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DHA, an essential fatty acid required for neurodevelopment, metabolism in healthy pregnancy and preeclampsia

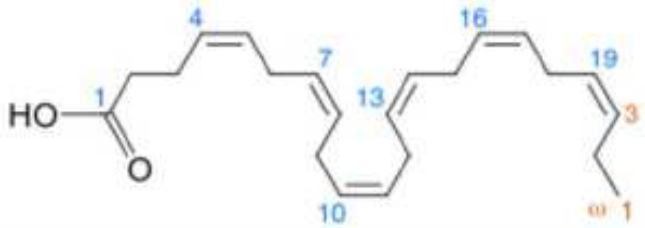
Dilys J Freeman
Institute for Cardiovascular and Medical Sciences
University of Glasgow

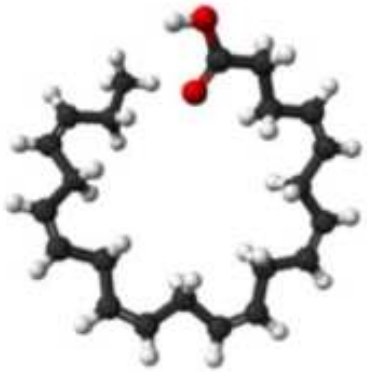
A long chain polyunsaturated fatty acid (LC PUFA) 22:6n-3

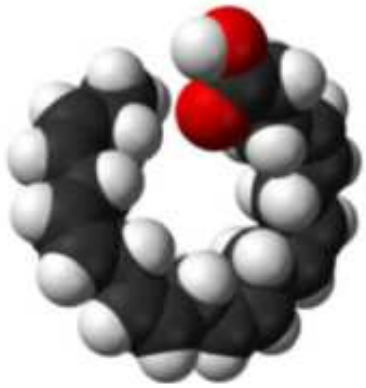
Docosahexaenoic acid

From Wikipedia, the free encyclopedia

Docosahexaenoic acid

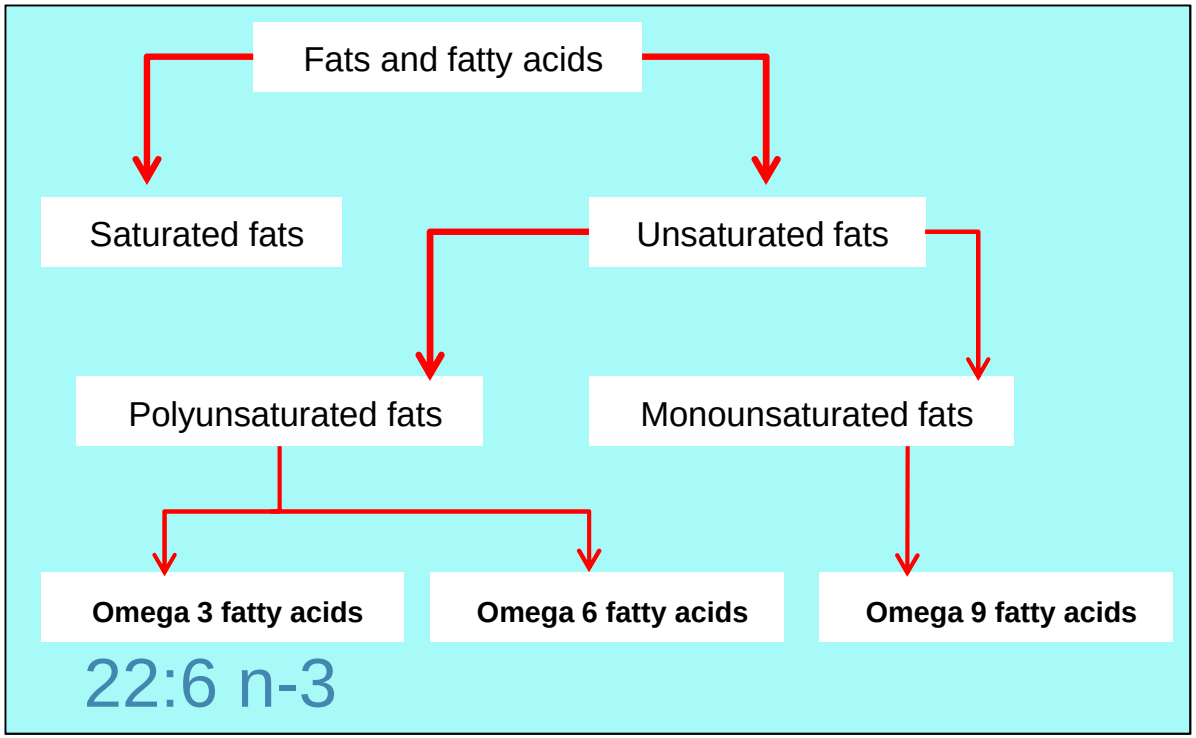




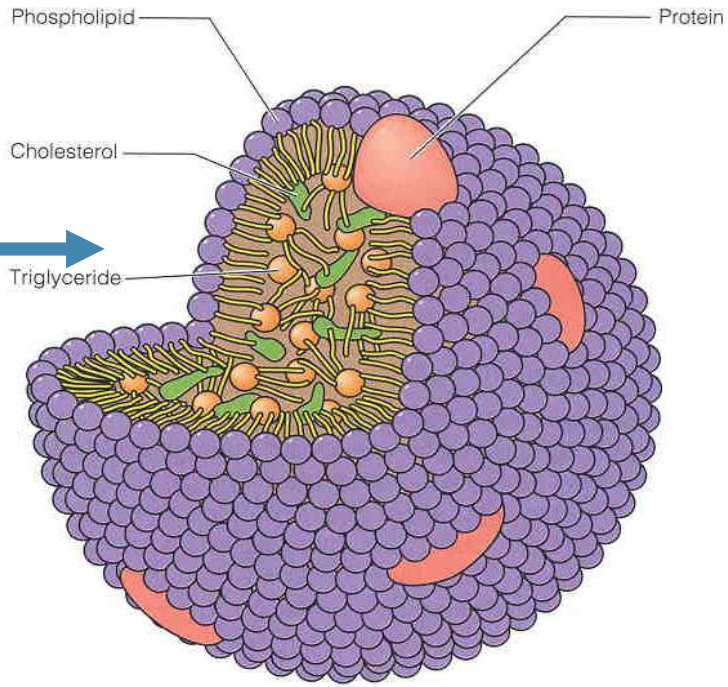


A bit of background

3 x NEFA + glycerol = TG



TG carried in lipoprotein core

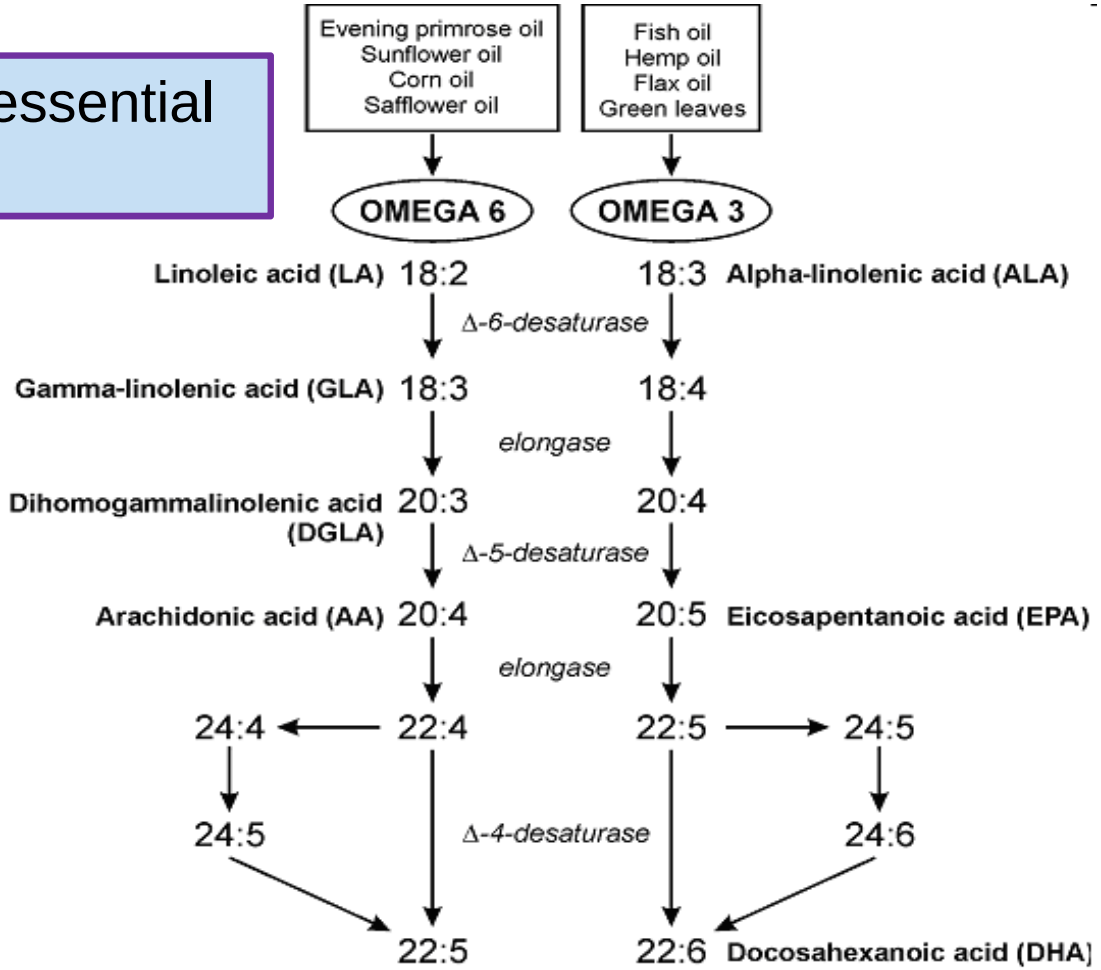


The main lipoprotein carrier of TG is very low density lipoprotein (VLDL)

