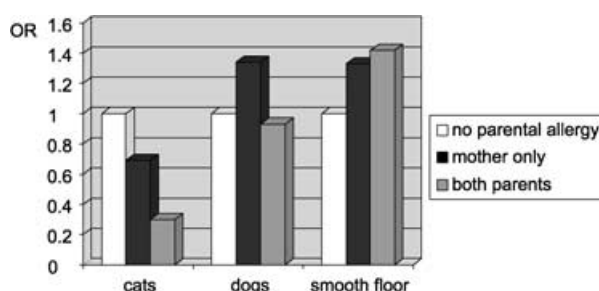


Fig. 7. Indoor environment and parental allergy (13).

this kind, it is also important that loss to follow-up is minimal. In the recruitment phase, it was made explicit to the prospective participants that a long-term commitment is necessary.

Effects of the intervention measures on mite-allergen levels were clearly detectable, although not large in absolute terms. The levels were low compared with earlier studies conducted by our group in the Netherlands (14,15). This may be related to selection phenomena, or to seasonal or actual long-term trends in allergen levels. Further details can be found in Van Strien et al. (16). At 2 years of age, no relevant effects of the intervention on atopic symptoms were noted (Koopman et al., 17), but at this young age, such effects were not expected to be clearly detectable.

The findings we reported recently (13) show that there is a clear indication of allergen and irritant avoidance in families with allergic parents, especially when both parents are allergic. As a consequence, children at high genetic risk of becoming allergic are born into a low-risk environment – which may lead to complicated associations among family history, allergen exposure and allergy development later on, if such selection phenomena are not properly taken into account.

The ongoing PIAMA cohort study will probably reveal useful information concerning the effects of allergen load and reduction in the setting of a relatively low mite-allergen exposure, as well as other variables on development of allergic manifestations and asthma.

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