Dietary fat, fatty acids and the specific health effects of omega-3 fatty acids in pregnancy and lactation

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The Essential Nature Fats In The Diet

- Most activity in the last 30 years in the area of perinatal nutrition has related to the role of the essential fatty acids, largely the long chain polyunsaturated fatty acids
- Much of this research has been about the bioactive omega-3 fatty acids, DHA & EPA
  - In all cell membranes
  - Putative roles in cell signaling and the regulation and resolution of inflammation
  - DHA especially concentrated in the brain

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The Balance of PUFA

	OMEGA 3	OMEGA 6
PUFA 18 carbons	ALA a-Linolenic Acid	LA Linoleic Acid
	⇩	⇩
LCPUFA 20 and 22 carbons	EPA, 20:5 Eicosapentaenoic Acid	AA, 20:4 Arachidonic Acid
	DHA, 22:6 Docosahexaenoic Acid	

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Omega-3 PUFA in Perinatal Nutrition

- Mostly about prematurity and developmental outcomes of children
- Earliest studies – high EPA fish oils to extend the duration of gestation
- Early 2000s – DHA enriched oils as supplements to improve neurodevelopmental outcomes of children
- Allergies
- Growth
- Now full circle back to pregnancy outcomes

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DOMInO – DHA to Optimize Mother Infant Outcome

- Designed to assess postnatal depression in women and neurodevelopmental outcome in early childhood
- 2399 women with singleton pregnancies randomly allocated to two groups
- Omega-3 group – 3x500mg capsules of DHA-rich fish oil concentrate providing **800mg of DHA/day**
- Control group – 3x500mg capsules containing a blend of 3 vegetable oils (to match Australian diet) with **no DHA**
- Intervene from study entry to birth

Makrides et al, JAMA 2010;304:1675-83

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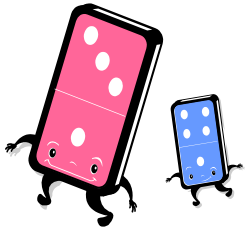
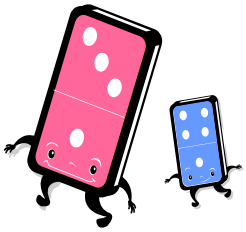
DOMInO: Risk of Postnatal Depression

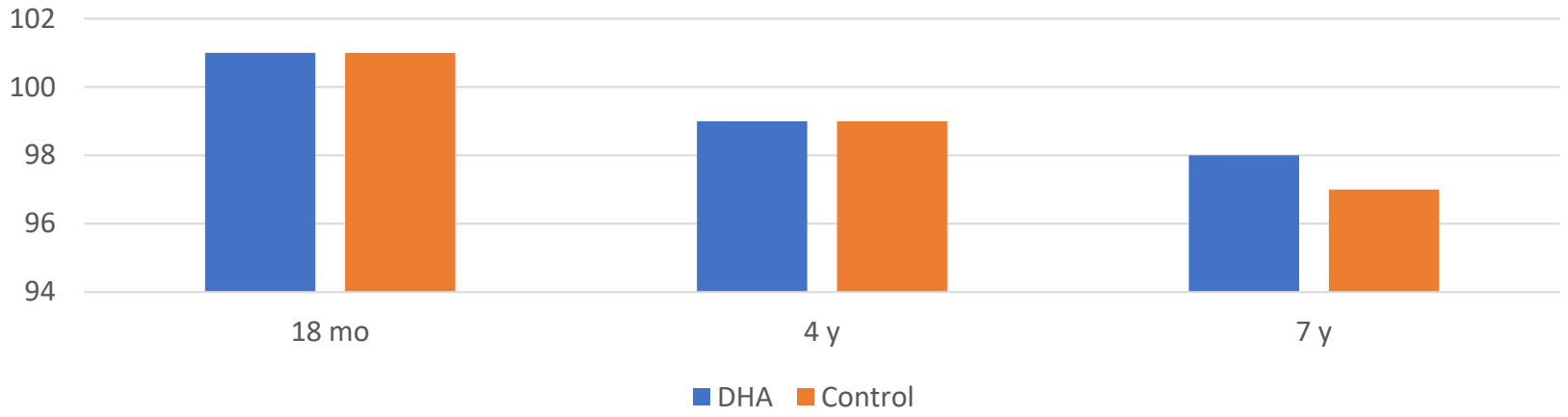


Variable	DHA n=1197	Control n=1202	Adj. RR (95% CI)
All women EPDS >12, %	**9.67**	**11.19**	**0.85 (0.70,1.02)**
6 wk	9.61	10.88	0.87 (0.68,1.10)
6 mo	9.74	11.50	0.83 (0.66,1.05)
New medical diagnosis during study, %	3.39	4.12	0.80 (0.62,1.02)
Subgroup, hi-risk women	N=298	N=287	
EPDS >12, %	**20.9**	**24.2**	**0.87 (0.68,1.12)**
6 wk	21.2	22.1	0.96 (0.71, 1.30)
6 mo	20.8	26.2	0.81 (0.60, 1.08)

Makrides et al, JAMA 2010;304:1675-83

DOMInO: Mean Developmental and Intelligence Quotients





Prenatal DHA – consistently no benefit to childhood development
(Makrides et al, JAMA 2010 & 2014; Gould et al, JAMA 2017)

It is likely that babies born at term, who are largely breastfed with milk containing 0.2% DHA, are adequate

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Synthesis Reviews: Development Outcomes

- Several recent reviews
- 12 trials included
- 240-3300mg ω-3 LCPUFA/d maternal supplementation
- Main focus - term children
- Few differences between groups
- Overall not confident of developmental benefit for children from term pregnancies

Childhood Allergies and Asthma

- Original story was all about diets **high** in omega-3 LCPUFA antagonizing AA and resulting in:
  - Displacement in cell membrane
  - Lower production of PGE2 → reduced synthesis of Th2 type cytokines and IgE antibodies – the hallmark of atopic responses