Din et al BMJ 2004: 328; 30-5

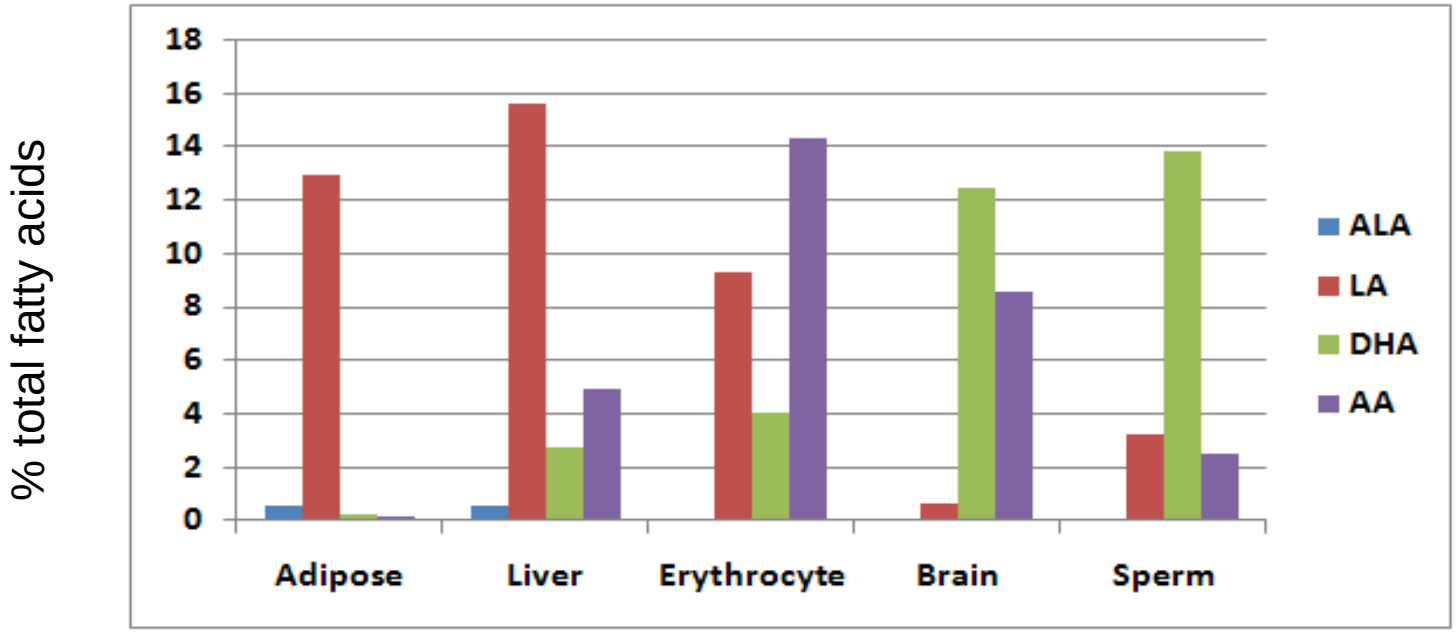
PUFA synthetic pathways

LA and ALA are essential fatty acids



LC-PUFA , especially DHA, are known to very important for neural development

DHA content of tissues



Courtesy of Barbara Meyer, University of Wollongong

DHA increases membrane fluidity

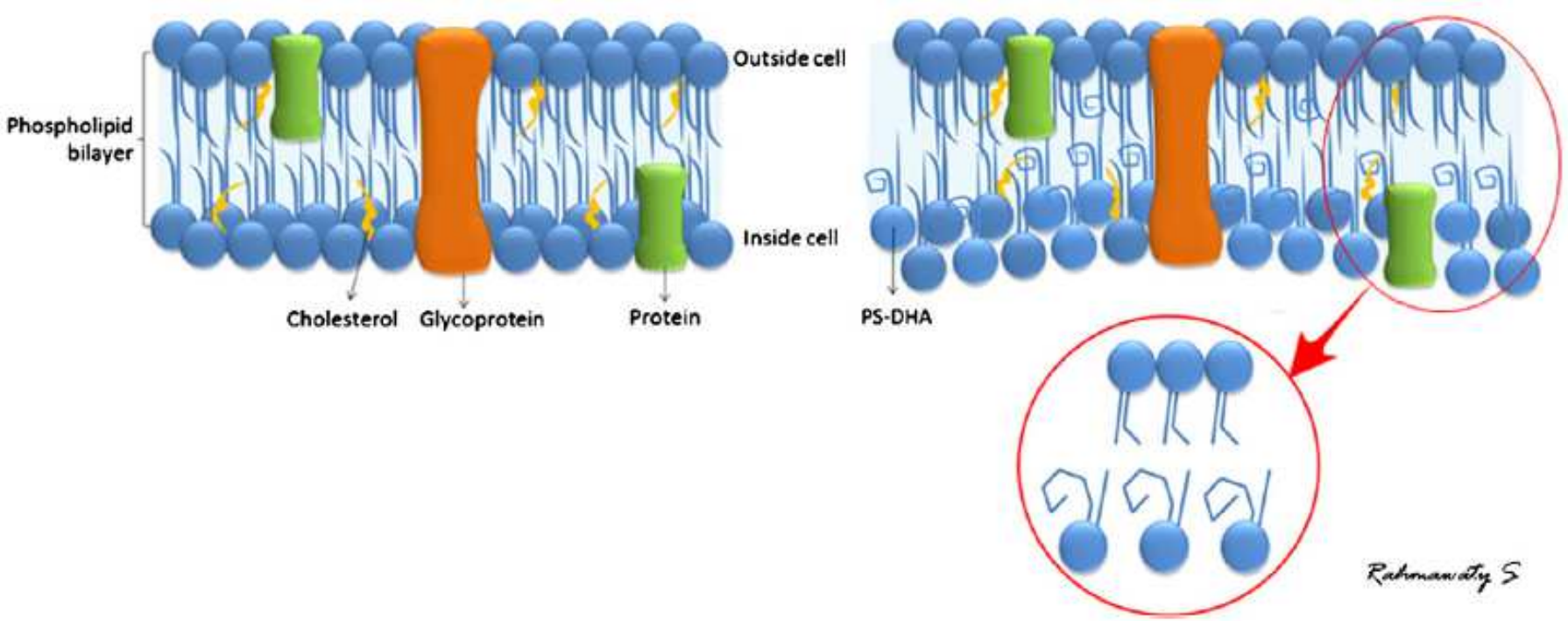


Diagram 3. Phospholipid bilayer DHA.

Parletta et al J Nutr Biochem 2013

DHA increases neurone survival

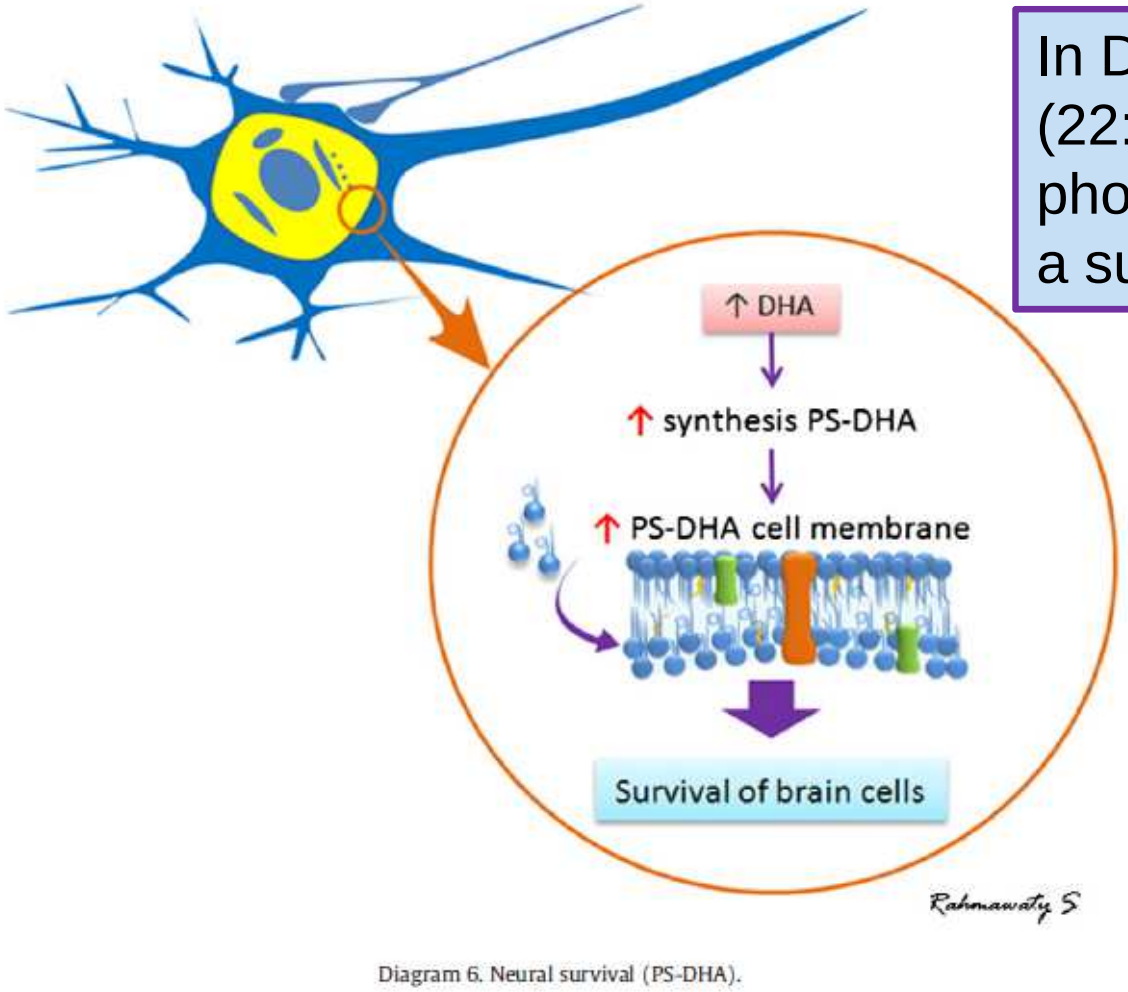


Diagram 6. Neural survival (PS-DHA).

