

The Effect of Prenatal Supplementation
with Omega 3 Long Chain Poly-
unsaturated Fatty Acids (n-3 LCPUFA) on
Childhood Allergic Disease
at Six Years of Age

Karen P Best RGN, RM

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Abstract

There is general consensus that the remarkable increase in allergic disease over the last 30-40 years is due to environmental influences including lifestyle and diet. Due to a number of factors associated with an industrialised world, the gross imbalance of n-6 (omega 6) and n-3 (omega 3) polyunsaturated fatty acids (PUFA) in our diet is no longer concordant with our genetically determined biology. Data from clinical and animal studies suggest that dietary n-3 LCPUFA in early life may influence immune system development and immune cell function reducing inflammatory responses, however clinically beneficial effects are more conflicting.

I conducted a systematic review of the literature including observational studies of increased maternal dietary intake of n-3 PUFA and RCT evidence of prenatal n-3 LCPUFA supplementation on outcomes of allergic disease in the offspring. Whilst limitations of cohort studies are well recognised, the concordance between outcomes from both study designs is noteworthy and suggestive of benefits. The paucity of RCT evidence beyond early childhood however, makes it difficult to draw any strong conclusions regarding the effect prenatal n-3 LCPUFA supplementation.

The six year allergy follow up study was a double blind randomised controlled trial designed to investigate the effect of supplementation of women with a fetus at high risk of atopy with 900mg of n-3 LCPUFA or a blended vegetable oil (with no n-3 LCPUFA) on outcomes of allergic disease in the offspring. 668 families were invited to take part in an allergy assessment to determine the incidence of allergic disease symptoms (eczema, wheeze or allergic rhinitis) and sensitisation to determine food and aeroallergen sensitisation.

603 children (90.2% of eligible cohort) completed an allergy assessment at six years of age. Results show that n-3 LCPUFA supplementation in pregnancy does not reduce the overall incidence of IgE-mediated allergic disease at six years of age, 116/367 (31.48%) vs 106/336 (31.46%) control, aRR 1.04 (0.82, 1.33), $p=0.73$. However, secondary outcomes suggest that the intervention reduces the incidence of 'sensitisation to house dust mite' and parent reported 'hayfever ever', 49/367 (13.42%) vs 68/336 (20.30%), aRR 0.67 (0.44, 1.00), $p=0.0495$; 81/367 (22.05%) vs 98/336 (29.05%), aRR: 0.77 (0.59, 1.01), $p=0.055$ respectively.

This cohort of children with high hereditary risk of allergy also completed assessment of allergic disease and sensitisation at 1 and 3 years of age. A longitudinal analysis was performed on 1, 3 and 6 year data indicating that there was not enough evidence to conclude that the relative risk of sensitisation (n-3 LCPUFA vs control) changed over time or was associated with any outcomes of allergic disease or sensitisation across all years.

There are plausible mechanisms by which increasing maternal dietary n-3 LCPUFA intake may modulate the fetal immune system and subsequent development of allergic disease in infants at risk of atopic disease. Although my results did not show a reduction in overall IgE associated disease at 6 years or impact on longitudinal outcomes (1, 3 and 6 years), they are consistent with previous studies and suggestive of benefits of prenatal n-3 LCPUFA supplementation on certain aspects of allergic disease, namely sensitisation. My results support the necessity to further investigate these outcomes and their relationship to the clinical expression of disease.

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution. This work, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide.

The systematic review and meta-analysis in this thesis (Chapter 2) is currently with the editors of the American Journal of Clinical Nutrition. I am first author and main contributor to the paper, written under the guidance of my supervisors Professor Maria Makrides, A/Professor Mike Gold and Professor Declan Kennedy.

I confirm that I personally completed the majority of the six year allergy assessments. When it became necessary to enlist the help of research staff of the Child Nutrition Research Centre to complete some of the 6 year allergy assessments (due to the number of assessments required and multiple clinic locations) I coordinated all aspects of study management including training, delegation and quality assurance.

I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968. I acknowledge that copyright of published works contained within this thesis resides with the copyright holder(s) of those works. I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library catalogue and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

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Karen P Best

Publications & presentations in support of this thesis

Publications

Best KP, Gold M, Kennedy D, Martin J, Makrides M. Omega-3 LCPUFA intake during pregnancy and allergic disease outcomes in the offspring: A systematic review and meta-analysis of observational studies and randomized controlled trials – submitted to the American Journal of Clinical Nutrition, (Chapter Two).

Published Abstracts

Best KP, Gold M, Makrides M. Effect of maternal dietary long chain polyunsaturated fatty acid intake during pregnancy on clinical outcomes of allergic disease in the offspring: a systematic review. Internal Medicine Journal, Volume 44, Issue Supplement S4, pages 1–29, September 2014, (Appendix 17).

Conference Presentations

Best K, Makrides Effect of maternal dietary LCPUFA intake during pregnancy on clinical outcomes of allergic disease in the offspring: A systematic review of prospective cohort studies and randomised controlled trials. Australian Society for Medical Research Congress, Adelaide, 2014, (Poster and abstract).

Best K, Gold M, Makrides M. Effect of maternal dietary long chain polyunsaturated fatty acid intake during pregnancy on clinical outcomes of allergic disease in the offspring: a systematic review. Florey International Postgraduate Research Conference, Adelaide 2014, (Poster and abstract).

Best K, Sullivan T, Gold M, Kennedy D, Martin J, Palmer D, Makrides M. Six Year Follow Up of Children at High Hereditary Risk of Allergy, Born To Mothers Supplemented With Docosahexaenoic Acid (DHA) in the DOMInO Trial. Perinatal Society of Australia & New Zealand, Melbourne Victoria, April 2015, (Oral presentation and abstract)

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Abbreviations

AA: Arachidonic acid

ACTRN: Australian clinical trials registry number

ALA: Alpha-linolenic acid

ANZCO: Australian & New Zealand Coding of Occupations

aRR: adjusted relative risk

CNRC: Child Nutrition Research Centre

CI: Confidence interval

CHQ: Child Health Questionnaire

CNRC: Child Nutrition Research Centre

CRF: Case report form

D. farinae: Dermatophagoides farinae

D. pteronyssinus: Dermatophagoides pteronyssinus

DHQ: Diet history questionnaire

DHA: Docosahexaenoic acid

DMAC: Data Management & Analysis Centre

DOMInO: Docosahexaenoic Acid to optimise maternal and infant outcomes

EFA: Essential fatty acid

EMBASE: Excerpta Medica Database

EPA: Eicosapentaenoic Acid

FFQ: Food Frequency Questionnaire

FMC: Flinders Medical Centre

GCP: Good Clinical Practice

HDM: House dust mite

HLA: Human-leucocyte antigen

HREC: Human Research Ethics Committee

IgE: Immunoglobulin-E

ITT: Intention to treat

LA: Linoleic Acid

n: number of participants

NHMRC: National Health and Medical Research Council

PUFA: Poly unsaturated fatty acid

RCT: Randomised controlled trial

RR: Relative risk

SEIFA: Socio-Economic Indexes for Areas

SCORAD: standardised scoring system for atopic dermatitis

SMS: Short message service

SOP: Standard operating procedure

SPT: Skin prick test

WCH: Women's & Children's Hospital

WCHN: Women's & Children's Health Network