- Renewed interest because of all the new bioactive derivatives for both EPA and DHA as well as AA and LA

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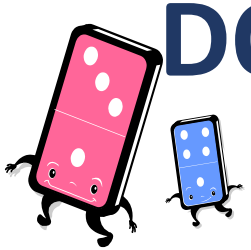
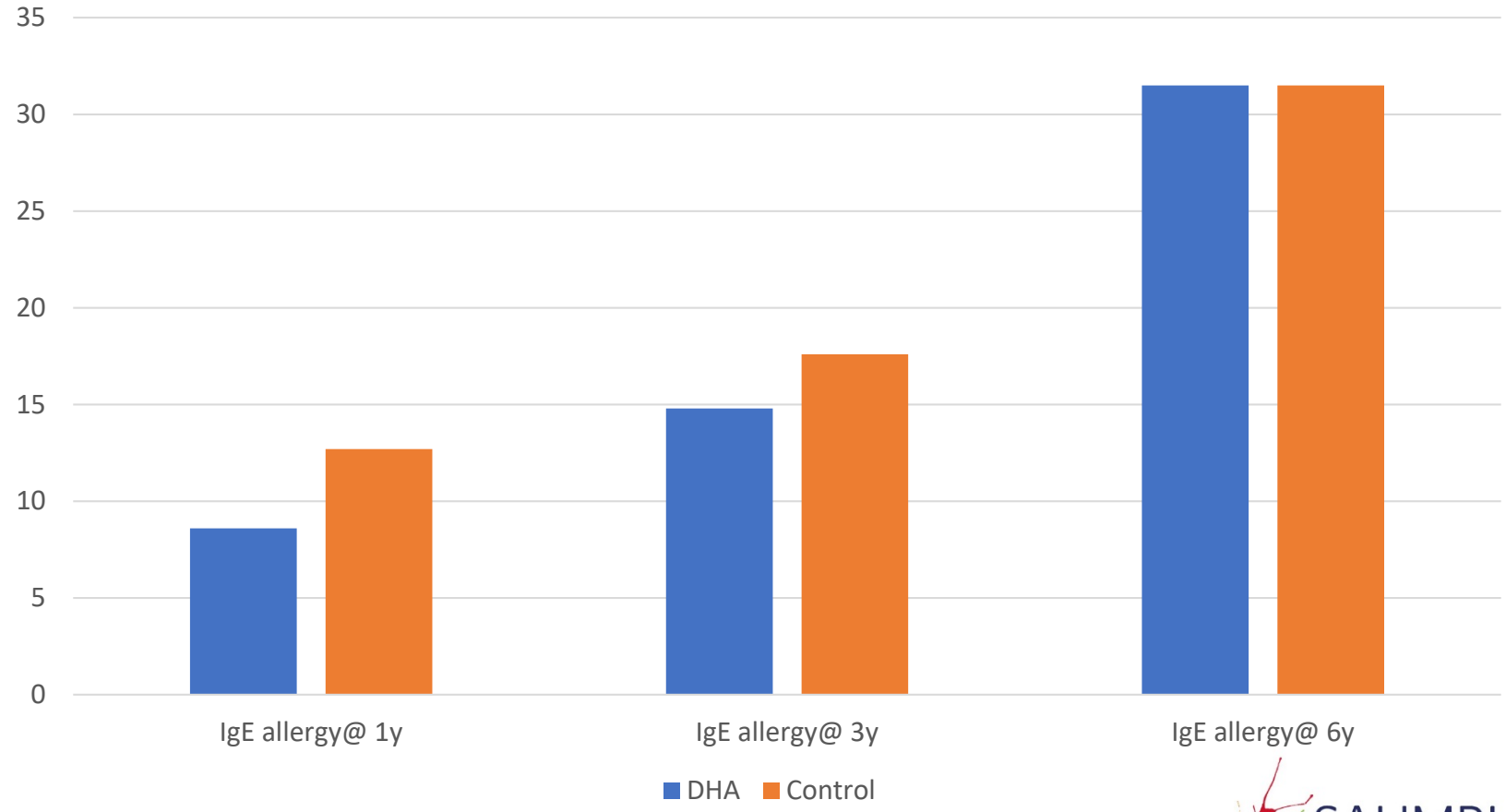
DOMInO: % of children with IgE associated allergies





Palmer et al, BMJ 2012; Palmer et al, Allergy 2013;
Best et al, Pediatr 2016

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Bisgaard et al, NEJM 2016;375:2530-9

P	736 pregnant women from 24 weeks' gestation
I	2.4g ω-3 LCPUFA/day as EPA-rich fish oil capsules
C	Olive oil capsules, no ω-3 LCPUFA
O	Persistent wheeze or asthma defined as 5 episodes of troublesome lung symptoms in the previous 6 months, each lasting for at least 3 days. Symptoms collected on diary cards at 1, 3, 6, 12, 18, 24, 30 and 36 months and yearly thereafter.