In DHA deficiency, omega-6 DPA (22:5n-6) used in place of DHA in brain phosphatidyl serine and is thought to be a survival mechanism

Akbar PNAS 2005, Kim JBC 2007, Kim JBC 2000; Parletta et al J Nutr Biochem 2013

DHA required for neurite outgrowth

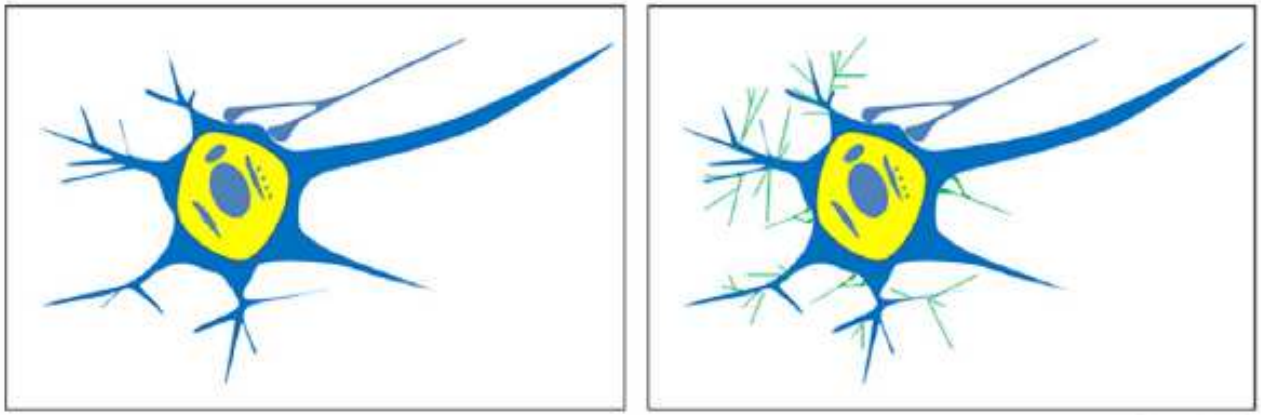


Diagram 2. The effect of DHA on neurite growth.

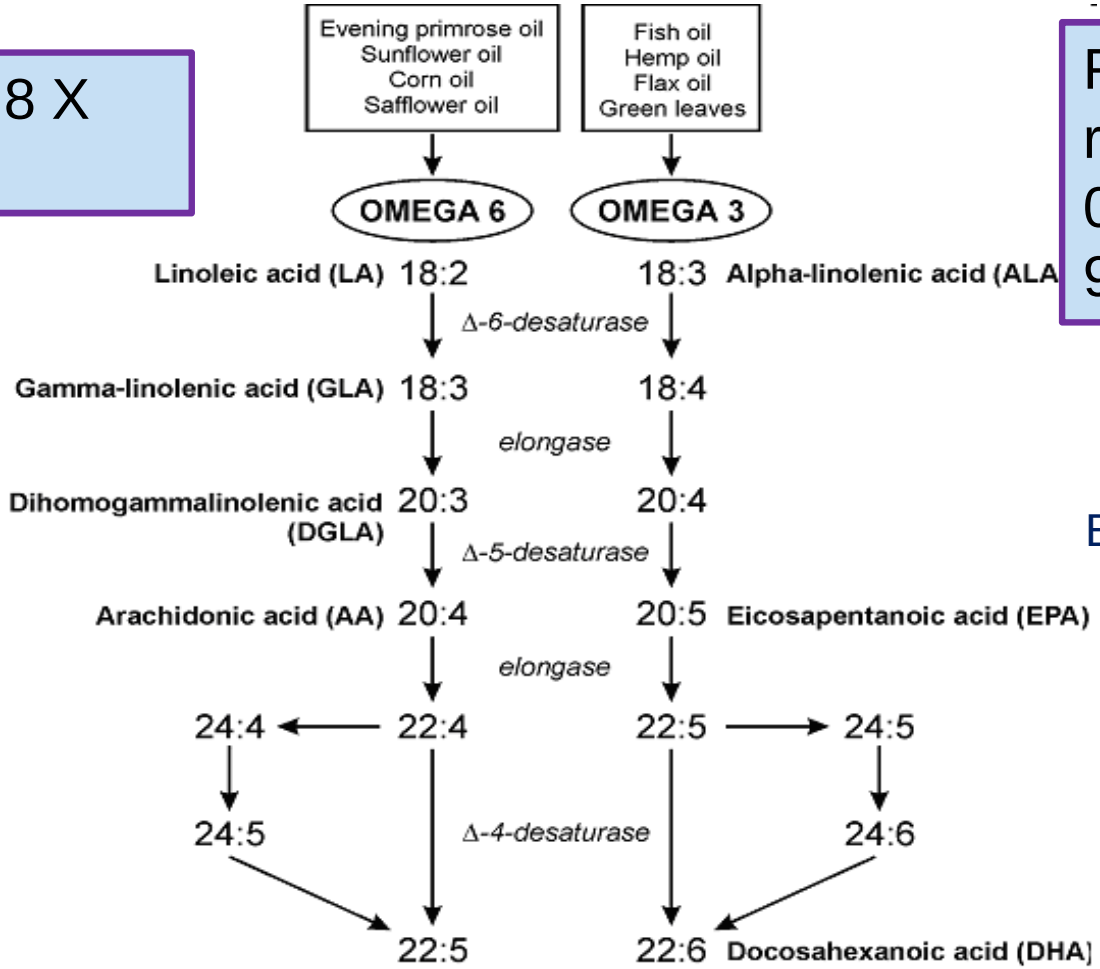
DHA interaction with the plasma membrane protein syntaxin 3 required for the membrane fusion necessary for neurite outgrowth in developing neurones

Darios et al Nature 2006

Parletta et al J Nutr Biochem 2013

Humans are not great at making DHA

Dietary LA intake is 8 X ALA intake



Fractional conversion rates of ALA to DHA
0.04% in men
9% in women

Burdge et al Br J Nutr 2002

The critical requirement of DHA for fetal brain development, and the poor efficiency of its synthesis in humans, is therefore a metabolic problem to be overcome in pregnancy!

Fetal plasma is enriched in DHA

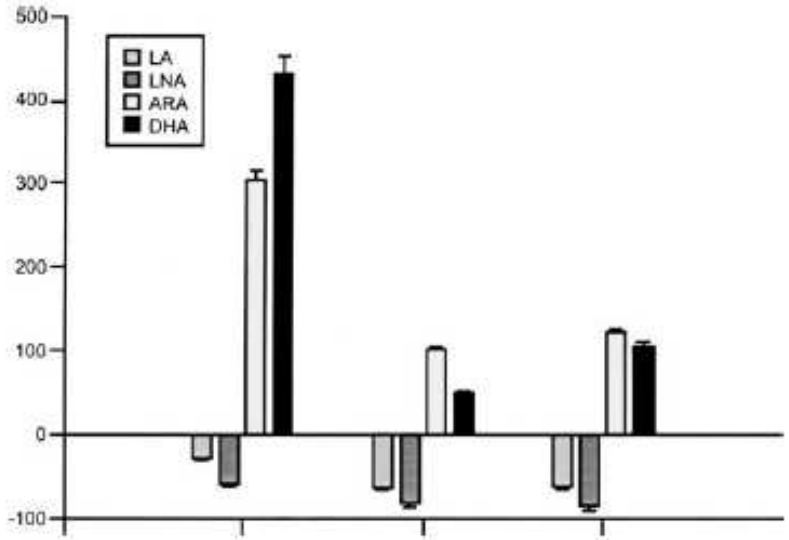


Fig 2. Fatty acid enrichment in fetal compared with maternal plasma. Relative enrichment of LA, LNA, ARA, and DHA in fetal compared with maternal plasma was calculated for each mother-fetal cord plasma pair as the difference in the given fatty acid in the maternal compared to fetal plasma/maternal plasma × 100%. Values shown are mean ± SEM, n = 55. Adapted from data published in Reference 89.

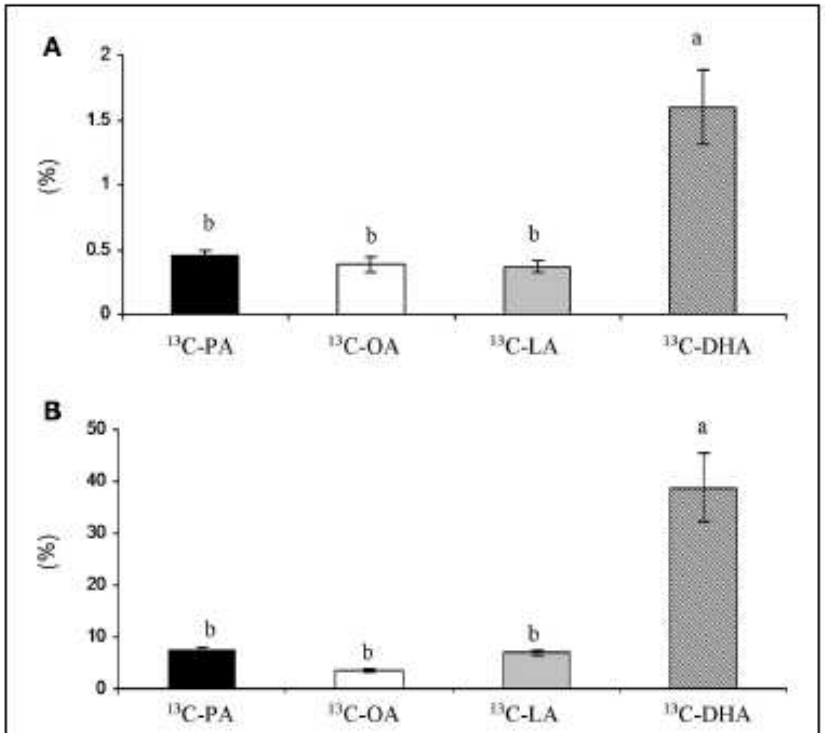


FIGURE 1 | (A) Ratio (%) between placenta and maternal plasma AUC concentration of ^{13}C-fatty acids administered 4 or 12 h before cesarean section. **(B)** Ratio (%) between cord plasma and maternal plasma AUC concentration of ^{13}C-fatty acids administered 4 or 12 h before cesarean section. Results are expressed as $\bar{x} \pm$ SEM. *T*-test, $^{*}P < 0.05$.

