

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

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TABLE OF CONTENTS

TABLE OF CONTENTS	i
LIST OF TABLES	iii
LIST OF FIGURES.....	vi
LIST OF ABBREVIATIONS.....	vii
DECLARATION	xi
ACKNOWLEDGEMENTS	xii
SUMMARY	xiii
Chapter 1: Introduction	1
1.1 Overview	1
1.2 Review of Allergy	4
1.3 Scope of the thesis	38
Chapter 2: Maternal n-3 LCPUFA supplementation for prevention of allergies in early childhood – a systematic review and meta-analysis.....	41
2.1 Introduction.....	41
2.2 Protocol for the systematic review.....	42
2.3 Methods.....	42
2.4 Results of the systematic review	53
2.5 Discussion.....	99
2.6 Conclusion and Rationale for Thesis	107
Chapter 3: Effect of prenatal n-3 LCPUFA supplementation on parental reports of allergic outcomes in children up to 3 years of age.....	109
3.1 Introduction.....	109
3.2 Subjects and Methods.....	110
3.3 Outcomes.....	112
3.4 Results	118
3.5 Discussion.....	135
3.6 Conclusion.....	143

Chapter 4: Validation of parental reports of allergy symptoms or diagnosis in children who participated in a RCT	144
4.1 Introduction	144
4.2 Methods	145
4.3 Results	148
4.4 Discussion	157
4.5 Conclusion	162
Chapter 5: Postnatal n-3 LCPUFA supplementation to prevent allergic disease in school age children who were born preterm	163
5.1 Introduction	163
5.2 Subjects and Methods	165
5.3 Methods of DINO7 follow-up	167
5.4 Results of DINO7 follow-up	174
5.5 Discussion	199
5.6 Conclusion	207
Chapter 6: Maternal n-3 LCPUFA supplementation for prevention of allergies in early childhood – an updated meta-analysis	208
6.1 Introduction	208
6.2 Aims and objectives	208
6.3 Methods	208
6.4 Results of the updated systematic review	210
6.5 Discussion	241
6.6 Conclusion	245
REFERENCES	248
APPENDICES	270
Appendices to chapter 2.....	270
Appendices to chapter 3.....	323
Appendices to chapter 5.....	327
Appendix to chapter 6.....	371

LIST OF TABLES

Table 2-1: Summary description of included studies	55
Table 2-2: Detailed description of included studies	56
Table 2-3: Summary of study quality and risk of bias of the included studies	67
Table 2-4: Characteristics of excluded studies	71
Table 2-5: Characteristics of on-going studies	71
Table 2-6: Summary of meta-analyses of n-3 LCPUFA supplementation on IgE mediated allergies using pooled analysis RR (M-H, Fixed/Random, 95% CI)	79
Table 2-7: Summary of meta-analyses of n-3 LCPUFA (fish or fish oil) supplementation on all allergies using pooled analysis RR (M-H, Fixed/Random, 95% CI)	80
Table 2-8: Summary of meta-analyses of n-3 LCPUFA (fish or fish oil) supplementation on skin prick results for food allergens using pooled analysis RR (M-H, Fixed, 95% CI)	85
Table 2-9: Summary of meta-analyses reporting the effects of n-3 LCPUFA (fish or fish oil) supplementation on post-partum haemorrhage and early childhood infections using pooled analysis RR (M-H, Fixed/Random, 95% CI)	87
Table 2-10: Summary of meta-analyses reporting the effects of n-3 LCPUFA supplementation on parental reports of allergy (non-validated questionnaires) using pooled analysis RR (M-H, Fixed, 95% CI)	89
Table 2-11: Summary of the significant effects of n-3 LCPUFA (fish or fish oil) supplementation on childhood allergies/allergen sensitisation	91
Table 2-12: Summary of meta-analyses reporting the effects of timing of n-3 LCPUFA (fish or fish oil) supplementation to mothers and allergy risk in infants using pooled analysis RR (M-H, Fixed, 95% CI)	95
Table 2-13: Summary of meta-analyses of n-3 LCPUFA (fish or fish oil) supplementation and allergy risk in infants/children using pooled analysis RR (M-H, Fixed, 95% CI)	97
Table 3-1: Baseline characteristics at trial entry	119
Table 3-2: Post randomisation characteristics	120
Table 3-3: Effects of n-3 LCPUFA supplementation on parental reports of eczema symptoms between 0–36 months of age	121
Table 3-4: Effects of n-3 LCPUFA supplementation on parental reports of local doctor diagnosed eczema between 0–36 months of age	122
Table 3-5: Effects of n-3 LCPUFA supplementation on parent reports of asthma symptoms between 0–36 months of age	124

