Gender-specific differences in essential fatty acid metabolism

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Power of Programming
Munich, 2010

Topics to be discussed

- Are there gender differences in fatty acid composition of biological samples?
- If there are gender differences, what might be the cause of the differences?
- If there are gender differences, might they influence results obtained in paediatric nutrition trials?

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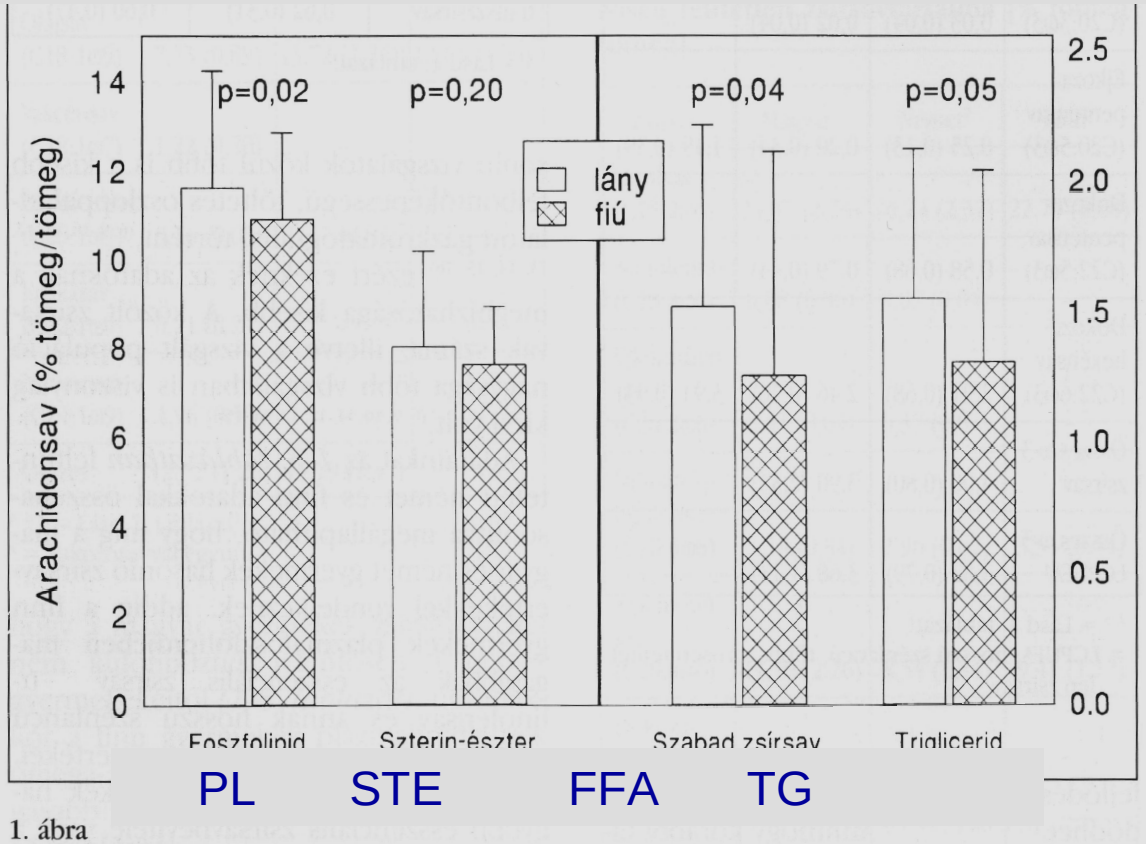
Arachidonic acid (% w/w; median IQR)

Girls (n = 43) Boys (n = 48)



1. ábra

Magyar iskolás lányok (n = 43) és fiúk (n = 48) plazmaarachidonsav értékei különböző lipidfrakciókban [% tömeg/tömeg, medián, 3. és 1. kvartális különbsége)

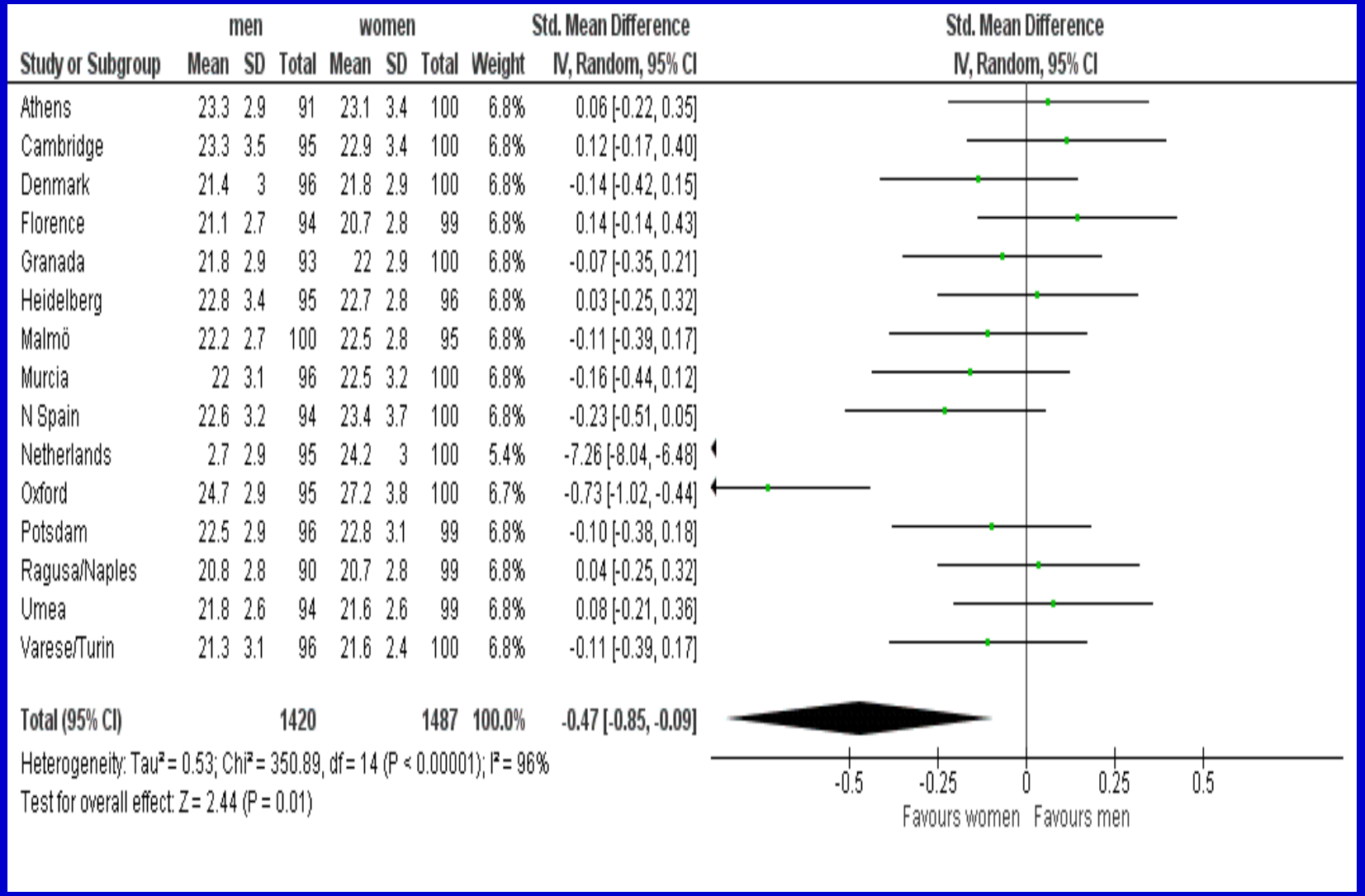
Molnár et al: Fatty acid composition of plasma lipid classes in schoolchildren in Hungary. *Gyermekgyogyaszat* 52: 260-265, **2001**

Plasma phospholipid fatty acid profiles and their association with food intakes: results from a cross sectional study within the European Prospective Investigation into Cancer and Nutrition

- A cross-sectional study design nested to the European Prospective Investigation into Cancer and Nutrition (EPIC) was conducted to determine plasma fatty acid profiles **in more than 3000 subjects** from 16 centers.
- Plasma fatty acids were assessed by capillary gas chromatography.

- *Saadatian-Elahi et al, Am J Clin Nutr* 89: 331-346, 2009.