Innis J Pediatr 2003,
original data Elias and Innis AJCN 2001

Gil-Sanchez et al Front Genet 2011:2;1

Placenta preferentially transports DHA

LA , ALA

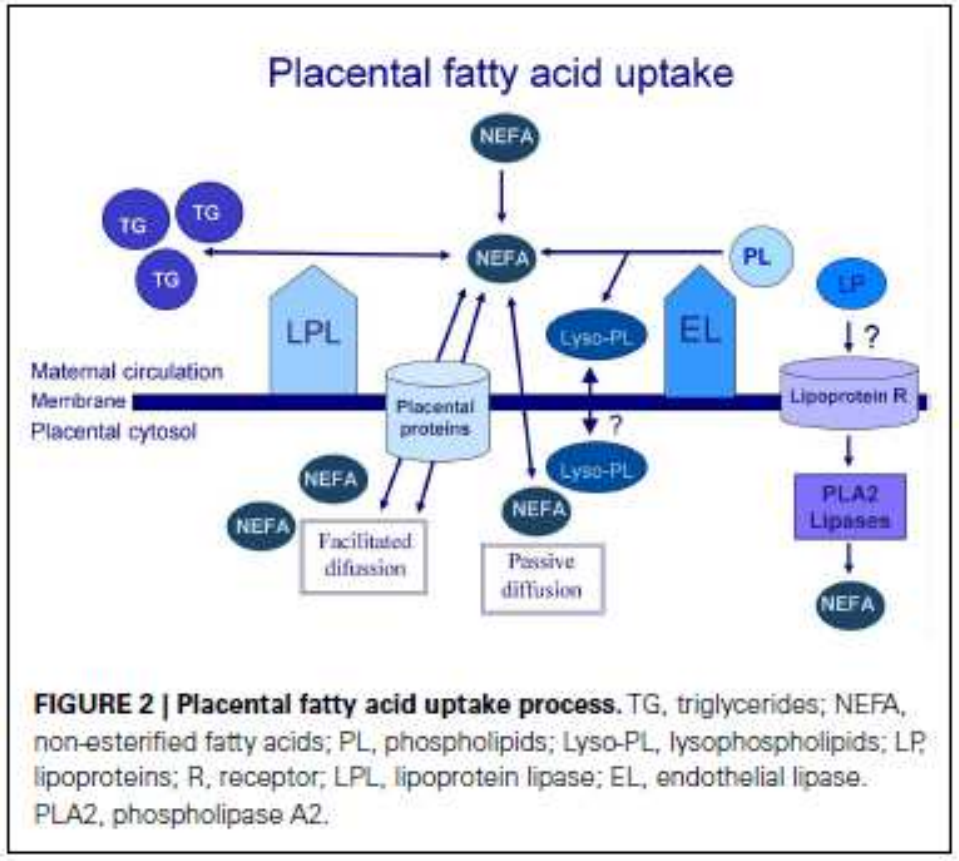


FIGURE 2 | Placental fatty acid uptake process. TG, triglycerides; NEFA, non-esterified fatty acids; PL, phospholipids; Lyso-PL, lysophospholipids; LP, lipoproteins; R, receptor; LPL, lipoprotein lipase; EL, endothelial lipase. PLA2, phospholipase A2.

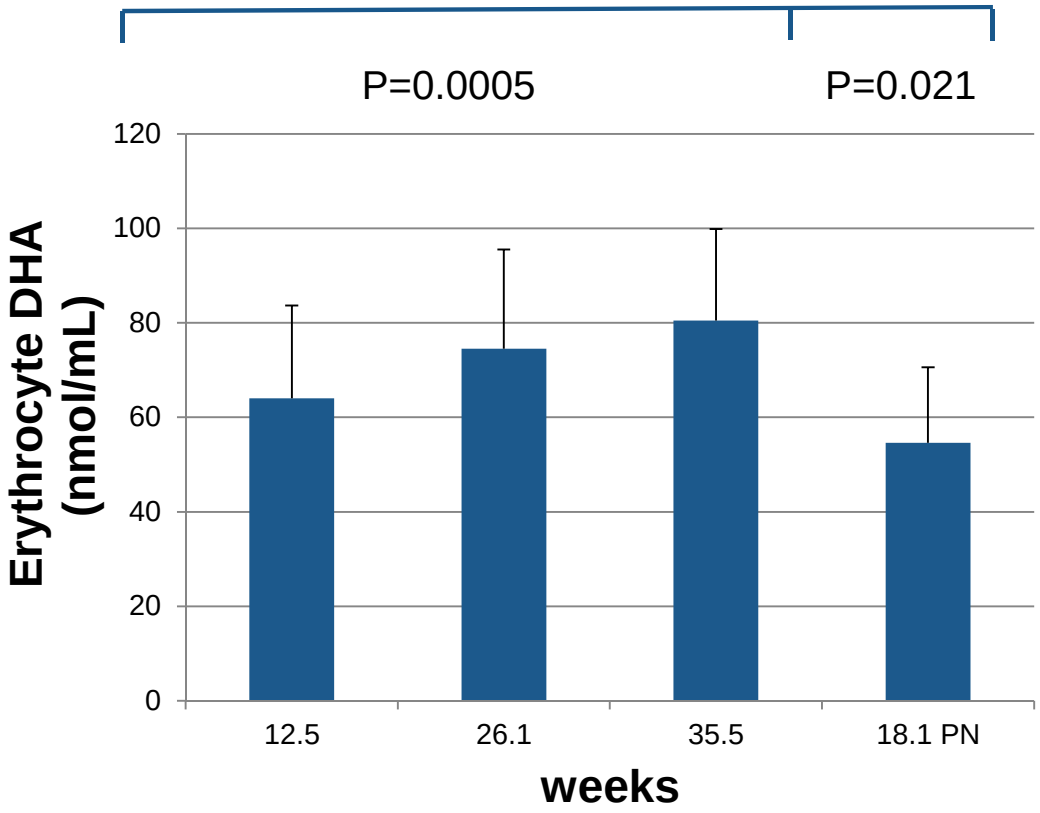
LA , ALA

DHA

DHA

Gil-Sanchez et al Front Genet 2011, Al et al Br J Nutr 1995, Montgomery et al Br J Nutr 2003

Maternal erythrocyte DHA concentration in pregnancy and post partum



18:2n-6 (LA) ↑ 12% T1 – T3

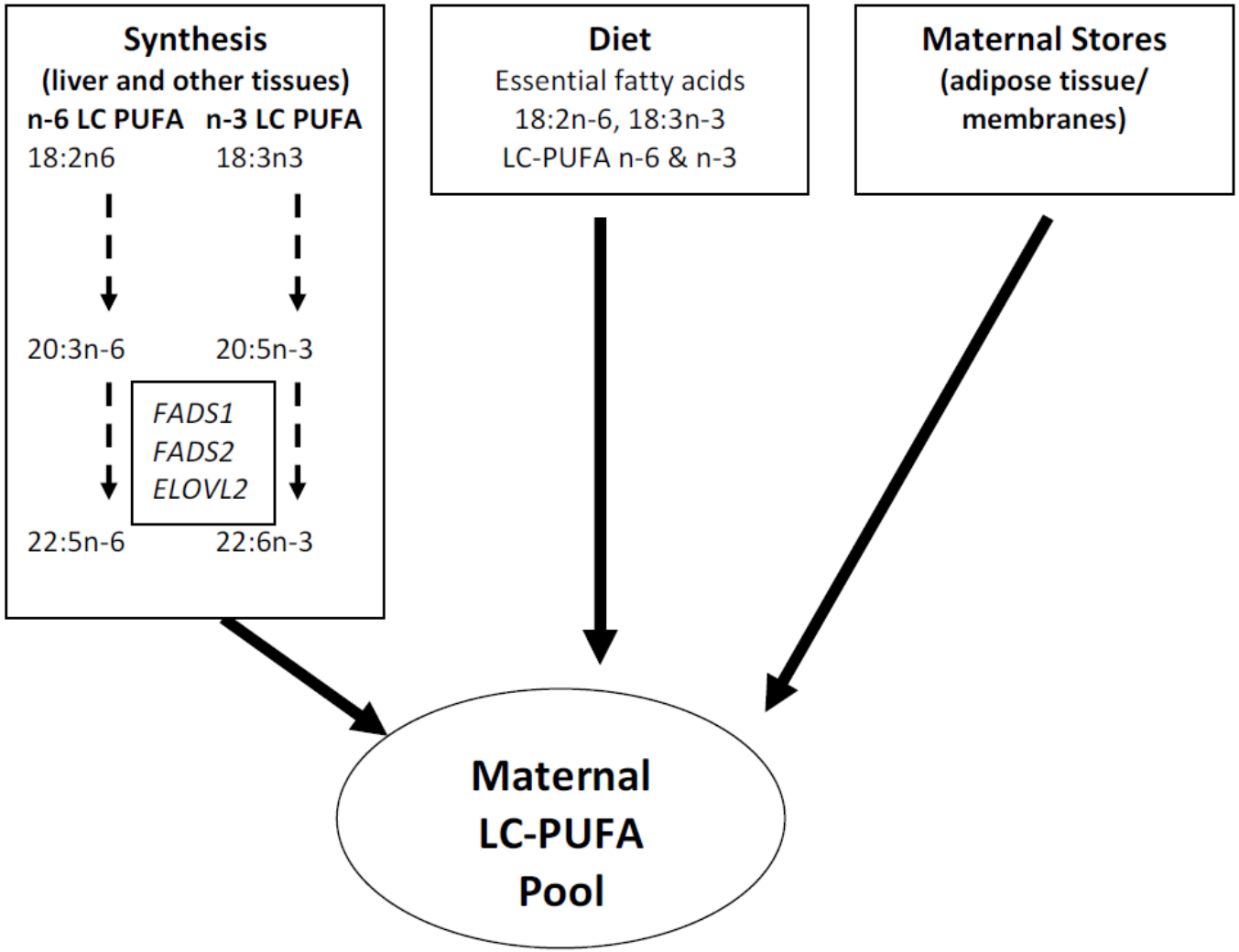
18:3n-3 (ALA) ↑ 68% T1 – T3

26% increase in erythrocyte DHA concentration from end of first to the end of the third trimester