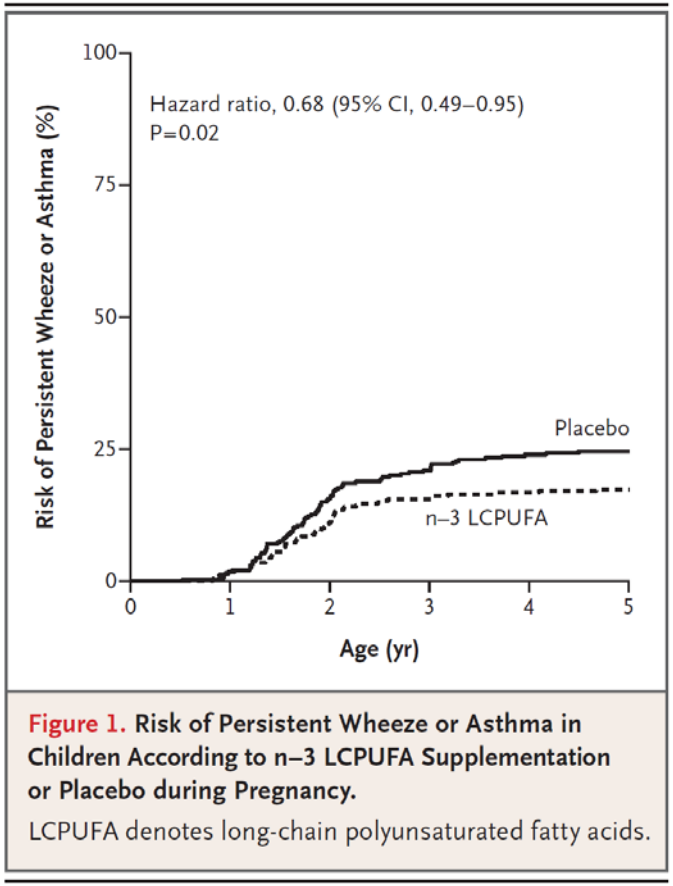

Figure 1. Risk of Persistent Wheeze or Asthma in Children According to n–3 LCPUFA Supplementation or Placebo during Pregnancy.

LCPUFA denotes long-chain polyunsaturated fatty acids.

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How Do We Reconcile the Two Largest and Most Well Conducted Studies?

DOMInO Allergy

- Children with hereditary risk
- Dose: 0.1g EPA, 0.8g DHA
- Hypothesis driven by IgE associated mechanism
- Marine oil reduced egg sensitisation at 12 months
- Marine oil reduced the risk of atopic eczema at 12 months
- No effects on atopic asthma
- No effects on respiratory illness

COPSAC Bisgaard et al

- Children with normal risk
- Dose 1.3g EPA, 0.9g DHA
- Hypothesis driven by general inflammatory mechanism/s
- No food sensitisation effects, but timing suboptimal
- No effects on eczema
- Marine oil reduced the risk of persistent wheeze/asthma
- Marine oil reduced risk of lower respiratory track infections

Birth Size and Childhood Growth

DOMInO

- Median gestation 181 d
- BW 3475g v 3407g; MD 66g
- Prematurity 5.6% vs 7.3%
- Similar to Australian average
- Other pregnancy complications similar to Australian average
- Birth weight effect probably linked with length of pregnancy and fetal growth

COPSAC

- Median gestation 181 d
- BW 3601g v 3504g; MD 97g
- Prematurity 3.5% vs 4%
- Lower than Danish average, 6.8%
- Very low rates of other pregnancy complications
- Birth weight effect probably linked with length of pregnancy and fetal growth

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Birth Size and Childhood Growth

DOMInO

- No long term effect on childhood growth
- BMI z score 0.56 vs 0.54
- BMI z score >90th percentile 22% v 22%
- Similar to national average
- Physical activity, screen time and snack intake similar

COPSAC

- Modest long term effect on childhood growth
- BMI z score -0.1 vs 0.1
- BMI z score >90th percentile 11% v 10%
- Couldn't link to national average
- Physical activity, screen time and snack intake not reported

May be too difficult to identify modest growth differences in the long term in heterogenous populations exposed to obesogenic environments

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Prematurity: a Global Issue

- Every year, about **15 million babies** are born preterm and this is rising
- Complications of preterm birth are a leading cause of death among children <5 years of age, responsible for nearly 1 million deaths
- Across 184 countries, the rate of preterm birth ranges from 5% to 18%

- 10 countries with the most preterm births per year
  - India: 3,519,100
  - China: 1,172,300
  - Nigeria: 773,600
  - Pakistan: 748,100
  - USA: 517,400
  - Indonesia: 675,700
  - Bangladesh: 424,100
  - Philippines: 348,900
  - Democratic Congo: 341,400
  - Brazil: 279,300

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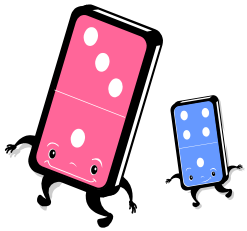
DOMInO Birth Outcomes
(800mg DHA, 100mg EPA)

	Omega-3 (n=1197)	Control (n=1202)
Early preterm birth <34 weeks	1.1%	2.3% p=0.03
Post-term induction or post-term pre-labour C-section	18%	14% p<0.01

Omega-3 intervention was also associated with:

- Fewer admission to neonatal intensive care
- Fewer cases of brain injury
- Fewer perinatal deaths



Makrides et al, JAMA 2010;304:1675-83

Zhou et al, AJCN 2012;95:1378-1384

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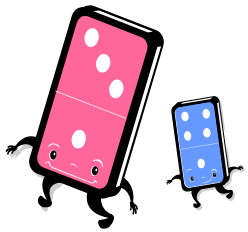
Gestation Length: Benefit vs Risk in DOMInO

- How to balance?
- NNT to prevent 1 birth <34 weeks is 87
- NNT to cause 1 post-term induction or C-section is 25
- Considerations:
  - Women's preferences
  - Pregnancy risk profile
  - Is there a way to minimise risk?