Table 3-6: Effects of n-3 LCPUFA supplementation on parental reports of local doctor diagnosed asthma between 0–36 months of age.....	125
Table 3-7: Effects of n-3 LCPUFA supplementation on parental reports of allergic rhinitis symptoms between 0–36 months of age.....	127
Table 3-8: Effects of n-3 LCPUFA supplementation on parental reports of local doctor diagnosed allergic rhinitis between 0–36 months of age.....	128
Table 3-9: Effects of n-3 LCPUFA supplementation on parental reports of food allergy symptoms between 0–36 months of age.....	130
Table 3-10: Effects of n-3 LCPUFA supplementation on parental reports of local doctor diagnosed food allergy between 0–36 months of age.....	131
Table 3-11: Effects of n-3 LCPUFA supplementation on parental reports of any allergy symptoms between 0–36 months of age.....	133
Table 3-12: Effects of n-3 LCPUFA supplementation on parental reports of doctor diagnosed any allergy between 0–36 months of age	134
Table 4-1: Kappa rating table	147
Table 4-2: Agreement between parental reports of eczema outcomes and medically diagnosed eczema (by study doctor) at 12 months of age	149
Table 4-3: Comparison of parental reports of eczema symptoms and medically diagnosed eczema (by study doctor).....	150
Table 4-4: Comparison of parental reports of local doctor diagnosed eczema and medically diagnosed eczema (by study doctor)	151
Table 4-5: Comparison of parental reports of asthma symptoms and medically diagnosed asthma (by study doctor)	152
Table 4-6: Comparison of parental reports of local doctor diagnosed asthma and medically diagnosed asthma (by study doctor)	153
Table 4-7: Comparison of parental reports of allergic rhinitis symptoms and medically diagnosed allergic rhinitis (by study doctor)	154
Table 4-8: Agreement between parental reports of food allergy symptoms and medically diagnosed food allergy with sensitisation (by study doctor)	155
Table 4-9: Comparison of parental reports of food allergy symptoms and medically diagnosed food allergy with sensitisation (by study doctor)	156
Table 5-1: Baseline characteristics at entry into DINO trial	176
Table 5-2: Neonatal characteristics at trial entry.....	177

Table 5-3: Effects of high DHA supplementation on parental reports of eczema symptoms in children between 6–7 years CA.....	179
Table 5-4: Effects of high DHA supplementation on parental reports of severe eczema symptoms in children between 6–7 years CA	180
Table 5-5: Effects of high DHA supplementation on parental reports of eczema and eczema symptoms in children from 0–7 years CA.....	181
Table 5-6: Effects of high DHA supplementation on parental reports of asthma symptoms in children between 6–7 years CA.....	183
Table 5-7: Effects of high DHA supplementation on parental reports of severe asthma symptoms in children between 6–7 years CA	184
Table 5-8: Effects of high DHA supplementation on parental reports of asthma and asthma symptoms in children between 0–7 years CA	185
Table 5-9: Effects of high DHA supplementation on parental reports of allergic rhinitis symptoms in children between 6–7 years CA	188
Table 5-10: Effects of high DHA supplementation on parental reports of severe allergic rhinitis symptoms in children between 6–7 years CA	189
Table 5-11: Effects of high DHA supplementation on parental reports of allergic rhinitis and allergic rhinitis symptoms in children from 0–7 years CA	190
Table 5-12: Effects of high DHA supplementation on parental reports of medically diagnosed asthma and eczema in children between 2–7 years CA.....	192
Table 5-13: Post randomisation characteristics	193
Table 5-14: Effects of high DHA supplementation on parental reports of eczema and eczema symptoms in children between 6–7 years CA and 0–7 years of age - breastfeeding group.....	195
Table 5-15: Effects of high DHA supplementation on parental reports of asthma and asthma symptoms in children between 6–7 years CA and 0–7 years of age - breastfeeding group.....	196
Table 5-16: Effects of high DHA supplementation on parental reports of allergic rhinitis and allergic rhinitis symptoms in children between 6–7 years CA and 0–7 years CA – breastfeeding group.....	197
Table 5-17: Effects of high DHA supplementation on parental reports of medically diagnosed asthma and eczema in children between 2–7 years CA – breastfeeding group.....	198
Table 6-1: Trial characteristics with new study components (which are underlined).....	213
Table 6-2: The effects of n-3 LCPUFA supplementation on IgE mediated allergies using pooled analysis RR (M-H, Fixed/Random, 95% CI).....	223