Plasma phospholipid linoleic acid



Study or Subgroup	men Mean	men SD	men Total	women Mean	women SD	women Total	Weight	Std. Mean Difference IV, Random, 95% CI
Athens	23.3	2.9	91	23.1	3.4	100	6.8%	0.06 [-0.22, 0.35]
Cambridge	23.3	3.5	95	22.9	3.4	100	6.8%	0.12 [-0.17, 0.40]
Denmark	21.4	3	96	21.8	2.9	100	6.8%	-0.14 [-0.42, 0.15]
Florence	21.1	2.7	94	20.7	2.8	99	6.8%	0.14 [-0.14, 0.43]
Granada	21.8	2.9	93	22	2.9	100	6.8%	-0.07 [-0.35, 0.21]
Heidelberg	22.8	3.4	95	22.7	2.8	96	6.8%	0.03 [-0.25, 0.32]
Malmö	22.2	2.7	100	22.5	2.8	95	6.8%	-0.11 [-0.39, 0.17]
Murcia	22	3.1	96	22.5	3.2	100	6.8%	-0.16 [-0.44, 0.12]
N Spain	22.6	3.2	94	23.4	3.7	100	6.8%	-0.23 [-0.51, 0.05]
Netherlands	2.7	2.9	95	24.2	3	100	5.4%	-7.26 [-8.04, -6.48]
Oxford	24.7	2.9	95	27.2	3.8	100	6.7%	-0.73 [-1.02, -0.44]
Potsdam	22.5	2.9	96	22.8	3.1	99	6.8%	-0.10 [-0.38, 0.18]
Ragusa/Naples	20.8	2.8	90	20.7	2.8	99	6.8%	0.04 [-0.25, 0.32]
Umea	21.8	2.6	94	21.6	2.6	99	6.8%	0.08 [-0.21, 0.36]
Varese/Turin	21.3	3.1	96	21.6	2.4	100	6.8%	-0.11 [-0.39, 0.17]
Total (95% CI)			**1420**			**1487**	**100.0%**	**-0.47 [-0.85, -0.09]**

Heterogeneity: Tau² = 0.53; Chi² = 350.89, df = 14 (P < 0.00001); I² = 96%

Test for overall effect: Z = 2.44 (P = 0.01)

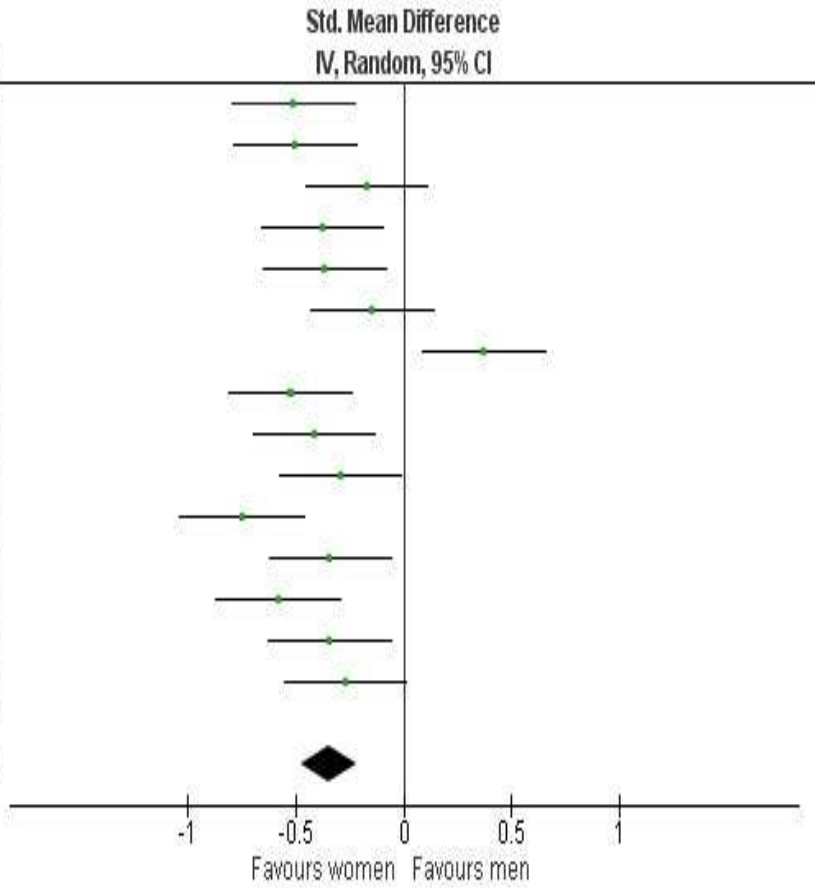
Drawn from Saadatian-Elahi et al, Am J Clin Nutr 89: 331-346, 2009.

Plasma phospholipid arachidonic acid

Study or Subgroup	men Mean	men SD	men Total	women Mean	women SD	women Total	Weight	Std. Mean Difference IV, Random, 95% CI
Athens	10.5	2	91	11.5	1.9	100	6.6%	-0.51 [-0.80, -0.22]
Cambridge	10.1	1.7	95	11.1	2.2	100	6.7%	-0.51 [-0.79, -0.22]
Denmark	10.6	1.7	96	10.9	1.8	100	6.7%	-0.17 [-0.45, 0.11]
Florence	11.9	1.8	94	12.6	1.9	99	6.7%	-0.38 [-0.66, -0.09]
Granada	11.5	1.9	93	12.2	1.9	100	6.7%	-0.37 [-0.65, -0.08]
Heidelberg	11.9	2.1	95	12.2	2	96	6.7%	-0.15 [-0.43, 0.14]
Malmö	10.5	1.6	100	9.9	1.6	95	6.7%	0.37 [0.09, 0.66]
Murcia	11.3	1.9	96	12.3	1.9	100	6.7%	-0.52 [-0.81, -0.24]
N Spain	11.5	2	94	12.4	2.3	100	6.7%	-0.42 [-0.70, -0.13]
Netherlands	11.2	2	95	11.8	2.1	100	6.7%	-0.29 [-0.57, -0.01]
Oxford	11.4	2.4	95	13.2	2.38	100	6.6%	-0.75 [-1.04, -0.46]
Potsdam	11.2	1.8	96	11.8	1.7	99	6.7%	-0.34 [-0.62, -0.06]
Ragusa/Naples	12	2.1	90	13.2	2	99	6.6%	-0.58 [-0.88, -0.29]
Umea	9.7	1.4	94	10.2	1.5	99	6.7%	-0.34 [-0.63, -0.06]
Varese/Turin	12.1	1.9	96	12.6	1.8	100	6.7%	-0.27 [-0.55, 0.01]
Total (95% CI)			**1420**			**1487**	**100.0%**	**-0.35 [-0.48, -0.22]**