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The Path to Reduce the Risk of Preterm Birth…

- **Synthesising all the available intervention studies in a systematic review and meta-analysis**

- **Conducting a new modern intervention study that aims to retain the benefit while minimising the risk**

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The New Cochrane Review

- 70 RCTs with 19,927 pregnant women (+23 on-going trials)
- Mainly from high income countries, but some from low-middle income countries
- Most trial included women with **singleton pregnancies**
- Test dose range 200mg - 2,700mg/d ω-3 LCPUFA
- Mainly as fish oil capsules; also oil, fish, eggs, bars, dairy products
- Mainly throughout second half of pregnancy

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Primary Outcomes of Cochrane Update

Variable	Effect size
Birth <34 weeks	RR 0.58 (95% CI 0.44 to 0.77) **42% reduction** from 4.6% to 2.7% 11 trials with 5,409 women
Birth <37 weeks	RR 0.89 (95% CI 0.81 to 0.97) **11% reduction** from 13.4% to 11.9% 25 trials with 10,256 women
Birth >42 weeks	RR 1.61 (95% CI 1.11 to 2.33) **61% increase** from 1.6% to 2.6% 6 trials with 5,141 women

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Some Other Important Outcomes of the Cochrane Update

Variable	Effect size
Gestational length	MD 1.67 days (0.95 to 2.39), 41 trials with 12517 women
Pre-eclampsia	RR 0.84 (0.69 to 1.01), 20 trials with 8306 women
Perinatal death	RR 0.75 (0.54 to 1.03), 10 trials with 7416 women
Birth Weight	MD 76g (38 to 113), 42 trials with 11584 women
Low birth weight <2500g	RR 0.90 (0.82 to 0.99), 15 trials with 8449 women
SGA	RR 1.01 (0.90 to 1.13), 8 trials with 6907 women
LGA	RR 1.15 (0.97 to 1.36), 6 trials with 3722 women

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What's Important About the Cochrane Update?

- Includes studies with low-risk, normal risk and high-risk women but almost all women have singleton pregnancies
- Dose: Most studies used >500mg ω-3 LCPUFA/day
- Reporting biases may underestimate or overestimate omega-3 effect on prematurity and other adverse birth outcomes
- But, sensitivity analysis with high quality trials only indicate consistent effect of omega-3 supplementation on prematurity

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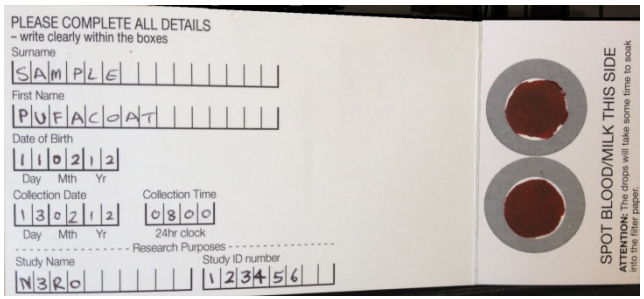
Omega-3 LCPUFA to Reduce the Incidence of Prematurity



- Blinded RCT in 6 centres
- **5544** women with singleton or multiple pregnancies
- Supplementation from <20 weeks until 34 weeks of gestation to reduce incidence of early preterm birth and prevent the need of obstetric intervention for post-term dates
- **Broad based strategy – few exclusions**
- DBS fatty acid profiles at entry and 34 weeks

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Makrides et al, NEJM 2019;381:1035-45

ORIP Results

- **Primary outcome - There was no difference between the DHA and control group on the incidence of early preterm birth (<34 weeks)**

Primary Outcome	Omega-3 (n=2734)	Control (n=2752)	Adjusted RR (95% CI)	Adjusted P Value
Early Preterm Birth (<34w)	**2.25%**	**1.98%**	**1.13 (0.79, 1.63)**	**0.50**

- **Secondary birth outcomes**

Outcome	Omega-3 (n=2734)	Control (n=2752)	Adjusted RR (95% CI)	Adjusted P Value
Pre-term Birth (<37w)	7.71%	8.93%	0.86 (0.72, 1.03)	0.11
Post term induction or pre-labour LSCS	5.16%	5.66%	0.91 (0.73, 1.14)	0.42
Gestational Age at birth (mean)	273.18	273.16	-	0.96

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Makrides et al, NEJM 2019;381:1035-45

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Discussion/Interpretation

- ORIP was specifically designed to assess a broad based supplementation strategy
- Inclusive of singleton and multiple pregnancies, inclusive of women regardless of prematurity risk, and inclusive of many women already taking low dose omega-3 supplements
- This contrasts with most other studies that included only singleton pregnancies and/or focused on women with low intakes
- **Why??**
  - Multiplicity
  - Baseline omega-3 status

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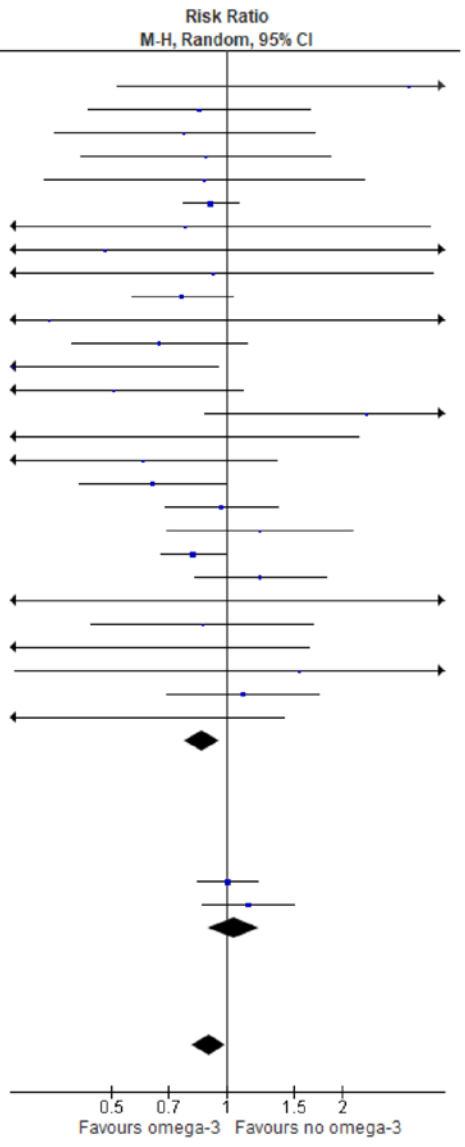
Cochrane Update: Preterm Birth <37 weeks