Table 6-3: The effects of n-3 LCPUFA supplementation on all allergies (+/- IgE sensitisation) using pooled analysis RR (M-H, Fixed, 95% CI)	224
Table 6-4: The effects of n-3 LCPUFA supplementation on skin prick results for allergens using pooled analysis RR (M-H, Fixed, 95%)	234
Table 6-5: Updated meta-analyses of n-3 LCPUFA supplementation on parental reports of allergy (non-validated questionnaires) using pooled analysis RR (M-H, Fixed, 95% CI).....	237

LIST OF FIGURES

Figure 1-1: The metabolic pathways for n-6 and n-3 poly unsaturated fatty acids -Linoleic acid and Alpha-Linolenic acid	19
Figure 1-2: n-3 and n-6 LCPUFA and inflammatory mediators	24
Figure 2-1: Flow chart presenting process for the selection of included studies	54
Figure 2-2: Risk of bias graph: judgements about each risk of bias item presented as percentages across all included studies.	69
Figure 2-3: Risk of bias summary: judgments about each risk of bias item for each included study.	70
Figure 2-4: Comparison: n-3 LCPUFA supplementation versus control (placebo or no oil)- Food allergies with IgE sensitisation.....	73
Figure 2-5: Comparison: n-3 LCPUFA supplementation versus control (placebo or no oil)- Eczema with IgE sensitisation.....	74
Figure 2-6: Comparison: n-3 LCPUFA supplementation versus control (placebo or no oil)-One or more allergies with IgE sensitisation	75
Figure 2-7: Comparison: n-3 LCPUFA (fish or fish oil) supplementation versus control (placebo or no oil)-Eczema with/without IgE sensitisation.....	77
Figure 2-8: Comparison: n-3 LCPUFA supplementation versus control (placebo or no oil)-One or more allergies with/without IgE sensitisation	78
Figure 2-9: Comparison: n-3 LCPUFA (fish or fish oil) supplementation versus control (placebo or no oil)-Skin prick sensitisation to egg.....	82
Figure 2-10: Comparison: n-3 LCPUFA (fish or fish oil) supplementation versus control (placebo or no oil)-Skin prick sensitisation to one or more allergen.....	84
Figure 3-1: Flow of the participants throughout follow-up periods	118
Figure 5-1: Flow of the participants throughout DINO trial follow-up periods.....	175

Figure 6-1: Flow chart presenting process for the selection of included studies	211
Figure 6-2: Risk of bias graph: judgements about each risk of bias item presented as percentages across all included studies.	219
Figure 6-3: Risk of bias summary: judgments about each risk of bias item for each included study.	220
Figure 6-4: Comparison: n-3 LCPUFA supplementation versus control (placebo or no oil)-One or more allergies with IgE sensitisation	225
Figure 6-5: Comparison: n-3 LCPUFA supplementation versus control (placebo or no oil)-One or more allergies with/without IgE sensitisation	225
Figure 6-6: Comparison: n-3 LCPUFA supplementation versus control (placebo or no oil)-Food allergies with IgE sensitisation.....	227
Figure 6-7: Comparison: n-3 LCPUFA supplementation versus control (placebo or no oil)-Food allergies with/without IgE sensitisation	228
Figure 6-8: Comparison: n-3 LCPUFA supplementation versus control (placebo or no oil)-Eczema with IgE sensitisation.....	229
Figure 6-9: Comparison: n-3 LCPUFA (fish or fish oil) supplementation versus control (placebo or no oil)-Eczema with/without IgE sensitisation.....	230
Figure 6-10: Comparison: n-3 LCPUFA (fish or fish oil) supplementation versus control (placebo or no oil)-Skin prick sensitisation to egg.....	233
Figure 6-11: Comparison: n-3 LCPUFA (fish or fish oil) supplementation versus control (placebo or no oil)-Skin prick sensitisation one or more allergen.....	233

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- κ B	Nuclear Factor kappa B cells
NPV	Negative predictive value
OR	Odds ratio
PGE2	Prostaglandin E2
PPAR- α	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.