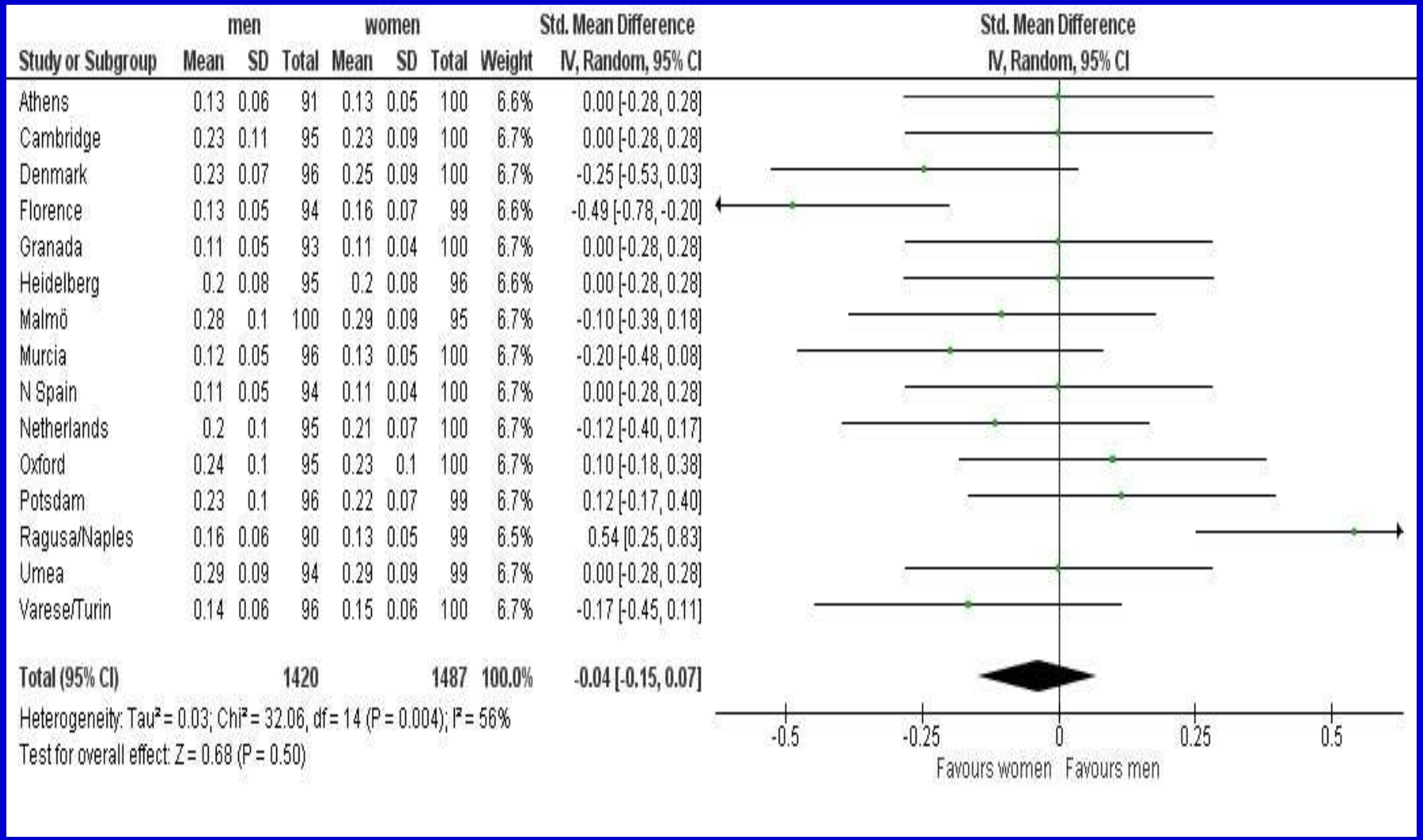
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 42.85$, df = 14 ($P < 0.0001$); $I^2 = 67\%$

Test for overall effect: $Z = 5.28$ ($P < 0.00001$)



Drawn from Saadatian-Elahi et al, Am J Clin Nutr 89: 331-346, 2009.

Plasma phospholipid α-linolenic acid



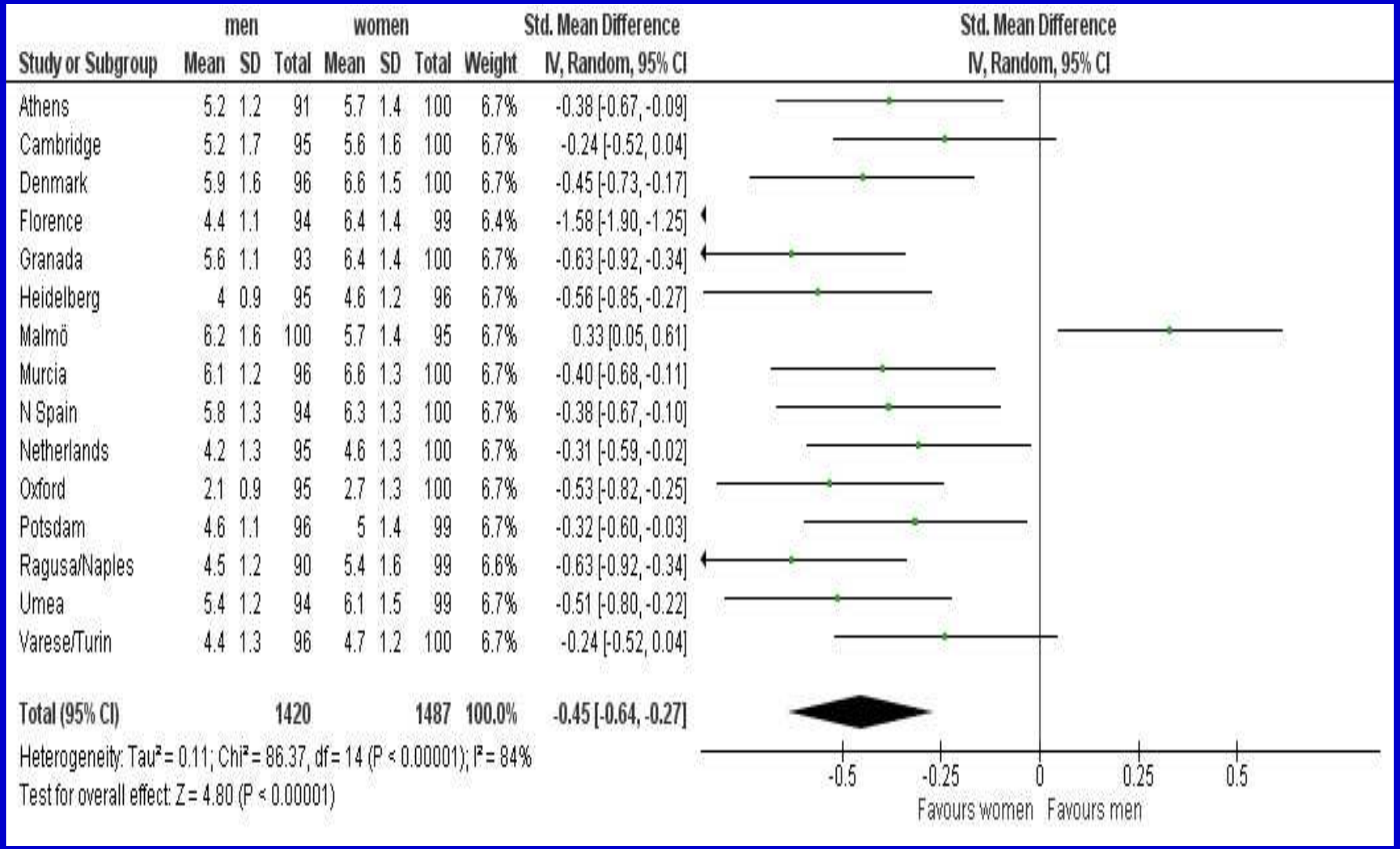
Study or Subgroup	men Mean	men SD	men Total	women Mean	women SD	women Total	Weight	Std. Mean Difference IV, Random, 95% CI
Athens	0.13	0.06	91	0.13	0.05	100	6.6%	0.00 [-0.28, 0.28]
Cambridge	0.23	0.11	95	0.23	0.09	100	6.7%	0.00 [-0.28, 0.28]
Denmark	0.23	0.07	96	0.25	0.09	100	6.7%	-0.25 [-0.53, 0.03]
Florence	0.13	0.05	94	0.16	0.07	99	6.6%	-0.49 [-0.78, -0.20]
Granada	0.11	0.05	93	0.11	0.04	100	6.7%	0.00 [-0.28, 0.28]
Heidelberg	0.2	0.08	95	0.2	0.08	96	6.6%	0.00 [-0.28, 0.28]
Malmö	0.28	0.1	100	0.29	0.09	95	6.7%	-0.10 [-0.39, 0.18]
Murcia	0.12	0.05	96	0.13	0.05	100	6.7%	-0.20 [-0.48, 0.08]
N Spain	0.11	0.05	94	0.11	0.04	100	6.7%	0.00 [-0.28, 0.28]
Netherlands	0.2	0.1	95	0.21	0.07	100	6.7%	-0.12 [-0.40, 0.17]
Oxford	0.24	0.1	95	0.23	0.1	100	6.7%	0.10 [-0.18, 0.38]
Potsdam	0.23	0.1	96	0.22	0.07	99	6.7%	0.12 [-0.17, 0.40]
Ragusa/Naples	0.16	0.06	90	0.13	0.05	99	6.5%	0.54 [0.25, 0.83]
Umea	0.29	0.09	94	0.29	0.09	99	6.7%	0.00 [-0.28, 0.28]
Varese/Turin	0.14	0.06	96	0.15	0.06	100	6.7%	-0.17 [-0.45, 0.11]
Total (95% CI)			**1420**			**1487**	**100.0%**	**-0.04 [-0.15, 0.07]**

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 32.06$, df = 14 (P = 0.004); $I^2 = 56\%$

Test for overall effect: Z = 0.68 (P = 0.50)

Drawn from Saadatian-Elahi et al, Am J Clin Nutr 89: 331-346, 2009.

Plasma phospholipid docosahexaenoic acid



Drawn from Saadatian-Elahi et al, Am J Clin Nutr 89: 331-346, 2009.