Study or Subgroup	Omega 3 Events	Omega 3 Total	No omega-3 Events	No omega-3 Total	Weight	Risk Ratio M-H, Random, 95% CI
1.95.1 singleton						
Bergmann 2007	3	48	2	96	0.3%	3.00 [0.52, 17.36]
Bisgaard 2016	15	365	18	371	2.1%	0.85 [0.43, 1.65]
Bulstra-Ramakers 1994	8	32	10	31	1.6%	0.78 [0.35, 1.70]
Carlson 2013	12	154	13	147	1.7%	0.88 [0.42, 1.87]
Dilli 2018	6	52	9	68	1.1%	0.87 [0.33, 2.29]
Harper 2010	164	434	174	418	14.8%	0.91 [0.77, 1.07]
Hauner 2012	3	92	4	96	0.5%	0.78 [0.18, 3.40]
Helland 2001	1	301	2	289	0.2%	0.48 [0.04, 5.27]
Horvaticek 2017	4	51	4	47	0.6%	0.92 [0.24, 3.48]
Makrides 2010	67	1197	88	1202	7.6%	0.76 [0.56, 1.04]
Malcolm 2003	0	31	1	32	0.1%	0.34 [0.01, 8.13]
Mardones 2008	22	493	32	477	3.2%	0.67 [0.39, 1.13]
Miller 2016	3	60	10	55	0.7%	0.28 [0.08, 0.95]
Min 2014	8	60	15	57	1.6%	0.51 [0.23, 1.10]
Min 2016	12	58	5	56	1.0%	2.32 [0.87, 6.15]
Oken 2013	0	31	2	17	0.1%	0.11 [0.01, 2.22]
Olsen 1992	9	266	15	267	1.5%	0.60 [0.27, 1.35]
Olsen 2000	23	108	40	120	4.4%	0.64 [0.41, 0.99]
Olsen 2019 (1)	96	3401	50	1717	6.6%	0.97 [0.69, 1.36]
Onwude 1995	22	113	19	119	2.9%	1.22 [0.70, 2.13]
ORIP	169	2654	209	2674	12.8%	0.81 [0.67, 0.99]
Ramakrishnan 2010	49	487	40	486	5.2%	1.22 [0.82, 1.82]
Razavi 2017	0	60	1	30	0.1%	0.17 [0.01, 4.04]
Smuts 2003a	14	142	17	149	2.1%	0.86 [0.44, 1.69]
Smuts 2003b	1	18	5	19	0.2%	0.21 [0.03, 1.64]
Taghizadeh 2016	3	29	2	30	0.3%	1.55 [0.28, 8.62]
Tofail 2006	30	125	27	124	4.1%	1.10 [0.70, 1.74]
Van Goor 2009	1	86	3	39	0.2%	0.15 [0.02, 1.41]
Subtotal (95% CI)		**10948**		**9233**	**77.7%**	**0.86 [0.77, 0.96]**
Total events	745		817			
Heterogeneity: Tau² = 0.01; Chi² = 29.81, df = 27 (P = 0.32); I² = 9%						
Test for overall effect: Z = 2.73 (P = 0.006)						
1.95.2 multiple						
Olsen 2000	129	286	127	283	13.7%	1.01 [0.84, 1.21]
ORIP	37	52	30	48	8.6%	1.14 [0.86, 1.51]
Subtotal (95% CI)		**338**		**331**	**22.3%**	**1.04 [0.90, 1.21]**
Total events	166		157			
Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.54 (P = 0.59)						
Total (95% CI)		**11286**		**9564**	**100.0%**	**0.90 [0.81, 0.99]**
Total events	911		974			
Heterogeneity: Tau² = 0.01; Chi² = 35.14, df = 29 (P = 0.20); I² = 17%						
Test for overall effect: Z = 2.06 (P = 0.04)						
Test for subgroup differences: Chi² = 4.10, df = 1 (P = 0.04), I² = 75.6%						



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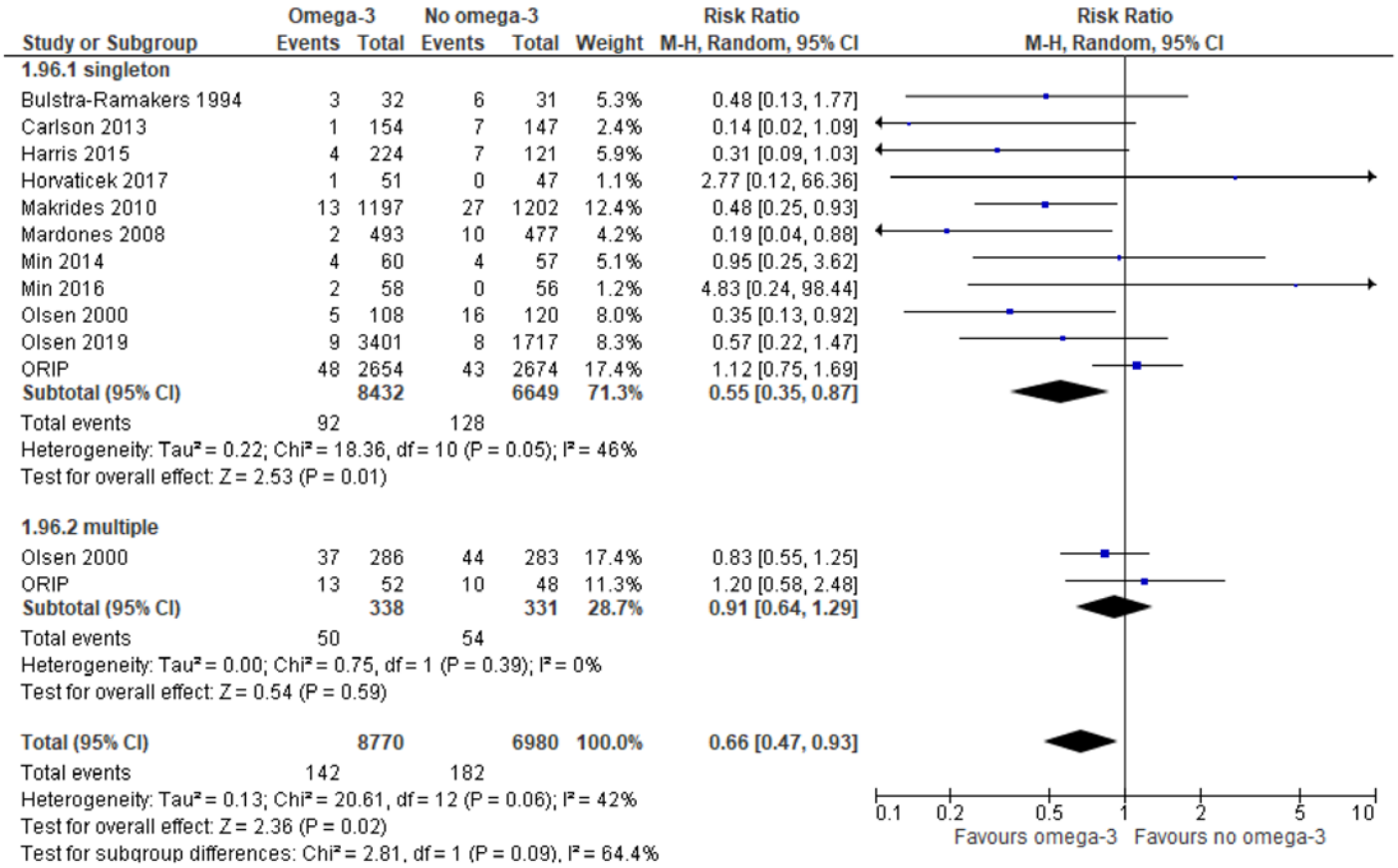
Cochrane Update: Preterm Birth <34 weeks



