Final report for CRC for Asthma 2006

Childhood Asthma Prevention Study (CAPS)

Introduction and aims

During the 1990s there was widespread concern about the high and increasing burden of illness due to asthma, particularly among children. Evidence from many clinical and epidemiological studies showed that diet and lifestyle factors had an important role in the aetiology of asthma. Furthermore, long-term cohort studies revealed that asthma in childhood is an important risk factor for asthma in later life. Exposure to house dust mites (HDMs) and their allergens was one environmental factor postulated to have an important role in promoting asthma. Sensitisation to HDM allergens was strongly linked to the presence of asthma, particularly in humid, coastal regions and there was evidence that exposure to high levels of HDM increased the risk of developing asthma. Diet, particularly dietary fatty acids were also hypothesized to have an effect on the development of asthma. Cross-sectional studies in Australia during the 1990s found that children who regularly consumed oily fish, which contain high levels of omega-3 fatty acids, were less likely to have airway hyperresponsiveness and asthma. In addition, pre-school children who regularly consumed oils and spreads containing poly-unsaturated fats that have a higher proportion of omega-6 fatty acids had an increased risk of asthma-like symptoms compared with those not consuming these products.

It was in this context that the Childhood Asthma Prevention Study (CAPS) was initiated as the first randomised controlled trial testing the effectiveness of both house dust mite allergen avoidance and omega-3 fatty acid supplementation in reducing the incidence of asthma and allergic sensitisation in children. CAPS is a collaborative project between the Children's Hospital Westmead, the Woolcock Institute of Medical Research, Liverpool Hospital, the University of Sydney and the CRC for Asthma, jointly funded by the NHMRC and the CRC for Asthma.

Recruitment

The study started in April 1997 and families were recruited to participate from six hospitals in Sydney's western and south- western suburbs. The main entry criterion was a family history of asthma. Exclusion factors were a pet cat at home, a strict vegetarian diet, non-singleton pregnancies, and infants born earlier than 36 weeks gestation. In addition there was a planned policy of withdrawing infants after randomisation if they had birth weights less than 2.5 kg, significant congenital malformations or other significant neonatal disease.

A total of 7171 women were screened of whom 2095 (29%) were eligible for the study and 616 (29% of those eligible) were enrolled as participants. Recruitment was completed in January 2000. Participants were randomly assigned him one of four groups using a factorial design;

Group A: control group with no interventions

Group B: active house dust mite intervention only

Group C: active diet intervention only

Group D: both active diet and active house dust mite interventions

Interventions

The active HDM avoidance intervention used both physical and chemical methods to reduce exposure where the child was sleeping and playing, commencing before the birth of the child. Physical methods included the application of an allergen-impermeable barrier to the child's bed and pillow and regular washing of bedding. At three monthly intervals, parents added a benzyl benzoate-containing solution, an acaricide (final concentration 0.03%) to the wash. Parents in both the active and control HDM avoidance groups were provided with advice about ensuring adequate ventilation, regular vacuuming and avoidance of humidifiers or vaporisers.

The active diet intervention was intended to increase the proportion of omega-3 long chain polyunsaturated fatty acids in the diet and reduce the content of omega-6 fatty acids. Parents were provided with oils and spreads for use with food preparation and food oil capsules to add once daily to the child's formula from the time he or she started bottle-feeding, or to solid foods from age six months, whichever was earlier. For the active diet group canola-based oils and spreads, which are low in omega-6 fatty acids, and tuna oil capsules, which contain omega-3 fatty acids were provided. For the control diet group polyunsaturated oils and spreads, containing 40% omega-6 fatty acids, and sunola oil capsules, which are low in omega-3 fatty acids were provided.

Home Visits and Assessments

Participants were visited at their homes by research nurses at one, three, six, nine and 12 months and then every six months until the child was aged five years. At the home visits data was collected about the child's health, the diet and also the home environment. Intervention goods were supplied and dust samples were collected from the child's bed, living room floor and bedroom floor to estimate exposure to house dust mite allergen.

Parents were asked to bring their child to the recruitment centres for a clinical assessment at 18 months, three years and five years. At the assessments parents were interviewed about symptoms and diagnoses relevant to asthma and allergic disease using a proforma questionnaire which was based on published questionnaires. Children were examined for the presence of flexural eczema. The presence of atopy was detected using skin prick tests to both ingested allergens (salmon, peanuts, cow's milk, egg white, egg yolk, and tuna), and inhalant allergens (*Dermatophagoides pteronyssinus* (HDM), cockroach, cat, *Alternaria alternata*, rye grass and a grass mix). Blood was collected for the measurement of serum total IgE and plasma fatty acids. Lung function was assessed from age three years. At the three year assessment, respiratory system resistance was measured using the forced oscillation technique. This was repeated at five years when spirometric function was also measured.

Results from First Clinical Assessments- 18 months

At age 18 months, 554 children (89.9% of enrolled cohort) completed the assessments.

The diet intervention resulted in a 9.8% reduction (P=0.02) in the prevalence of any wheeze, a 7.8% reduction (P=0.04) in prevalence of wheeze > 1 week but had no effect on serum IgE, atopy or doctors' diagnosis of asthma.