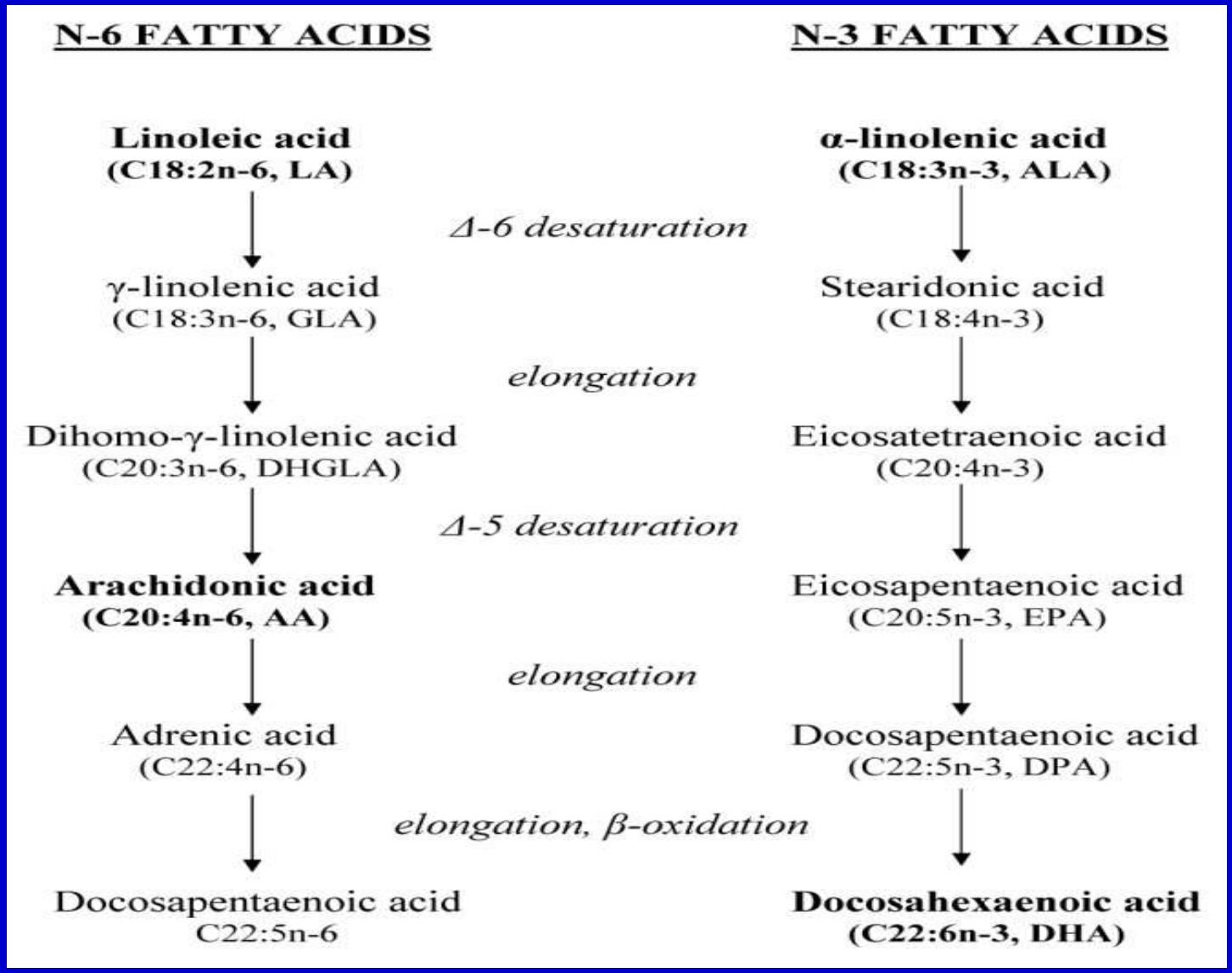
Are there gender differences in fatty acid composition of biological samples?

- Strong evidence indicate that there are significant differences in fatty acid composition of plasma lipids between women and men.
- However, the extent of differences appears to be less than 5% of the mean for AA and less than 10% of the mean for DHA.
- There are some data suggesting that there might be differences between boys and girls.

Topics to be discussed

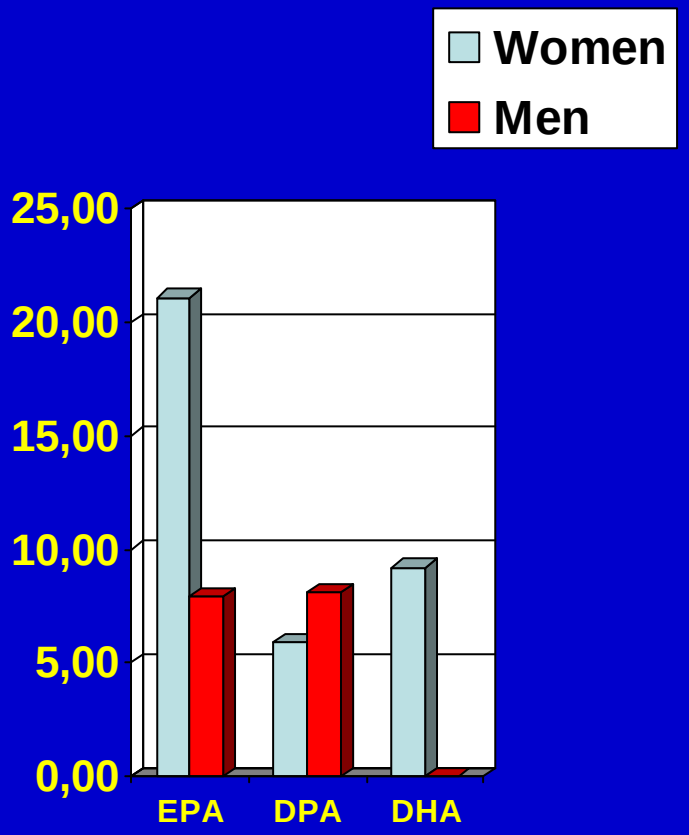
- Are there gender differences in fatty acid composition of biological samples?
- If there are gender differences, what might be the cause of the differences?
- If there are gender differences, might they influence results obtained in paediatric nutrition trials?

Pathways of LCPUFA synthesis



Estimated net fractional inter-conversion of the tracer [U-^{13}C] alpha-linolenic acid

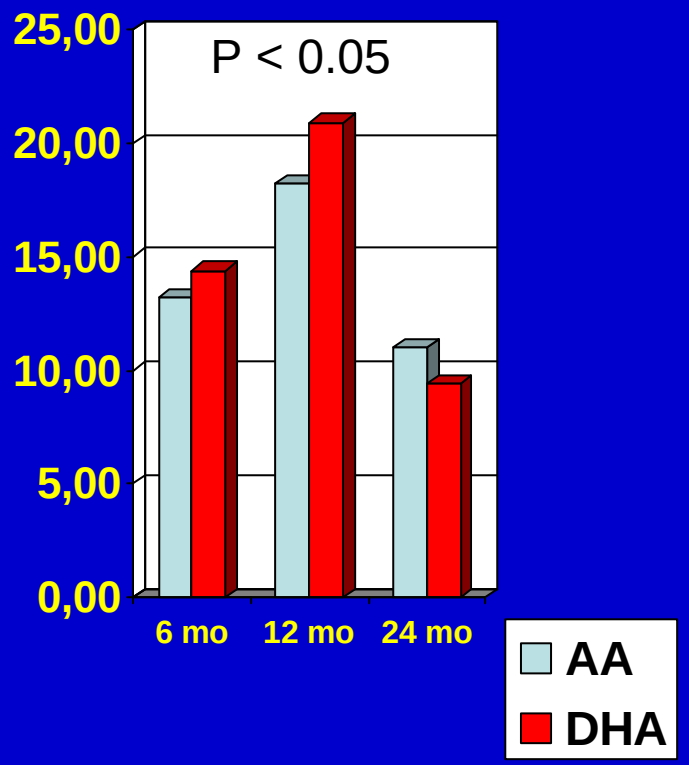
- Six women and six men
- 700 mg [U-^{13}C] alpha-linolenic acid
- blood samples collected 24, 48 and 72 hours and 1, 2 and 3 weeks
- data shown from day 21