Study or Subgroup	Omega-3 Events	Omega-3 Total	No omega-3 Events	No omega-3 Total	Weight	Risk Ratio M-H, Random, 95% CI
1.96.1 singleton						
Bulstra-Ramakers 1994	3	32	6	31	5.3%	0.48 [0.13, 1.77]
Carlson 2013	1	154	7	147	2.4%	0.14 [0.02, 1.09]
Harris 2015	4	224	7	121	5.9%	0.31 [0.09, 1.03]
Horvaticek 2017	1	51	0	47	1.1%	2.77 [0.12, 66.36]
Makrides 2010	13	1197	27	1202	12.4%	0.48 [0.25, 0.93]
Mardones 2008	2	493	10	477	4.2%	0.19 [0.04, 0.88]
Min 2014	4	60	4	57	5.1%	0.95 [0.25, 3.62]
Min 2016	2	58	0	56	1.2%	4.83 [0.24, 98.44]
Olsen 2000	5	108	16	120	8.0%	0.35 [0.13, 0.92]
Olsen 2019	9	3401	8	1717	8.3%	0.57 [0.22, 1.47]
ORIP	48	2654	43	2674	17.4%	1.12 [0.75, 1.69]
Subtotal (95% CI)		**8432**		**6649**	**71.3%**	**0.55 [0.35, 0.87]**
Total events	92		128			
Heterogeneity: Tau² = 0.22; Chi² = 18.36, df = 10 (P = 0.05); I² = 46%						
Test for overall effect: Z = 2.53 (P = 0.01)						
1.96.2 multiple						
Olsen 2000	37	286	44	283	17.4%	0.83 [0.55, 1.25]
ORIP	13	52	10	48	11.3%	1.20 [0.58, 2.48]
Subtotal (95% CI)		**338**		**331**	**28.7%**	**0.91 [0.64, 1.29]**
Total events	50		54			
Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 1 (P = 0.39); I² = 0%						
Test for overall effect: Z = 0.54 (P = 0.59)						
Total (95% CI)		**8770**		**6980**	**100.0%**	**0.66 [0.47, 0.93]**
Total events	142		182			
Heterogeneity: Tau² = 0.13; Chi² = 20.61, df = 12 (P = 0.06); I² = 42%						
Test for overall effect: Z = 2.36 (P = 0.02)						
Test for subgroup differences: Chi² = 2.81, df = 1 (P = 0.09), I² = 64.4%						

ORIP Secondary Analysis

Key questions for singleton pregnancies

- Does baseline omega-3 status predict the risk of early preterm birth?
- Does baseline omega-3 status modify the effect of omega-3 LCPUFA supplementation on early preterm birth?
- What is the best biomarker of omega-3 status for early preterm birth?