The house dust mite avoidance intervention did not affect these outcomes but was associated with a reduced use of oral steroids.

Second Clinical Assessments- three years

At age three years, 536 children (87% of enrolled cohort) were available for assessment.

At this age, the diet intervention was associated with a 10.0% reduction in the prevalence of cough among atopic subjects (P = 0.003) but no reduction in the prevalence of cough among non-atopic subjects.

There was a 7.2% reduction in sensitisation to house dust mites in the active house dust mite avoidance group at this age (P = 0.05).

However, neither intervention had any effect on the prevalence of wheeze at this age.

Third Clinical Assessment- five years

At age five years there were 516 children (84% of the enrolled cohort) available for assessment.

The ratio of omega-6 to omega-3 fatty acids in plasma was lower in the active diet group (5.8 vs 7.4, P < 0.0001). However, the prevalence of asthma, wheezing, eczema or atopy did not differ between the diet groups (P > 0.1).

The house dust mite avoidance intervention resulted in a 61.2% reduction in HDM allergen levels in the child's bed but no difference in the prevalence of asthma, wheeze or atopy (P > 0.1). The prevalence of current eczema was higher in the active house dust mite avoidance group compared with the control group (25.7% vs 18.5%, P = 0.06).

Summary of other findings

Characteristics of CAPS participants

A survey of 200 eligible non-participants revealed that the main reasons for non participation were a lack of interest, ineligibility (on further questioning), inability to be contacted and being 'too busy', During the first 2.5 years of the trial, 10% of participants withdrew and most withdrawals occurred before the 18-month follow-up. The most common reasons for withdrawal from the study were loss of contact, family moving interstate or overseas and medical reasons. In families that withdrew from the trial or who were eligible but did not participate, the parents were significantly younger, mothers were less educated and fathers were less likely to be in full-time employment but the parents did not differ in age, or in the proportion who were Australian-born. Women who had withdrawn their children from participation at age five years were younger than those who allowed their children to continue to participate and those children who had been withdrawn were more likely to have older siblings. Rates of withdrawal did not differ between active and control groups of the HDM or diet interventions.

Adherence to the study interventions

The presence of the study mattress cover on the child's bed and use of the benzyl benzoate-containing solution for washing bedding were assessed on 13 occasions in the active HDM avoidance group. Covers were in place on 11 or more occasions in 53% of participants and on eight or more occasions in 90% of participants. The use of of the benzyl benzoate-containing solution was confirmed on 11 or more occasions in 71% of participants and on eight or more occasions in 96% of participants.

The proportion of parents who reported that they remembered to use the study spreads and oils "all of the time" or "most of the time" during the study was 88%. This was the same in the active and control diet intervention groups. However, median adherence to oil capsules during the period after age 2.5 years, was only 56% and was higher in the control diet group (62%) than the active diet group (51%)

Effect of HDM avoidance intervention

The active HDM avoidance intervention achieved an average 61% reduction (95% CI 57-65%) in the concentration of HDM allergen in dust collected from the child's bed over the period from one month to five years, compared with the control group. At the five-year follow-up, there was a 54% reduction in the active HDM intervention group.

Effect of dietary fatty acid modification

At ages 18 months, three years and five years the proportion of plasma fatty acids that were omega-3 was higher in the active diet group than in the control diet group and the proportion that were omega-6 was higher in the control diet group than in the active diet group. In the control diet group the median ratios of omega-3 fatty acids to omega-6 fatty acids were 1:7.2, 1:7.7 and 1:7.4 at 18 months, three years and five years, respectively and in the active diet group the median ratios were 1:4.9, 1:5.9 and 1:5.8, respectively.

Summary and Future Directions

We found that neither house dust mite avoidance nor omega-3 fatty acid supplementation had a beneficial effect in reducing the risk that children will develop asthma or allergy in the first five years. We are currently undertaking a fourth clinical assessment on the cohort at age eight years because it is possible that the benefits of the measures taken in early life may not become apparent until this time. We are also collaborating with other research teams, including those interested in nutrition and cardiovascular disease, because the interventions and some of the information we have collected may be relevant to these aspects of health, as well as to asthma and allergy. The eight year assessments are due to be completed in January 2008.

At the present time (June, 2006) there have been 12 original publications in peer-reviewed journals and at least 30 presentations arising from this project.

Publications

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11. Webb K, Rutishauser I, Katz T, Knezevic N, Lahti-Koski M, Peat J, Mihrshahi S. Meat consumption among 18 month old children participating in the Childhood Asthma Prevention Study. Nutrition and Dietetics 2005 ;62:X-X.
12. Marks GB, Mihrshahi S, Kemp AS, Tovey ER, Webb K, Almqvist C, Ampon RD, Crisafulli D, Belousova EG, Mellis CM, Peat JK, Leeder SR; CAPS Team. Prevention of asthma during the first 5 years of life: a randomised controlled trial. Journal of Allergy and Clinical Immunology 2006 (*in press).*