Burdge et al, *Brit J Nutr* 88: 335-363 and 411-420, 2002

Percentage change in plasma cholesteryl ester fatty acids

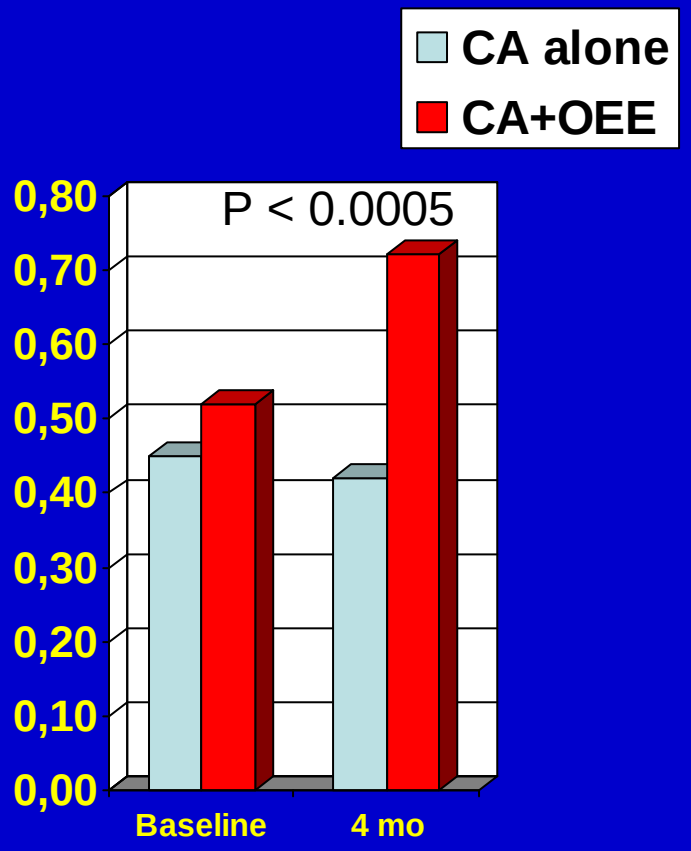
- Postmenopausal women (n = 24)
- treated with 0.625 mg conjugated equine estrogens combined with 2.5 mg medroxyprogesterone acetate



Giltay et al, *J Endocrinol* 182: 399-408 2004

Plasma cholesteryl ester DHA

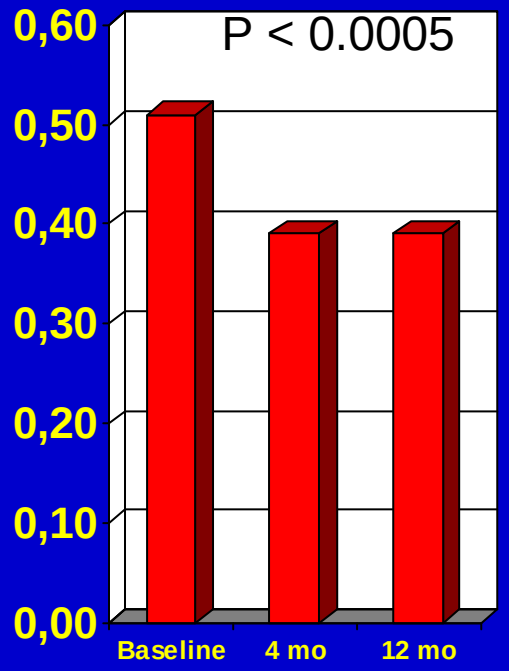
- Transsexual (M → F) subjects
- treated with cyproterone acetate (CA, n = 10)
- or CA + oral ethynil estradiol (CA + OEE, n = 15)



Giltay et al, *Am J Clin Nutr* 80: 1167-1174, 2004

Plasma cholesteryl ester DHA

- Transsexual (F → M) subjects
- treated with testosterone (n = 14)



Giltay et al, *Am J Clin Nutr* 80: 1167-1174, 2004

If there are gender differences, what might be the cause of the differences?

- The activity of the synthesis of LCPUFA from essential fatty acids appears to be higher in females than in males.
- Differences in sexual hormones may explain (at least in part) for the gender differences in LCPUFA status.

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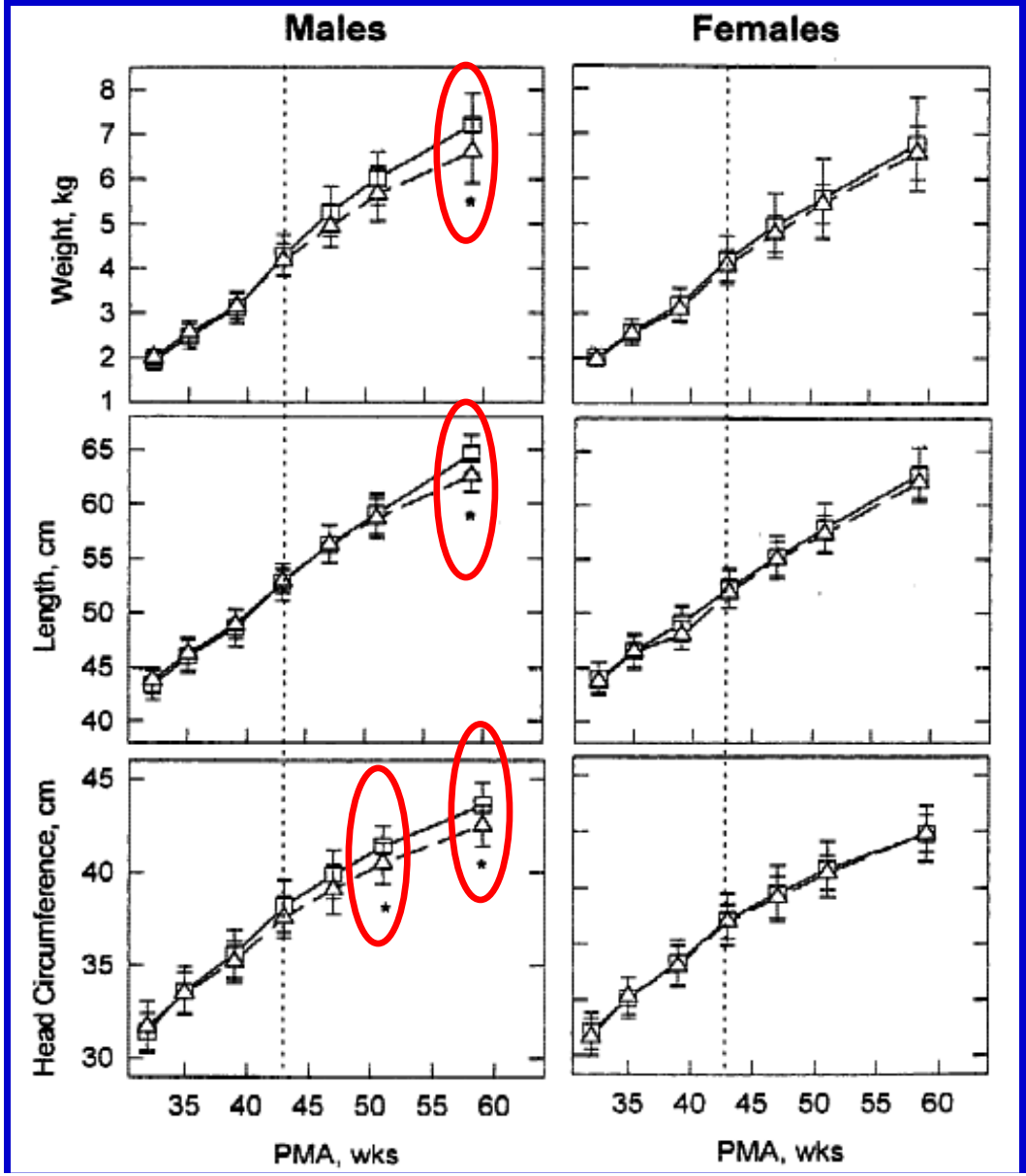
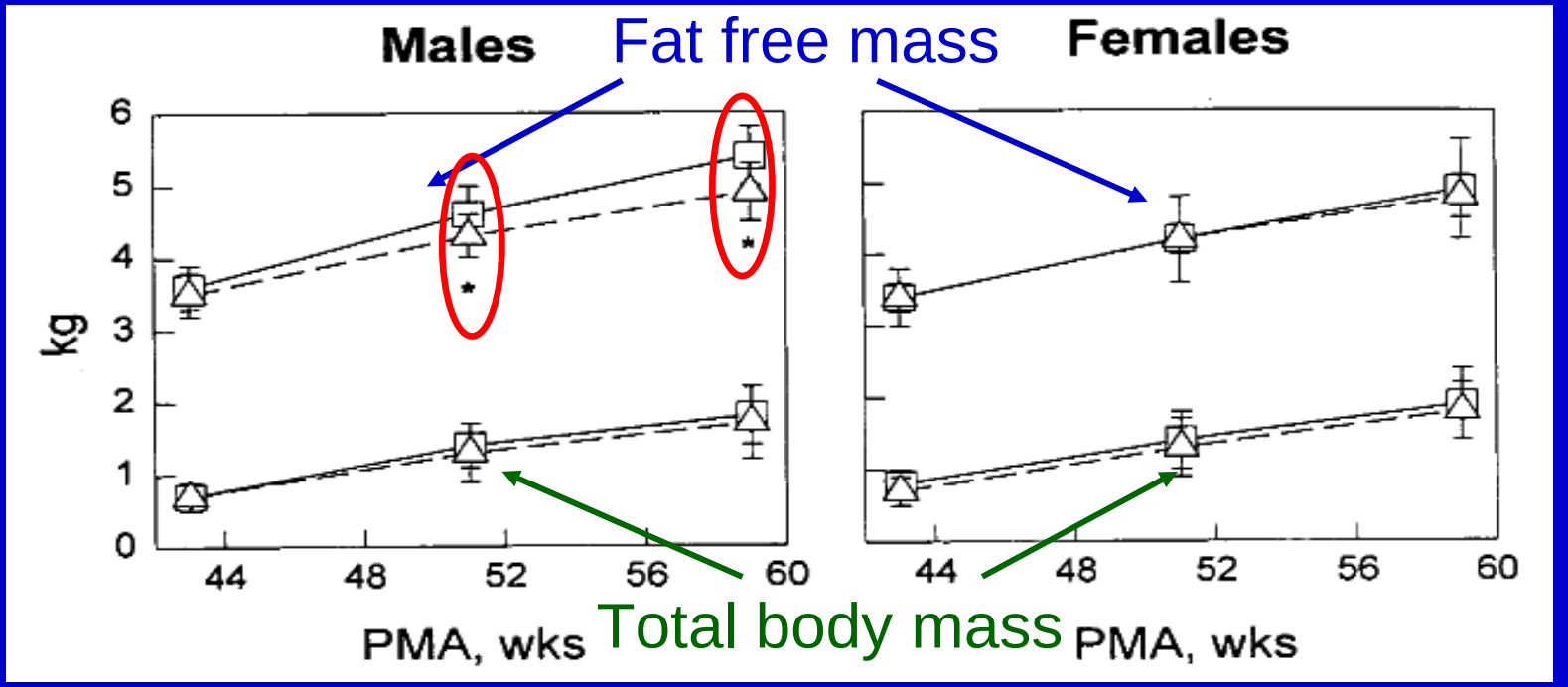
Effect of DHA-Containing Formula on Growth of PRETERM Infants to 59 Weeks Postmenstrual Age



