A RANDOMISED CONTROLLED TRIAL OF DHA-RICH FISH OIL SUPPLEMENTATION DURING PREGNANCY AND SUBSEQUENT DEVELOPMENT OF ATTENTION, WORKING MEMORY AND INHIBITORY CONTROL IN EARLY CHILDHOOD

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SUMMARY

The last trimester of pregnancy is the period during which the fetal brain is growing at its greatest velocity, particularly the frontal lobes and hippocampus. This is also the peak period for the accumulation of omega-3 long chain polyunsaturated fatty acid (LCPUFA) docosahexaenoic acid (DHA) in neural tissues. The amount of DHA required by the fetus is thought to exceed the DHA intake of women of child-bearing age who consume a Western-style diet. This has led to the belief that maternal DHA supplementation during pregnancy will enhance child cognitive development in these populations. Cohort studies have supported this belief by linking intake of foods rich in DHA (primarily seafood) during pregnancy to enhanced child cognitive development. However, only randomised controlled trials (RCTs) can establish causality.

In this thesis I report a comprehensive systematic review of the current RCTs of DHA supplementation during pregnancy (Chapter 1) using procedures described by the Cochrane collaboration and the PRISMA statement. Results of globalised standard assessments in the reviewed RCTs were compared in meta analyses. No effect of DHA supplementation was found in any age group, except in the 2-5 year-olds where the LCPUFA group was advantaged. A risk of bias assessment revealed that the majority of the trials were of poor quality, particularly those in which there was a finding of significance. Furthermore the majority of trials used standardised tests of global development or cognition. Fetal DHA availability is thought to primarily effect the frontal lobes and hippocampus, which are responsible for higher order cognitive skills known as Executive Functions (EFs). The global assessments used in the RCTs capture performance across multiple neural systems simultaneously and lack the sensitivity to detect development in specific areas of cognition. Thus, global tests may not be suitable for detecting subtle effects of DHA supplementation on neurodevelopment. There has been a call for nutrition researchers to use specialised measures of cognitive functions that are appropriate for assessing the specific neural systems thought to be effected by an intervention, rather than global measures.

I addressed the need for a specialised measure of frontal lobe and hippocampus development in a RCT of DHA supplementation during pregnancy. The systematic review identified the DOMInO Trial as being a high-quality trial with a lower risk of bias compared with the other published RCTs. No one task can represent overall executive functioning abilities so I applied a range of specialised, age-appropriate assessments of EFs in two-year-old children. Attention, working memory (WM) and inhibitory control (IC) were the EFs selected for assessment in a subgroup of healthy, term-born toddlers (aged 27-months) from the DOMInO Trial. Two tests, the Attention Assessment involving three measures of attention, and the Working Memory and Inhibitory Control (WMIC) Assessment were identified from the developmental psychology literature. The Attention Assessment involved providing the child with toys to play with and measuring their attention (looking) to the toy(s) in three different scenarios; 1. the child had one toy to play with and their attention to the toy was measured in the absence of any competition for attention or distractions, 2. The child had five toys to play with and the number of times their attention switched between the toys competing for attention was measured, 3. The child had one toy to play with while a television in the periphery offered a distraction, and the time the child took to be distracted, from the toy, by the television was measured. The WMIC Assessment involved training a child to search for a hidden figurine in a specific location in a large box of lentils, and then hiding the figurine in an alternate location and delaying them from retrieving the figurine. Accuracy of searching for the figurine hidden in the alternate location was measured.

There was no effect of supplementation on the primary outcomes; latency to be distracted during Focused attention (Attention Assessment), and accuracy of searching for a hidden figurine during Test Trials (WMIC Assessment). The majority of the secondary outcomes supported the findings of null effect in the primary outcomes. There was one outcome in which there was a possible benefit of supplementation, but the effect was small and is likely to be due to chance. I conducted a large number of comparisons (n=18 pre-specified) on a relatively small sample (n=~152 per task) which increases the risk of a Type I error (finding a difference that is the result of chance). Furthermore, no other benefit was shown in any other outcomes, primary, secondary or exploratory. Associations between cord plasma DHA and outcomes of the Attention and WMIC assessments were inconsistent, indicating no true association.

Overall, the results of the two assessments I used suggest no effect of DHA supplementation during pregnancy on the cognitive development of healthy, otherwise well-nourished term-born children.

The findings of the specialised attention and WMIC assessments used in my study support the findings of global tests used in other RCTs of DHA supplementation during pregnancy. Increasing fetal exposure to DHA may not enhance cognitive development because growth of the brain is protected during in-utero development. Maternal stores of DHA, up-regulation of DHA synthesis and preferential transfer of DHA across the placenta during pregnancy may protect neurological structures from suboptimal development so that greater fetal exposure to DHA does not enhance child cognitive development.

Future research will be needed to determine whether specific at-risk sub-groups, such as children from pregnancies with placental insufficiency or who are growth restricted in utero, benefit from DHA supplementation during pregnancy.

DECLARATION

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

One chapter of this thesis is set to be published in a peer-reviewed journal. The systematic review and meta analysis in Chapter 1 (Literature Review) has been accepted for publication in the American Journal of Clinical Nutrition (in press) with myself as first author and main contributor to the paper, written with and under the guidance of my supervisors Dr Lisa Smithers and Prof Maria Makrides.

I consent to this copy of my thesis being deposited in the University of Adelaide Library to be available for loans 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 this work to be made available on the web, via the Australasian Digital Theses Program (ADTP) and also through web search engines.

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GLOSSARY

AA	Arachidonic Acid
ALA	alpha-linolenic acid
ALSPAC	Avon Longitudinal Study of Pregnancy and Childhood
BSID	Bayley Scales of Infant Development
CENTRAL	Cochrane Central Register of Controlled Trials
CNS	Central nervous system
CNRC	Child Nutrition Research Centre
CRF	Case Report Form
cs	Centiseconds
DINO	DHA for the Improvement of Neurodevelopmental Outcome in preterm infants
DOMInO	DHA to Optimise Mother Infant Outcome
DHA	Docosahexaenoic acid
DPA	Docosapentaenoic acid
DSS	Developmental Standard Score
EFs	Executive functions
FA	Fatty acid
GMDS	Griffith Mental Development Scales
HSQ	Home Screening Questionnaire
IC	Inhibitory Control
IQ	Intelligence quotient
ITT	Intention-to-treat
K-ABC	Kaufman Assessment Battery for Children
LCPUFA	Long-chain polyunsaturated fatty acid
n-3/6 LCPUFA	Omega-3/6 long-chain polyunsaturated fatty acid

NHMRC	National Health and Medical Research Council
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PUFA	Polyunsaturated fatty acid
RCT	Randomised controlled trial
RDI	Recommended Daily Intake
s	Seconds
SD	Standard deviation
SOP	Standard operating procedure
WHO	World Health Organisation
WM	Working Memory
WMIC	Working Memory and Inhibitory Control
WPPSI	Weschler Preschool and Primary Scale of Intelligence

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