First trimester DHA is 17% above post natal levels

Stewart et al Lipids 2007

Sources of maternal DHA



Adapted from Mackay et al Hypertension 2012

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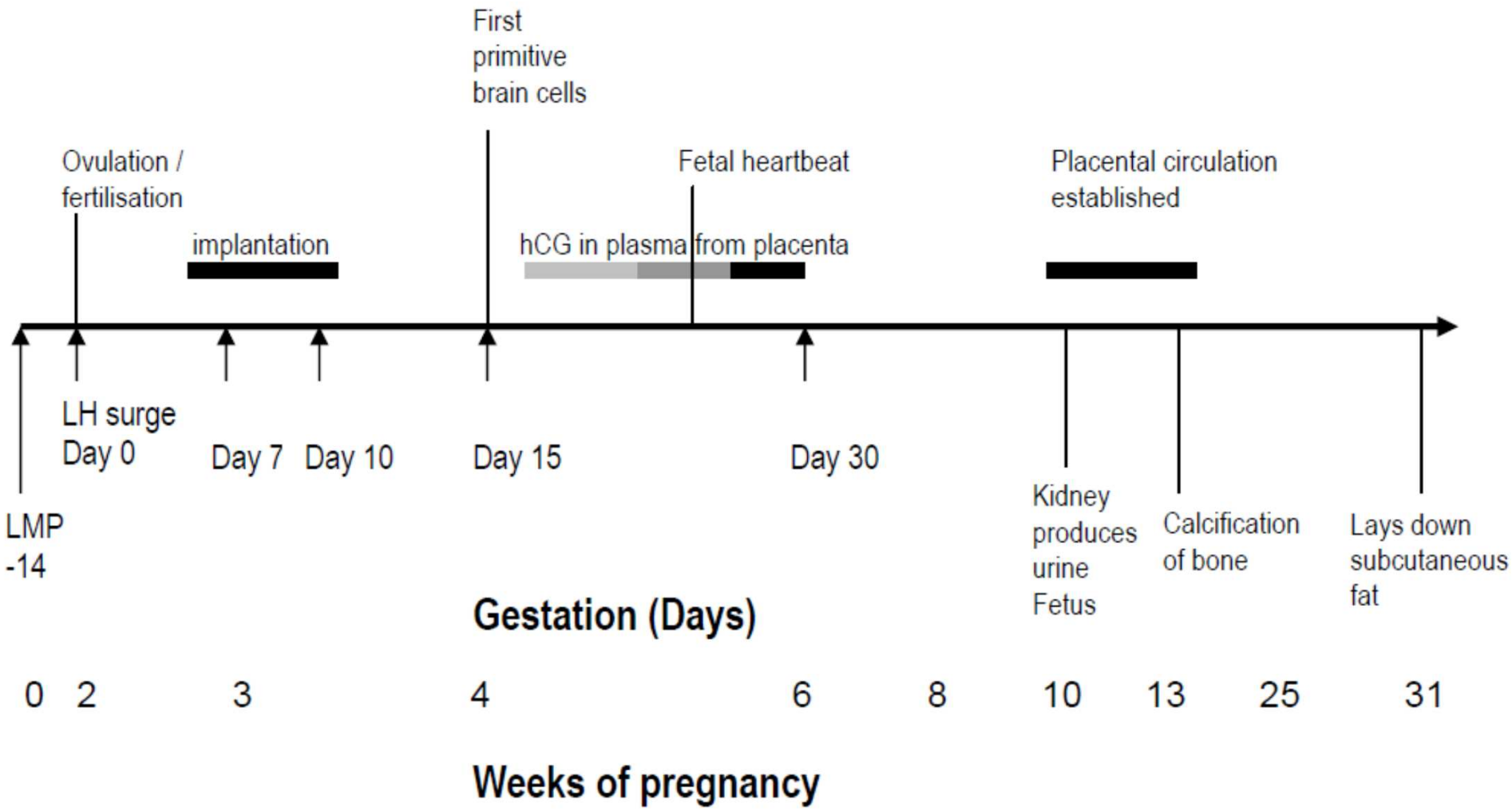
Timeline of pregnancy

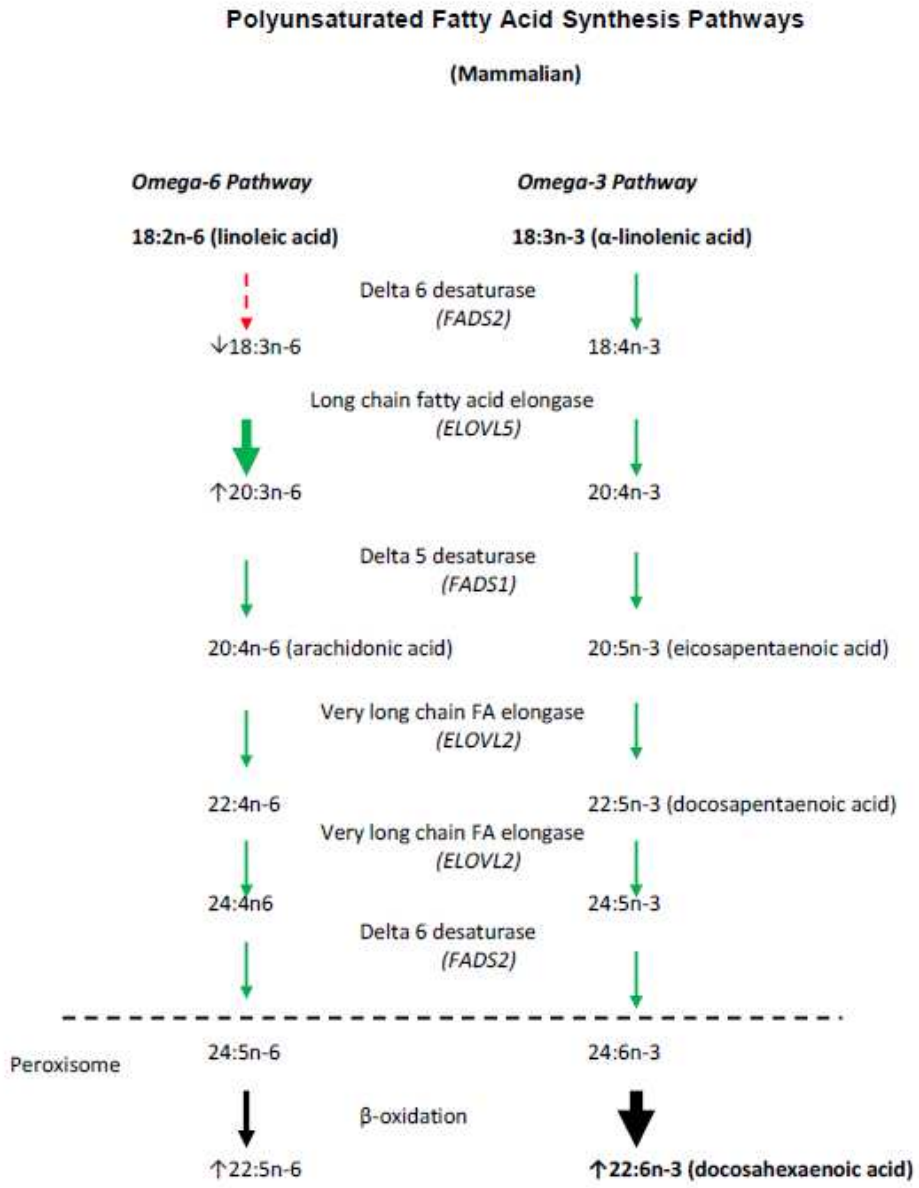


Rates of change of DHA concentration correlates with delta 6 desaturase activity

In rats, plasma and liver DHA levels and *FADS2* expression increased over gestation. *FADS2* expression correlated with oestradiol and progesterone.

Childs et al Prost Leuk Ess Fatty Acids 2012

LA concentrations are decreased, relieving inhibition on n-3 pathway?



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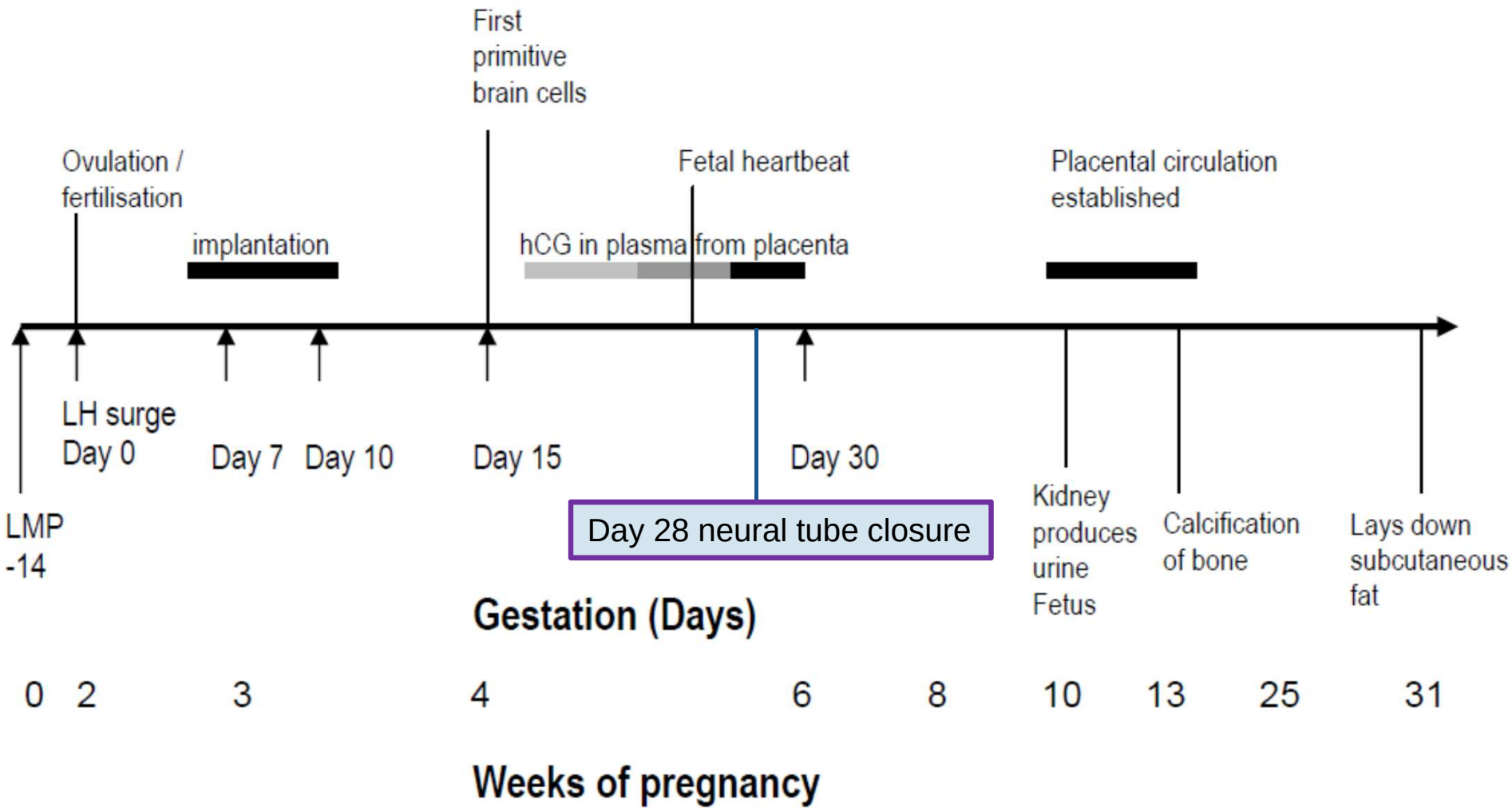
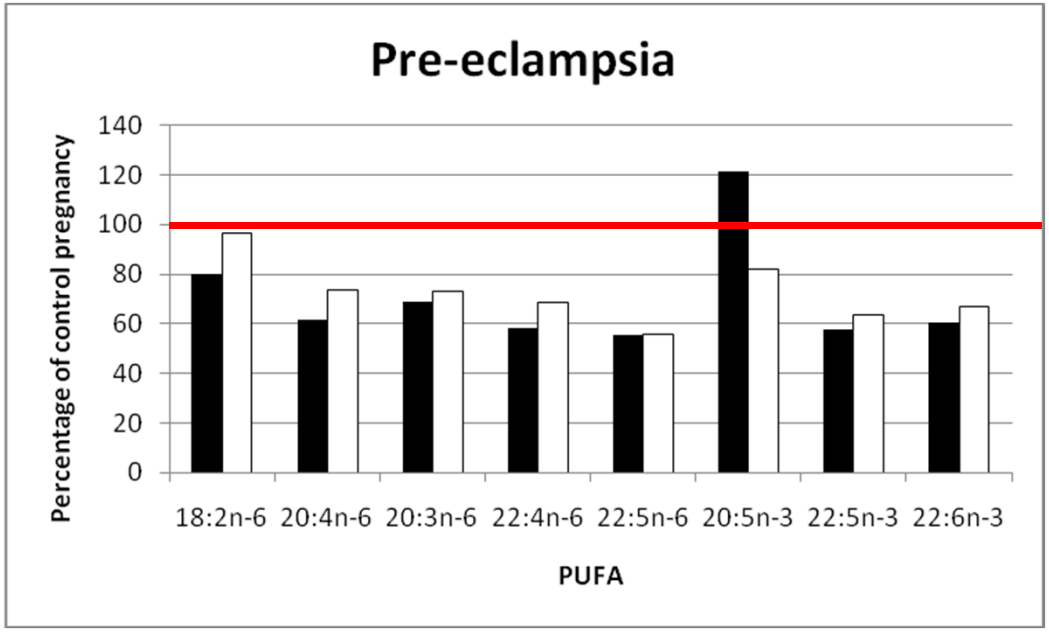
Timeline of pregnancy