- healthy, preterm infants
- fed formula with DHA (n = 31, Δ)
-or fed formula without DHA (n = 32, □)
- AA contents were identical in both formulae

Ryan et al: *Am J Hum Biol 11: 457-467,* **1999**

Effect of DHA-Containing Formula on Growth of PRETERM Infants to 59 Weeks Postmenstrual Age



Ryan et al: *Am J Hum Biol 11: 457-467,* **1999**

Ryan et al: *Am J Hum Biol 11: 457-467,* **1999**

Authors explanation for supplemented boys having lower growth, fat-free mass, EI :

i) possible gender specific differences in growth regulation,

ii) Testosterone + FSH (peak 6-12 weeks) mediated by eicosanoids derived from LCPUFAs may find males more sensitive.

RANDOMIZED, DOUBLE-BLIND TRIAL OF LONG-CHAIN POLYUNSATURATED FATTY ACID SUPPLEMENTATION WITH FISH OIL AND BORAGE OIL IN PRETERM INFANTS

- Preterm (<35 weeks, ≤ 2000 g birth weight) infants (n = 238) randomly assigned to unsupplemented or LCPUFA-supplemented formula to 9 months after term.
- The main outcome measure was the Bayley Mental and Psychomotor Indexes (MDI, PDI) at 18 months after term.
- Safety outcome measures were anthropometry (9 and 18 months), feed tolerance, infection, and clinical complication.

Fewtrell, Abbott, Kennedy et al, *J Pediatr* 144: 471-479, 2004

Gender differences in effect of LCPUFA supplementation in PRETERM infants

	Difference (95% CI)	Difference (95% CI)
	Overall (LCP: 122, control: 116)	Boys (LCP: 62, control: 55)
Weight at 9 mo (kg)	0.26 (-0.15 to 0.58)	0.50* (0.08 to 0.93)
Bayley MDI at 18 months	1.5 (-2.8 to 5.7)	5.7* (0.3 to 11.1)

Fewtrell, Abbott, Kennedy et al, *J Pediatr* 144: 471-479, 2004

Fewtrell, Abbott, Kennedy et al,
J Pediatr 144: 471-479, 2004

Authors explanation for the difference in neurodevelopment:

Boys (preterm) had previously shown to be neurologically more sensitive to sup-optimal nutrition *(Lucas et al, BMJ, 1998).*

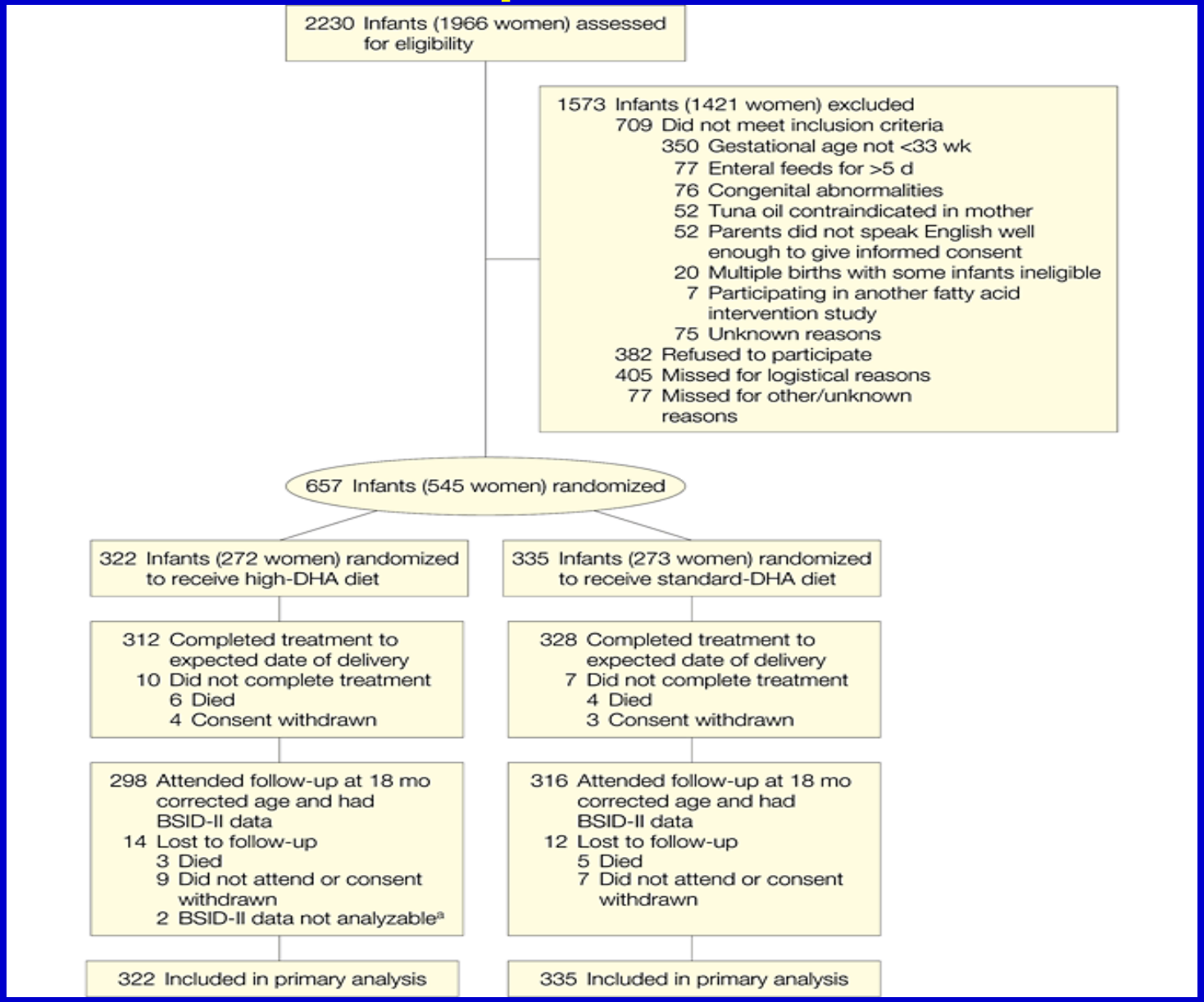
Neurodevelopmental Outcomes of PRETERM Infants Fed High-Dose Docosahexaenoic Acid

A Randomized Controlled Trial

- **Design, Setting, and Participants** Randomized, double-blind controlled trial enrolling infants born at less than 33 weeks' gestation.
- **Intervention** High-DHA (approximately 1% total fatty acids) enteral feeds compared with standard DHA (approximately 0.3% total fatty acids) from day 2 to 4 of life until term corrected age.
- **Main Outcome Measures** Bayley Mental Development Index (MDI) at 18 months' corrected age.