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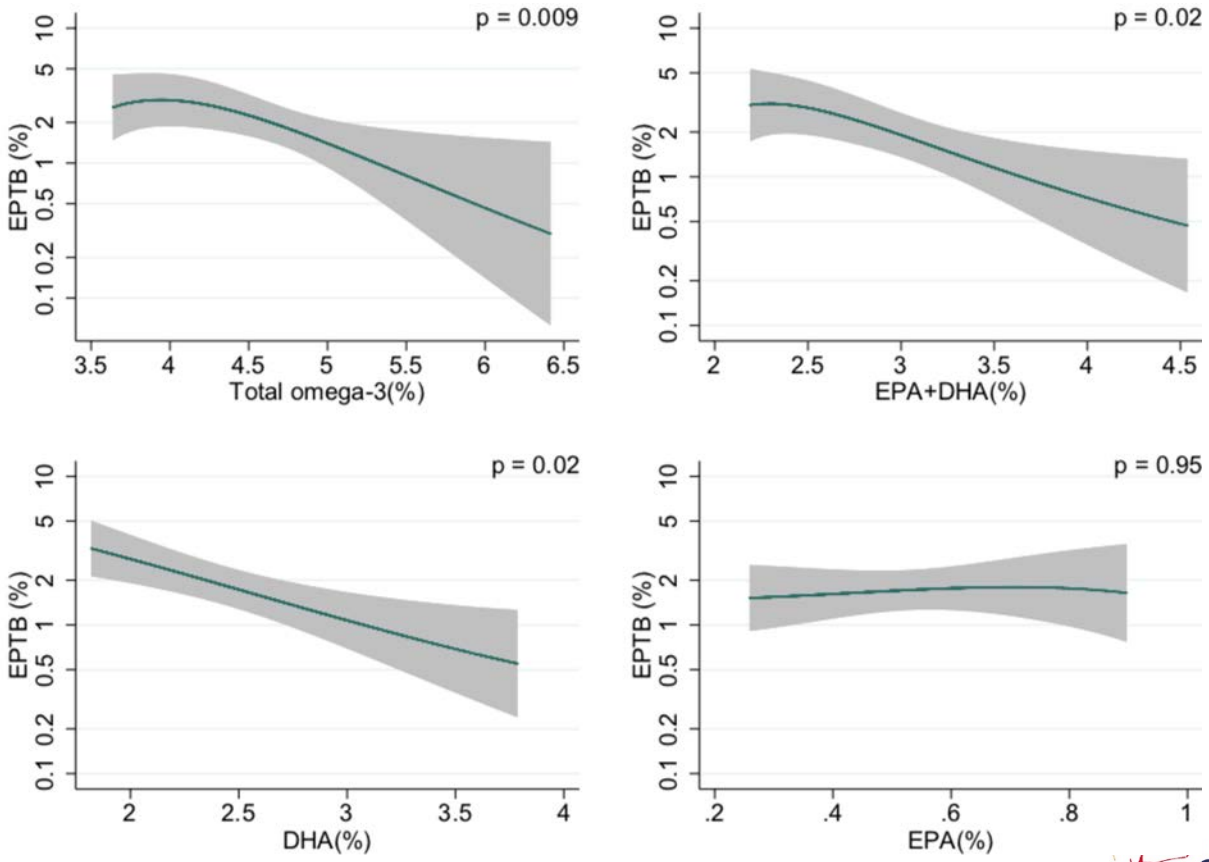
Early Preterm Birth as a Function of Omega-3 Status in Early Pregnancy in the ORIP Control Group



Simmonds et al, accepted BJOG

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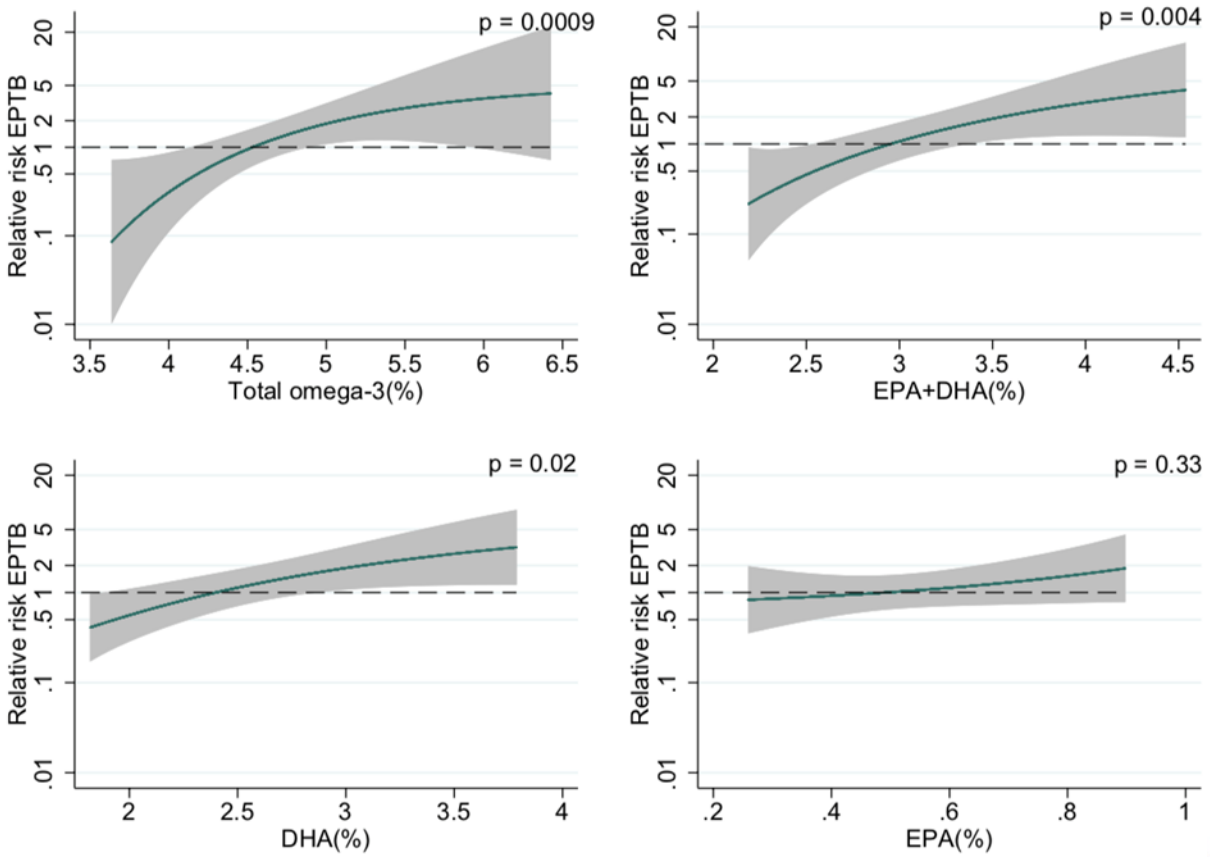
Relative Risk of Early Preterm Birth by Baseline Omega-3 Status in ORIP Singleton Pregnancies



Simmonds et al, accepted BJOG

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Summary

- Total omega-3 fatty acids, biomarker with strongest relationship
- Lower omega-3 status in early pregnancy is associated with a higher risk of early preterm birth
- Supplementation with DHA-enriched fish oil in women with <4.1% total fatty acids in whole blood reduced the risk of early preterm birth (RR 0.23, 95% CI 0.07 to 0.79)
- Supplementation with DHA-enriched fish oil in women with >4.9% total fatty acids in whole blood increased the risk of early preterm birth (RR 2.27, 95% CI 1.13 to 4.58)