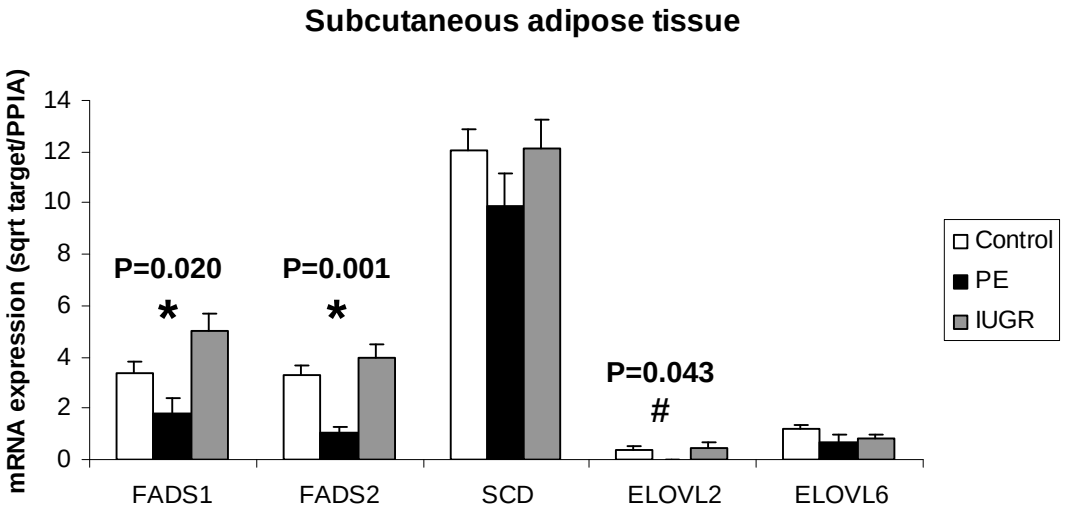
Reduced maternal and cord blood DHA in preeclampsia

Maternal and cord blood erythrocyte LC PUFA concentrations



■ Maternal □ Cord

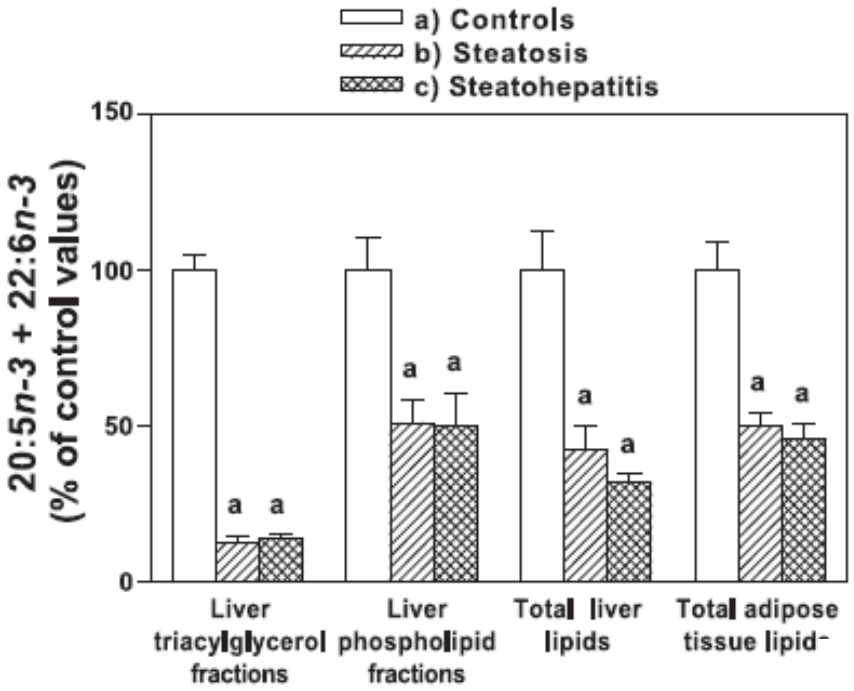
Subcutaneous adipose tissue enzyme mRNA expression



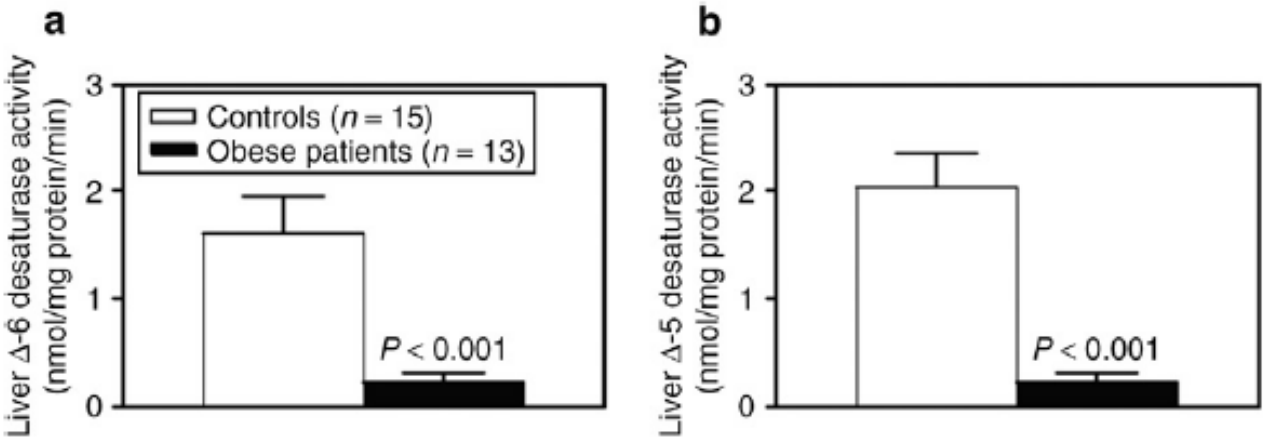
FADS1 - Δ5 desaturase
FADS2 - Δ6 desaturase
SCD - stearoyl coA desaturase
ELOVL2- very long chain FA elongase
ELOVL6 – long chain FA elongase

MacKay et al Hypertension 2012

Decreased synthesis of LC PUFA in non-alcoholic fatty liver disease (NAFLD)



Videla et al, Free Radic Biol Med 2004



Araya et al, Obesity 2009

Hypertrophy vs hyperplasia of adipocytes

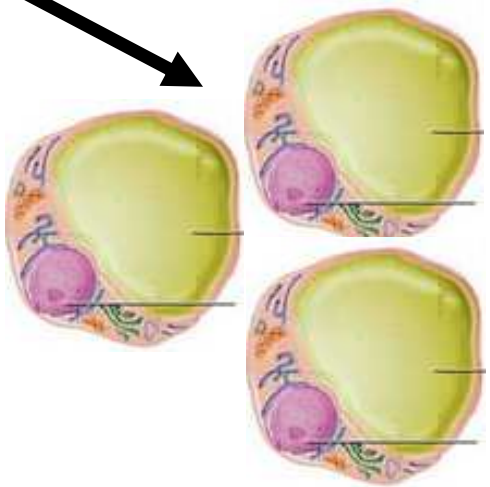
Increased flux of non-esterified fatty acids (NEFA)