Makrides et al, *JAMA* 301: 175-182, 2009

Participant flow



Makrides et al, *JAMA* 301: 175-182, 2009

Table 2. Outcomes on Bayley Scales of Infant Development, Second Edition

Outcomes	High-/Standard-DHA Diet, No.	Mean Scores (SD)		Unadjusted Mean Difference in Scores (95% CI)	Unadjusted *P* Value	Adjusted Mean Difference in Scores (95% CI)[a]	Adjusted *P* Value
		High-DHA Diet	Standard-DHA Diet				
Mental Development Index (MDI)							
Standardized score	322/335	94.9 (14.5)	93.0 (17.3)	1.9 (−1.0 to 4.7)	.20	1.6 (−1.2 to 4.3)	.26
Birth weight <1250 g[b]	147/149	94.8 (15.6)	90.0 (18.4)	4.7 (0.2 to 9.2)	.04	3.8 (−0.5 to 8.0)	.08
Birth weight ≥1250 g[b]	175/186	95.1 (13.4)	95.5 (16.1)	−0.4 (−3.7 to 2.9)	.81	−0.40 (−3.7 to 3.0)	.83
Girls[c]	149/153	99.1 (13.9)	94.4 (17.5)	4.7 (0.5 to 8.8)	.03	4.5 (0.5 to 8.5)	.03
Boys[c]	173/182	91.3 (14.0)	91.9 (17.2)	−0.6 (−4.3 to 3.1)	.76	−1.0 (−4.5 to 2.6)	.60
Psychomotor Development Index (PDI)							
Standardized score	322/335	93.1 (16.1)	92.1 (16.3)	0.9 (−1.8 to 3.6)	.50	0.9 (−1.8 to 3.6)	.51
Birth weight <1250 g[d]	147/149	91.2 (16.8)	89.6 (17.8)	1.6 (−2.7 to 5.9)	.47	0.9 (−3.3 to 5.1)	.67
Birth weight ≥1250 g[d]	175/186	94.7 (15.2)	94.2 (14.8)	0.5 (−2.9 to 3.8)	.78	0.5 (−2.9 to 3.8)	.78
Girls[e]	149/153	94.5 (16.3)	93.9 (16.0)	0.6 (−3.4 to 4.5)	.78	0.5 (−3.4 to 4.4)	.80
Boys[e]	173/182	91.8 (15.8)	90.6 (16.5)	1.2 (−2.6 to 5.0)	.53	1.2 (−2.4 to 4.9)	.51

Abbreviations: CI, confidence interval; DHA, docosahexaenoic acid.
[a]Adjusted for gestational age at delivery, sex, maternal education, and birth order. Further adjustment for pilot phase vs multicenter phase did not alter results.
[b]For MDI × birth weight interaction, *P*=.05 unadjusted, *P*=.07 adjusted.
[c]For MDI × sex interaction, *P*=.06 unadjusted, *P*=.04 adjusted.
[d]For PDI × birth weight interaction, *P*=.68 unadjusted, *P*=.87 adjusted.
[e]For PDI × sex interaction, *P*=.82 unadjusted, *P*=.78 adjusted.

Makrides et al, *JAMA* 301: 175-182, 2009

Table 3. Mild and Significant Developmental Delay Derived From BSID-II MDI Outcomes

Outcomes	High-/ Standard-DHA Diet, No.	No. (%) of Infants		Unadjusted Relative Risk (95% CI)	Unadjusted *P* Value	Adjusted Relative Risk (95% CI)[a]	Adjusted *P* Value
		High-DHA Diet	Standard-DHA Diet				
All infants							
Mild mental delay (MDI <85)	322/335	64 (19.8)	90 (27.0)	0.73 (0.53-1.01)	.06	0.75 (0.55-1.04)	.08
Significant mental delay (MDI <70)	322/335	17 (5.2)	35 (10.5)	0.49 (0.26-0.97)	.03	0.50 (0.26-0.93)	.03
Birth weight <1250 g							
Mild mental delay (MDI <85)[b]	147/149	27 (18.1)	49 (33.0)	0.55 (0.34-0.87)	.01	0.57 (0.36-0.91)	.02
Significant mental delay (MDI <70)[c]	147/149	11 (7.2)	19 (12.9)	0.56 (0.24-1.28)	.17	0.58 (0.26-1.38)	.17
Birth weight ≥1250 g							
Mild mental delay (MDI <85)[b]	175/186	37 (21.3)	41 (22.1)	0.96 (0.62-1.49)	.86	0.96 (0.62-1.49)	.87
Significant mental delay (MDI <70)[c]	175/186	6 (3.4)	16 (8.6)	0.39 (0.15-1.03)	.06	0.36 (0.14-0.95)	.04
Girls							
Mild mental delay (MDI <85)[d]	149/153	16 (11.0)	40 (26.0)	0.42 (0.22-0.80)	.01	0.43 (0.23-0.80)	.01
Significant mental delay (MDI <70)[e]	149/153	3 (1.9)	16 (10.2)	0.18 (0.04-0.74)	.02	0.17 (0.04-0.72)	.02
Boys							
Mild mental delay (MDI <85)[d]	173/182	47 (27.4)	51 (27.8)	0.98 (0.68-1.44)	.94	1.01 (0.70-1.47)	.94
Significant mental delay (MDI <70)[e]	173/182	14 (8.0)	20 (10.7)	0.74 (0.35-1.56)	.43	0.76 (0.37-1.60)	.47

Abbreviations: BSID-II, Bayley Scales of Infant Development, Second Edition; CI, confidence interval; DHA, docosahexaenoic acid; MDI, Mental Development Index.
[a] Adjusted for gestational age at delivery, sex, maternal education, and birth order. Further adjustment for pilot phase vs multicenter phase did not alter results.
[b] For mild mental delay × birth weight interaction, $P = .04$ unadjusted, $P = .07$ adjusted.
[c] For significant mental delay × birth weight interaction, $P = .59$ unadjusted, $P = .46$ adjusted.
[d] For mild mental delay × sex interaction, $P = .02$ unadjusted, $P = .02$ adjusted.
[e] For significant mental delay × sex interaction, $P = .09$ unadjusted, $P = .08$ adjusted.

