Effects of n-3 LCPUFA supplementation for pregnant and lactating women in preventing allergic diseases in early childhood

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LIST OF ABBREVIATIONS

AA	Arachidonic acid
AAAAI	American Academy of Allergy Asthma and Immunology
ALA	α-Linoleic acid
APC	Antigen presenting cells
ASCIA	Australian Society of Clinical Immunology and Allergy
AUD	Australian dollars
BMI	Body mass index
CA	Corrected age
CD4+	Cluster of differentiation 4 cells
CI	Confidential intervals
CRF	Case report form
DHA	Docosahexaenoic acid
DINO	DHA for the Improvement of Neurodevelopmental Outcomes in Preterm Infants
DMAC	Data Management and Analysis Centre
DOMInO	DHA to Optimise Mother Infant Outcome
DPA	Docosapentaenoic acid
EDD	Expecting Date of Delivery
EFSA	The European Food Safety Authority
EPA	Ecosapentaenoic acid
FMC	Flinders Medical Centre
GA	Gestational age
GA2LEN	Global Allergy and Asthma European Network
GEE	Generalised estimating equation
IFN-γ	Interferon gamma

IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL-2	Interleukin 2
IL-4	Interleukin 4
IL-5	Interleukin 5
IL-10	Interleukin 10
IL-13	Interleukin 13
IL-17	Interleukin 17
ISAAC	International Study of Asthma and Allergies in Childhood
ITT	Intention to treat
LA	Linoleic acid
LCPUFA	Long chain poly unsaturated fatty acids
NF-κB	Nuclear Factor kappa B cells
NPV	Negative predictive value
OR	Odds ratio
PGE2	Prostaglandin E2
PPAR- ɤ	Peroxisome Proliferator Activated Receptors
PPV	Positive predictive value
PUFA	Polyunsaturated fatty acids
RAST	Radioallergosorbent test
RR	Risk ratio
SAP	Statistical analysis plan
SOP	Standard operation procedures
SPT	Skin prick test
Th1	Type 1 T helper cells

Th2	Type 2 T helper cells
Th17	Type 17 T helper cells
Treg	Regulatory T cells
TNF	Tumor Necrosis Factor
TGF	Transforming Growth Factor
TGF-β	Transforming Growth Factor Beta
USD	American dollars
UK	United Kingdom
WAO	World Allergy Organization
WCH	Women's and Children's Hospital
WHO	World Health Organization

DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, 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 in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide.

A combination of Chapter 2 and 6 of this thesis (systematic review and meta-analysis) has been published in The Cochrane Library, Issue 7, 2015 and the protocol of the systematic review has been published in The Cochrane Library, Issue 9, 2012. I am responsible for conceiving, designing, developing, co-ordinating and writing the review, under the guidance of my supervisors Professor Maria Makrides and Dr Carmel T Collins.

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SUMMARY

It is postulated that maternal n-3 (omega 3) long chain polyunsaturated fatty acids (LCPUFA) supplementation may modulate a range of inflammatory and immune pathways involved in the development of allergic diseases in early childhood, potentially leading to a reduction of allergic diseases in children. Thus the focus of this thesis was to determine whether maternal n-3 LCPUFA supplementation during pregnancy or lactation could prevent allergies in children.

Two nested follow-up studies from two randomised controlled trials (RCTs) were performed, as well as a Cochrane systematic review to address this question. Of the two nested follow-up studies, one was a prenatal n-3 LCPUFA supplementation and the other a postnatal n-3 LCPUFA supplementation study. Parental reports of allergy outcomes were evaluated in children between birth to three years of age and birth to seven years of age in these studies. The Cochrane systematic review and meta-analysis was used to determine overall effects of maternal n-3 LCPUFA supplementation on allergy outcomes of the children involved. All relevant RCTs to date and the data from my two follow-up studies were included in the systematic review. Eight trials involving 3366 women and their 3175 children were included and in these trials, women were supplemented with n-3 LCPUFA during pregnancy (five trials), lactation (two trials) or both pregnancy and lactation (one trial). All trials randomly allocated women to either a n-3 LCPUFA supplement or a control group. The risk of bias varied across the eight included trials in this review with only two trials with a low risk of selection, performance and attrition bias. Overall, there is limited evidence to support maternal n-3 LCPUFA supplementation during pregnancy and/or lactation for reducing allergic disease in children. Few differences in childhood allergic disease were seen between women who were supplemented with n-3 LCPUFA and those who were not.

N-3 LCPUFA supplementation showed a clear reduction in the primary outcome of any allergy (medically diagnosed IgE mediated) in children aged 12 to 36 months (risk ratio (RR) 0.66,

95% confidence interval (CI) 0.44 to 0.98; two RCTs; 823 children), but not beyond 36 months (RR 0.86, 95% CI 0.61 to 1.20; one RCT, 706 children). For any allergy (medically diagnosed IgE mediated and/or parental report), no clear differences were seen in children either at 12 to 36 months (RR 0.89, 95% CI 0.71 to 1.11; two RCTs, 823 children) or beyond 36 months of age (RR 0.96, 95% CI 0.84 to 1.09; three RCTs, 1765 children).

For the secondary outcomes of specific allergies there were no clear differences for food allergies at 12 to 36 months and beyond 36 months, but a clear reduction was seen for children in their first 12 months with n-3 LCPUFA (both for medically diagnosed IgE mediated and medically diagnosed IgE mediated and/or parental report). There was a clear reduction in medically diagnosed IgE mediated eczema with n-3 LCPUFA for children 12 to 36 months of age, but not at any other time point for both medically diagnosed IgE mediated and medically diagnosed IgE mediated and/or parental report. No clear differences for allergic rhinitis or asthma/wheeze were seen at any time point for both medically diagnosed IgE mediated, and medically diagnosed IgE mediated and/or parental report. There was a clear reduction in children's sensitisation to egg and sensitisation to at least one allergen between 12 to 36 months of age when mothers were supplemented with n-3 LCPUFA. In terms of safety for the mother and child, n-3 LCPUFA supplementation during pregnancy did not show increased risk of postpartum haemorrhage or early childhood infections.

The data obtained in one of the nested follow-up studies in this thesis was used to compare the validity of parental reports of allergy outcome measures against medical diagnosis of allergies. This revealed that parental reports of doctor diagnosed eczema were the most reliable for the diagnosis of eczema in infants, but further studies are needed to validate other allergy outcomes before parent reports of allergy symptoms can be considered as a useful tool to evaluate early childhood allergies in large scale research.