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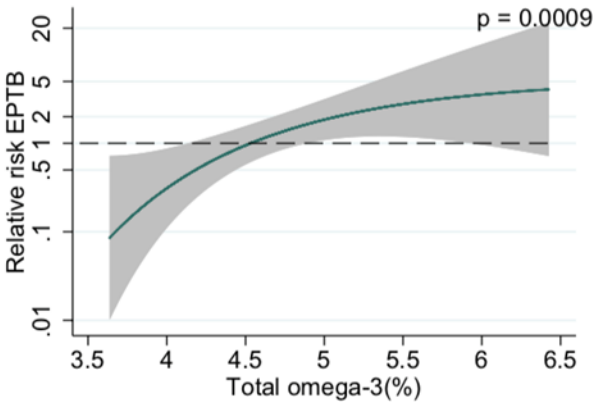
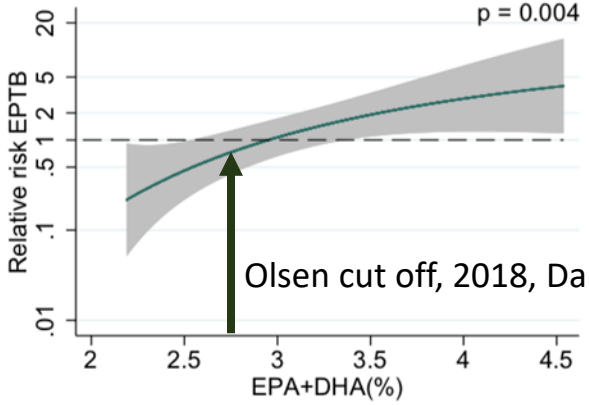
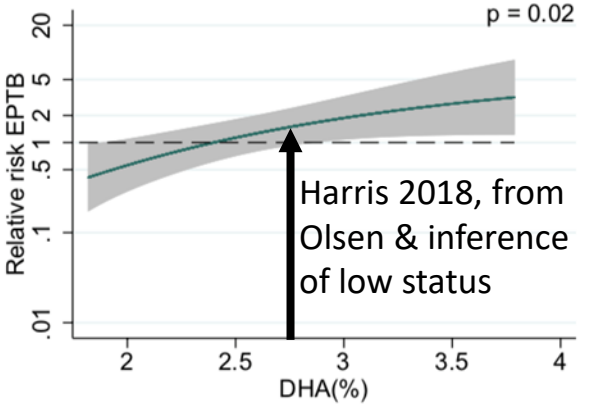
How Do We Compare Cut Offs for Benefit?

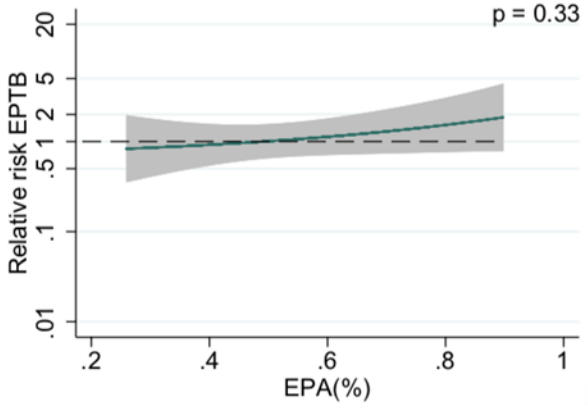




Olsen cut off, 2018, Danish Birth Cohort



Harris 2018, from Olsen & inference of low status



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Avoiding Omega-3 Supplementation In Pregnant Women Who Are Replete

- Women with higher omeg-3 status are already at lower risk of prematurity
- Possibility of harm
- Implies a narrower window than originally thought, especially with the wide-spread use of prenatal vitamin and mineral supplements with DHA
- “Replete” status can be achieved by regularly eating fish, or a varied omnivorous diet with modest fortification/supplementation (200-400mg DHA)
- Remarkably consistent with epidemiological studies

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Effects of Omega-3 Fatty Acids In Pregnancy and Lactation…

- Prematurity
  - Omega-3 LCPUFA have a role to play
  - Probably limited to women with low omega-3 status
- Childhood growth
  - Effect may be too small to see in broad, representative populations
- Childhood Neurodevelopment
  - Probably not, especially for healthy, term infants
- Childhood Allergies and Asthma
  - Needs more work!

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Some Unanswered Questions

- Utility of a screen and treat approach
- Usefulness of monitoring omega-3 status during pregnancy
- Ability to predict omega-3 status from dietary intake and markers of socio-economic status
- Definition of “low” status for different outcomes
- What to do with multiple pregnancies?
- Sustainability

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My Interests….

- Primary prevention of preterm birth
- Scalable implementation study that requires:
  - Ability to reach all pregnant women
  - Pathology and analytical testing providers that provide fatty acid testing
  - Barriers and enablers for coverage, delivery and appropriate interpretation of results

Trajan Nutrition

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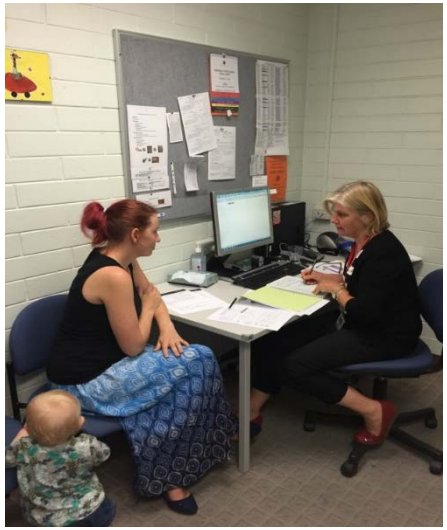

Thank-you for your attention