Makrides et al, *JAMA* 301: 175-182, 2009

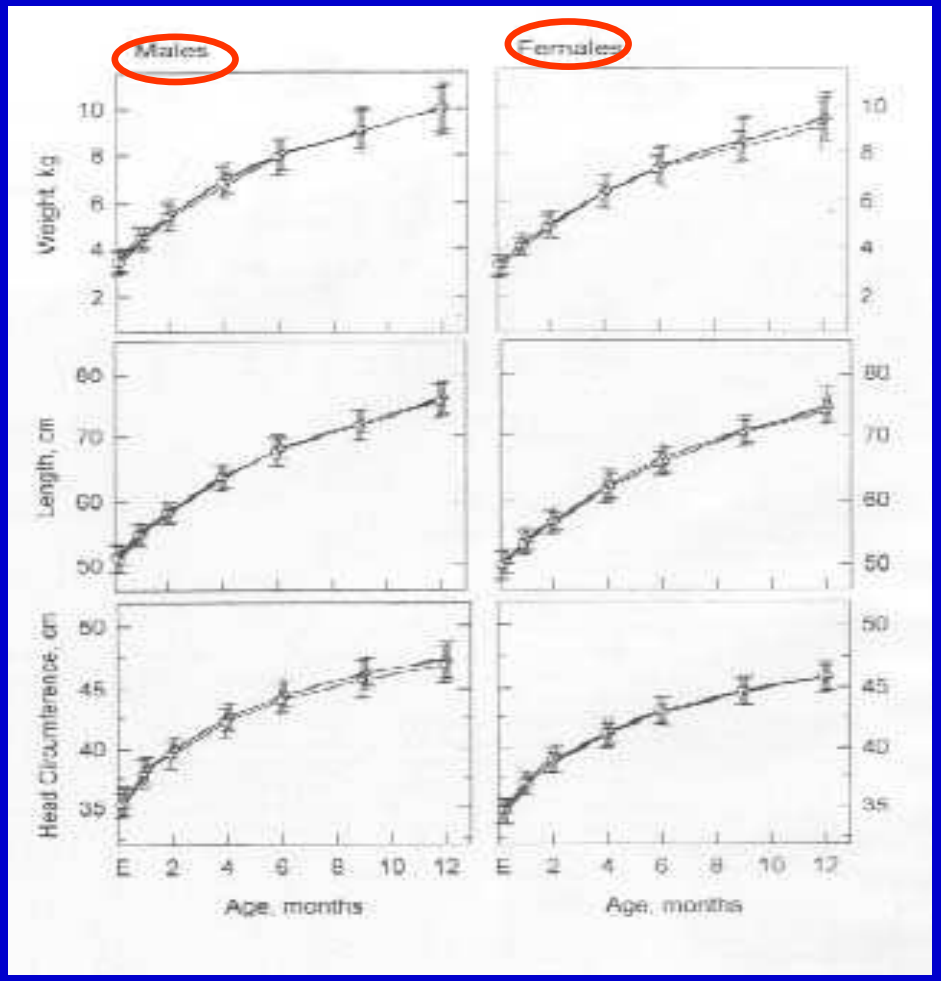
Makrides et al, *JAMA* 301: 175-182, 2009

Authors' explanation, comments on supplemented girls improved MDI at 18 months:

Girls may have a higher rates of endogenous DHA synthesis from α-linolenic acid to DHA, the supplementation may have met the girls requirements but boys may require yet higher intakes due to lower endogenous conversion.

Weight, length, and head circumference in healthy TERM infants fed formulas with or without AA+DHA

- Term infants were fed formulas with or without AA+DHA for 1 year (*N* = 239).
- Infants in the formula groups were randomized at 9 days of age to a control formula with no AA or DHA (*n* = 77) or 1 of 2 otherwise identical formulas containing AA+DHA (AA, 0.46% and DHA, 0.14% of total fatty acids).



Auestad et al, *Pediatrics* 108: 372-381, 2001

Maternal Fish Oil Supplementation during Lactation May Adversely Affect Long-Term Blood Pressure, Energy Intake, and Physical Activity of 7-Year-Old Boys

- Danish mothers (n = 122) were randomized to fish oil [FO, 1.5 g/d (n-3) LCPUFA],
- or olive oil (OO) supplementations during the first 4 month of lactation.
- Ninety-eight children were followed-up with blood pressure and anthropometry measurements at 7 years.

Asserhøj et al, *J Nutr* 139: 298-304, 2009

Mean arterial pressure

	Fish oil	Olive oil	Difference
All (mm Hg)	78.4 (5.4)	75.6 (5.0)	2.8 (1.3)*
Girls (mm Hg)	78.9 (6.1)	77.9 (3.7)	1.0 (1.7)
Boys (mm Hg)	78.1 (5.1)	72.4 (4.8)	5.6 (1.8)**

Mean (SD), * = P < 0.05, ** = P < 0.01; Asserhøj et al, *J Nutr* 139: 298-304, 2009

Asserhøj et al, *J Nutr* 139: 298-304, 2009

Authors' explanation as to why fish oil supplemented boys had higher blood pressure at 7 years:

i) Adverse effects of fish oil could be, at least in theory, due to toxic oxidation products.

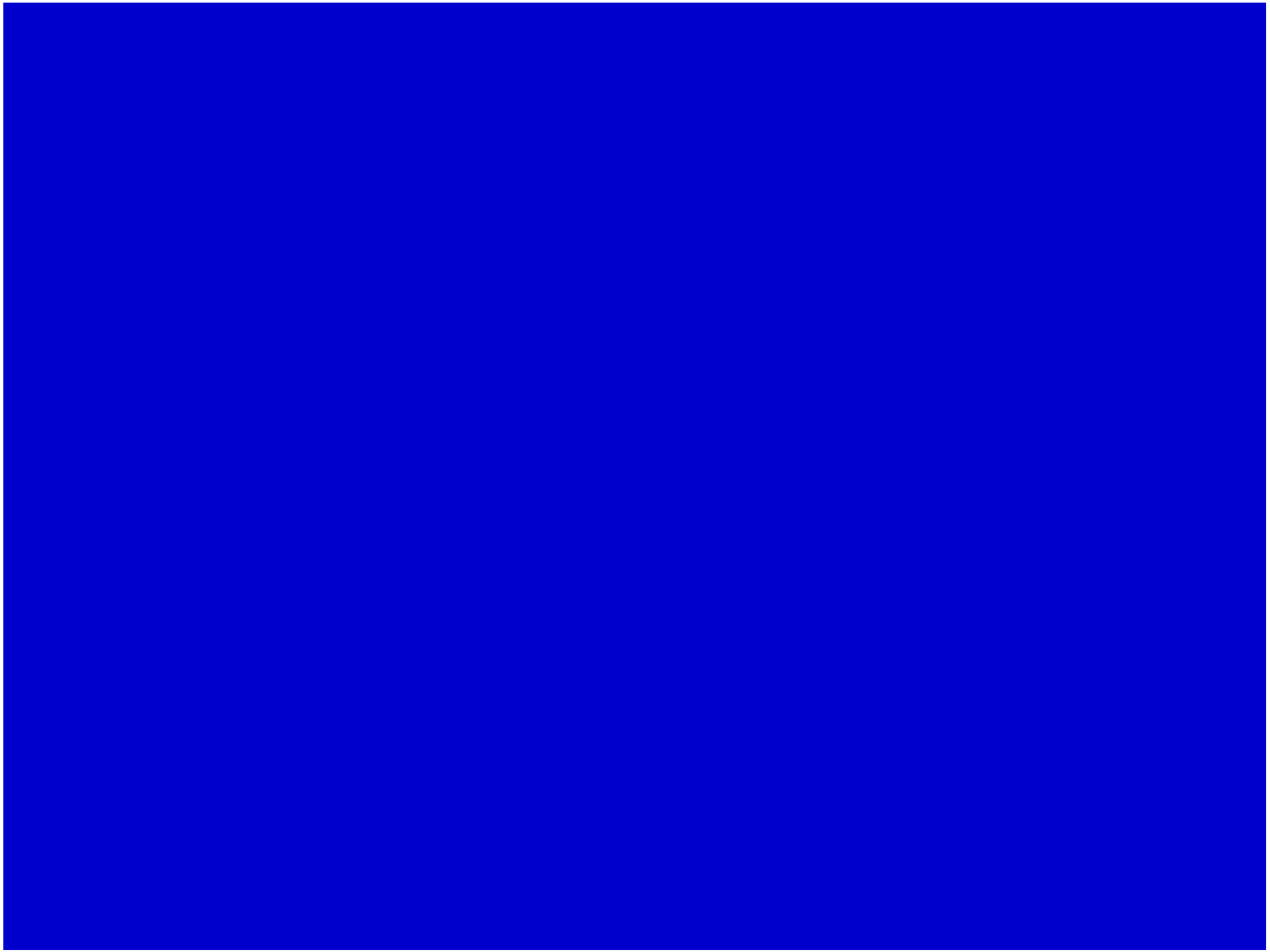
ii) Boys having a more unhealthy lifestyle compared to girls.

If there are gender differences, might they influence results obtained in paediatric nutrition trials?

- There are (at least) three studies in preterm infants and two studies in term infants indicating gender specific differences in some study outcome parameters.

Conclusions

- It is certainly useful to evaluate data obtained in neonatal feeding trials also according to gender.
- It may be useful to consider gender at sample size calculations for neonatal feeding trials.



Factors to consider for interpretation and the future

1. Source of supplement – background factors, toxic effects…

2. Concentration + ratio of LCPUFAs – mimic levels seen in breast milk – *from which population*? n-3 LCPUFAs highly variable...

3. LCPUFAs are highly bio-active molecules effecting aspects of health, some outcomes more likely to show differences between genders…