Central obesity

Non-obese or lower body obesity

Hypertrophy

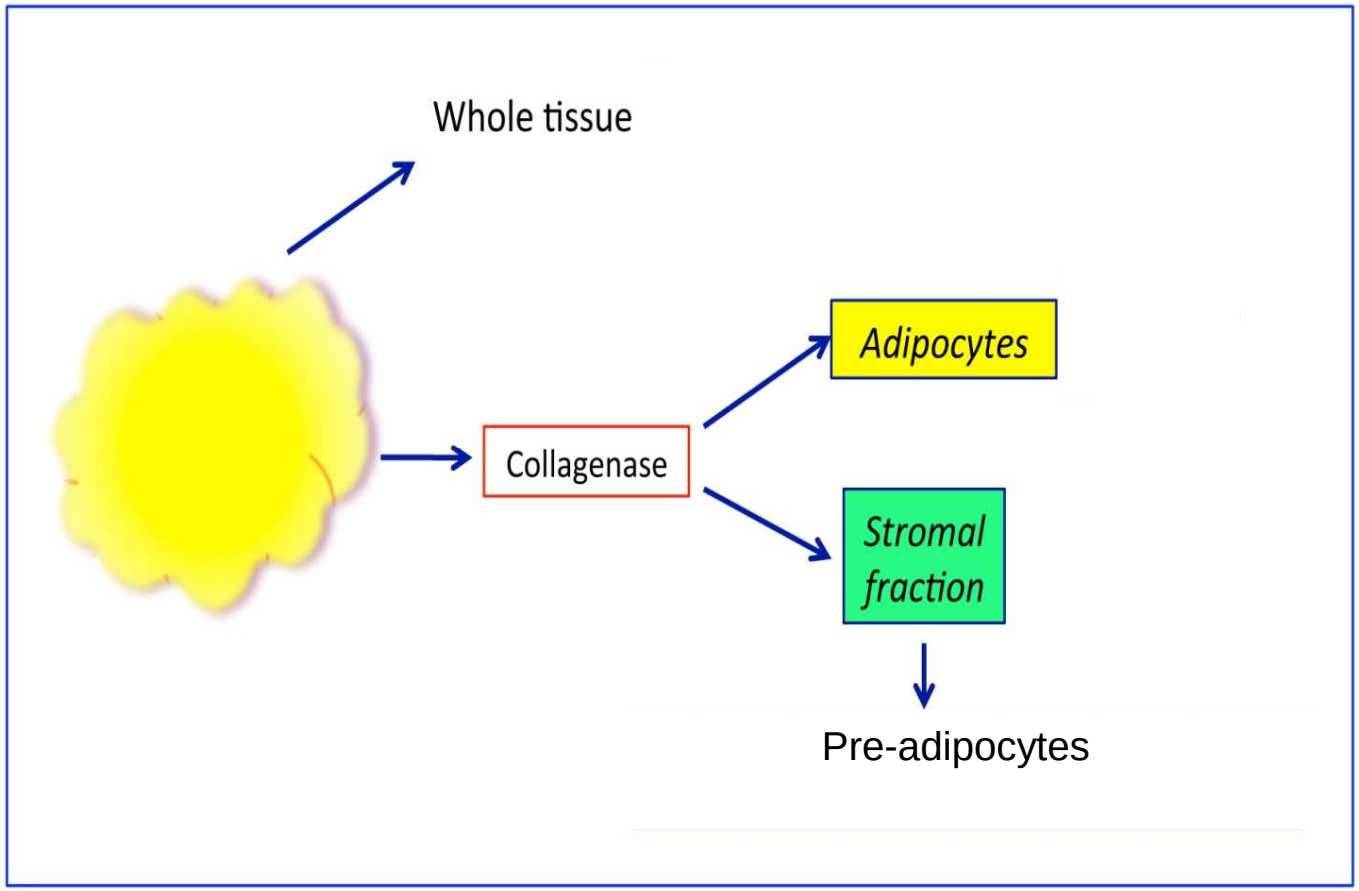
Hyperplasia



lipolysis

macrophage infiltration and adipokine secretion

Adipose tissue is more than mature adipocytes



In the stromal fraction there are pre-adipocytes and macrophages

Adipocyte expandability

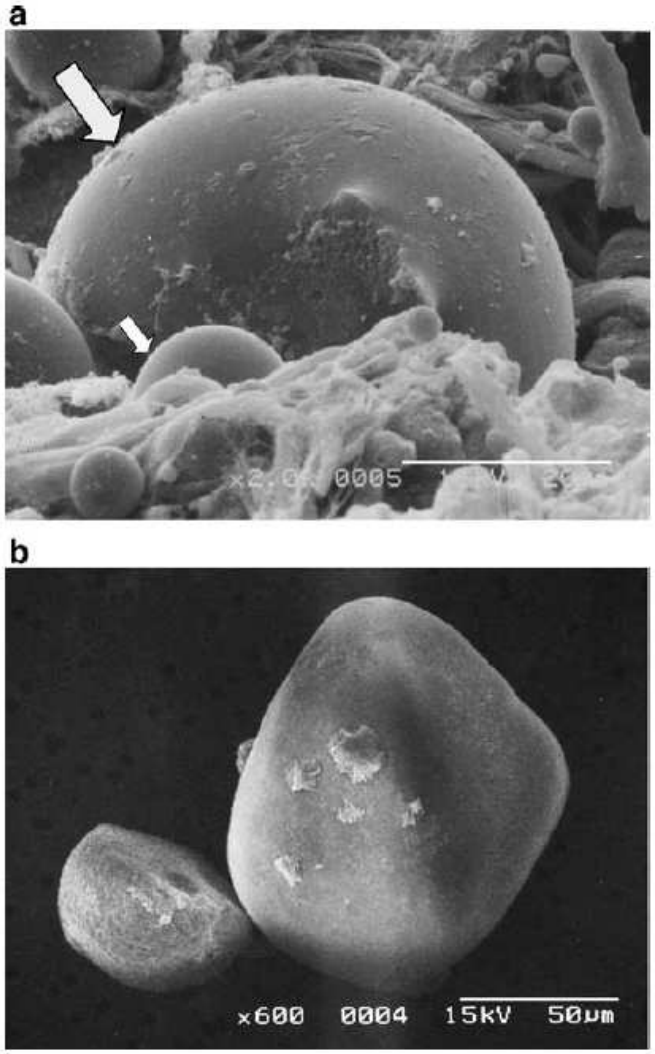


Fig. 2 Photographic examples of human adipose cells of widely varying cell size. a Scanning electron micrograph of paraformaldehyde-fixed tissue, showing small and very small adipose cells (arrows indicate cells of approximately 45 and 10 µm diameters). b Scanning electron micrograph of osmium-fixed cells, showing large and small adipose cells

- Insulin resistant individuals have more small adipocytes and decreased expression of genes related to adipose cell differentiation
- Individuals who are unable to recruit an additional population of mature adipocytes for TG storage are hypothesised to develop insulin resistance.

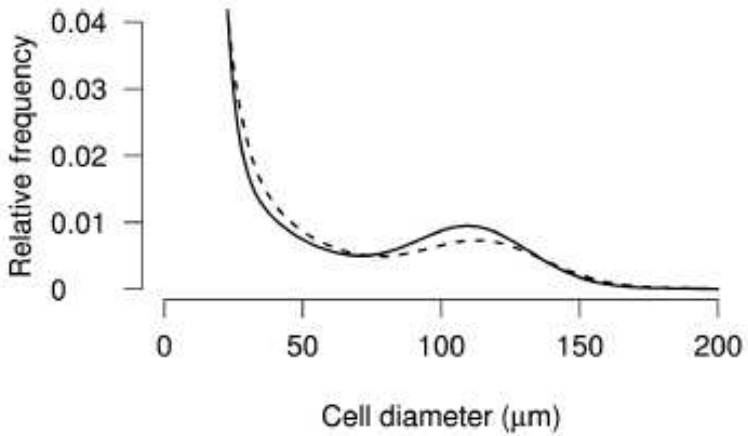


Fig. 4 Multisizer profiles of the adipose cell-size using the mean parameters from the curve-fitting formula for insulin-sensitive (*solid line*) and insulin-resistant (*dashed line*) subjects (p=0.03 using MANOVA)

McLaughlin et al Diabetol 2007

The ability of fat depots to store fat in the subcutaneous depot

Healthy weight

Obese with adipocyte expansion

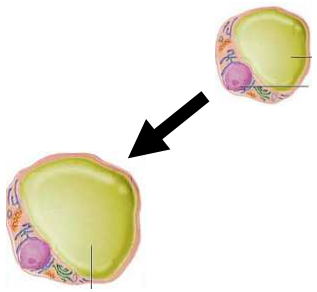
Obese with failure to differentiate preadipocytes

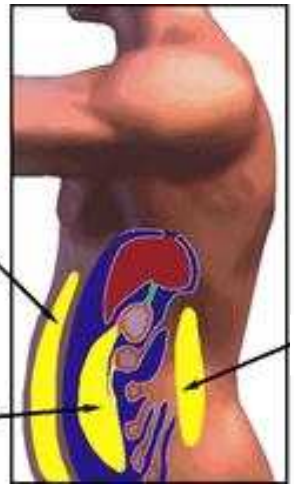
Adapted from Hocking et al End Rev 2013; 34: 463

Is adipocyte function the link between NAFLD and preeclampsia?

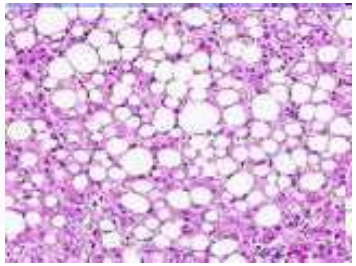
Gestational fat deposition

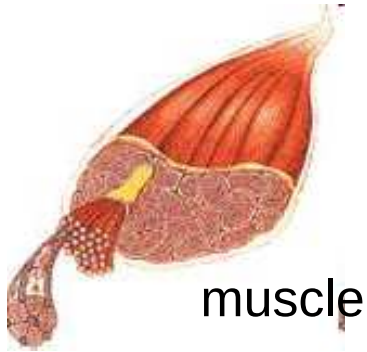
Hypertrophic obesity





Ectopic lipid accumulation also in placenta

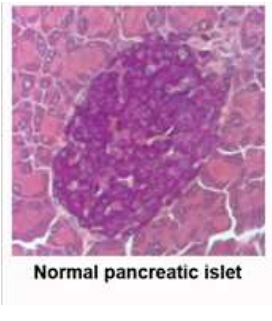




muscle

NEFA spillover

pancreatic beta cell



More small adipocytes in preeclampsia - reduced ability to expand?

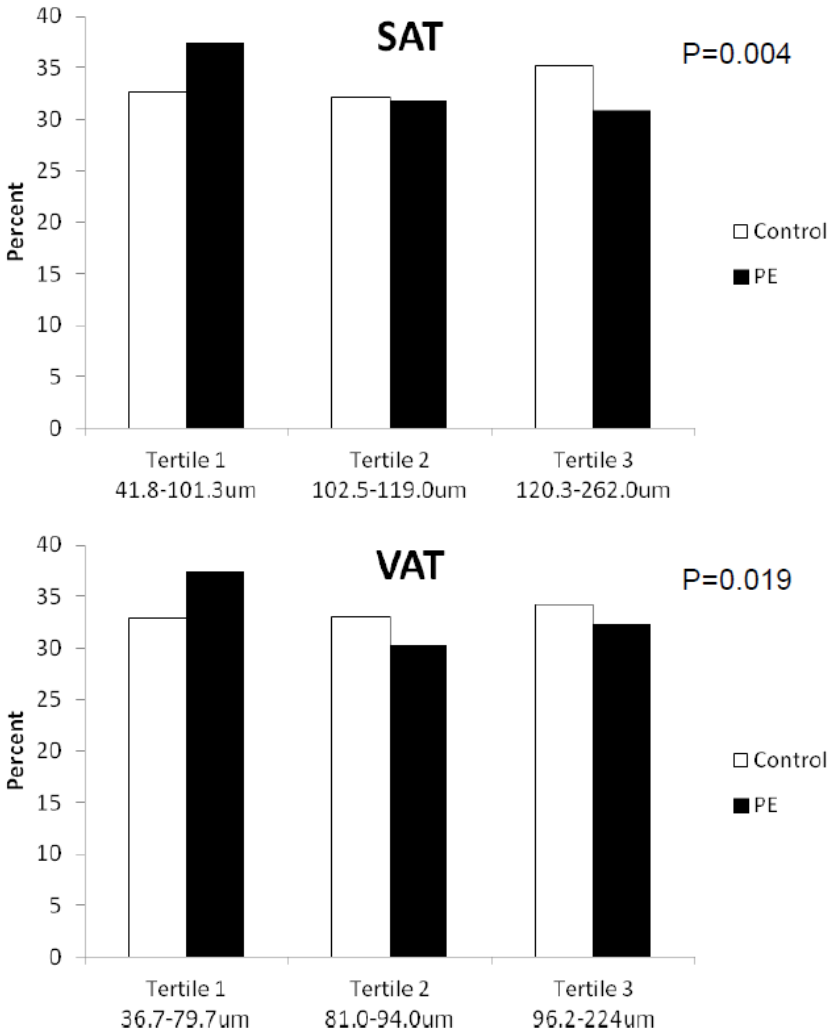


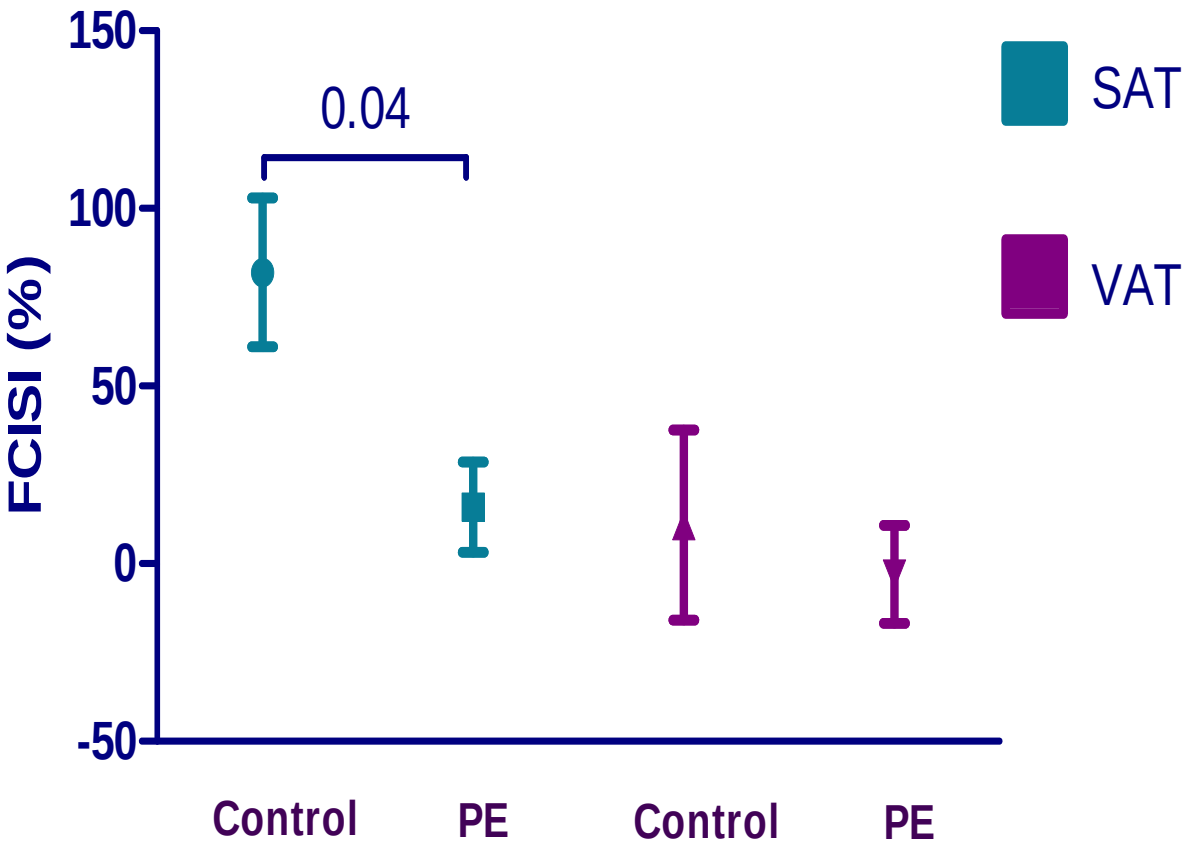
Figure S1. Subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) adipocyte diameter distribution in control and preeclamptic (PE) pregnancy. Adipocyte diameter was measured in n=100 adipocytes from each adipocyte preparation. SAT and VAT adipocyte diameters were divided into tertiles and percent adipocytes within the diameter ranges calculated for healthy and PE samples. Percentage adipocytes in each tertile for the whole control and PE groups are shown.

Huda et al Hypertension 2014

Adipocyte insulin resistance in PE

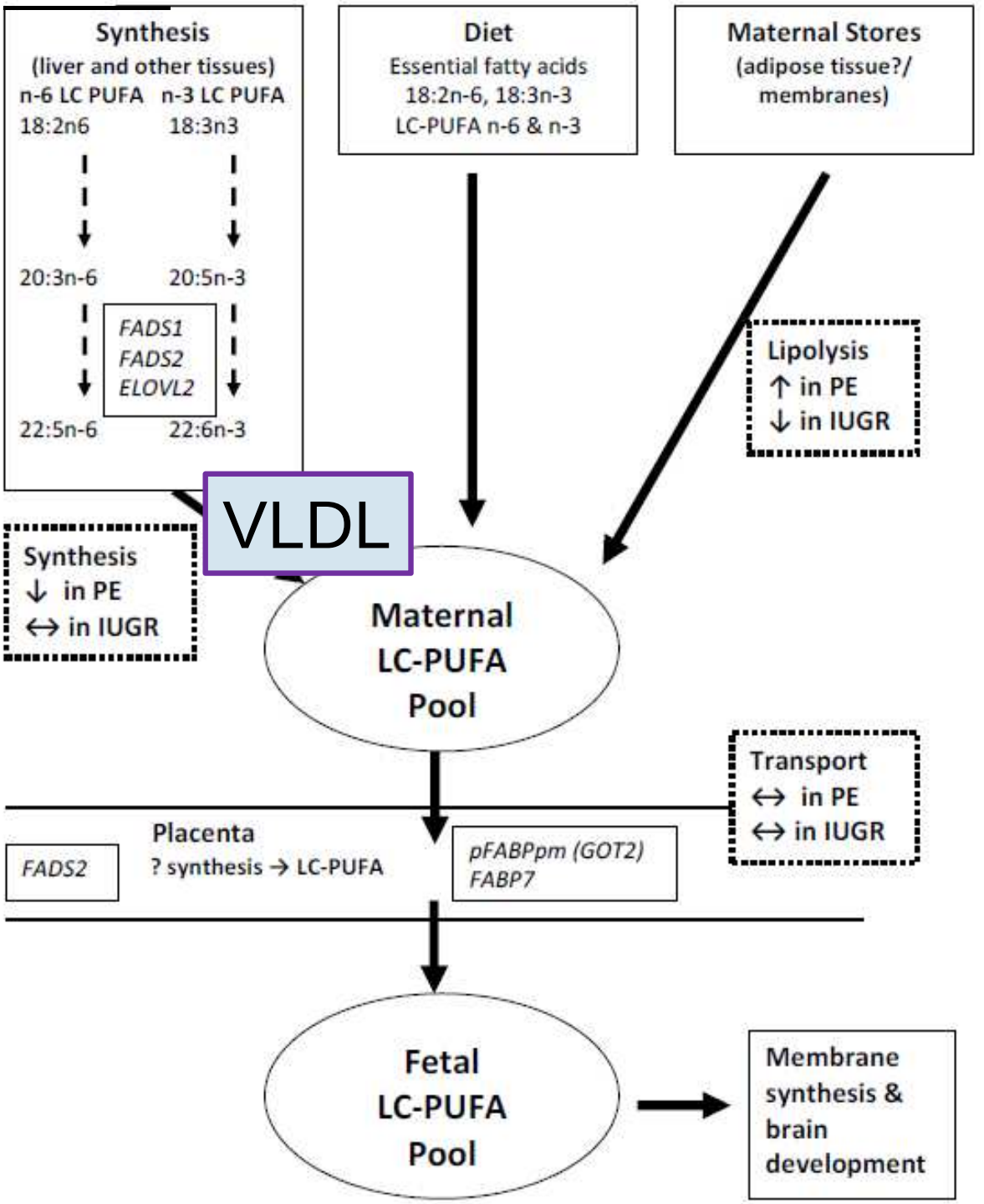
FCISI
Control vs. PE

Fat cell insulin sensitivity index (FCISI) – the ability of insulin to suppress beta adrenergic stimulated lipolysis



In PE, SAT adipocytes as insulin resistant as VAT

Huda et al Hypertension 2014


Synthesis
(liver and other tissues)
n-6 LC PUFA
n-3 LC PUFA
18:2n6
18:3n3
20:3n-6
20:5n-3
FADS1
FADS2
ELOVL2
22:5n-6
22:6n-3
Diet
Essential fatty acids
18:2n-6, 18:3n-3
LC-PUFA n-6 & n-3
Maternal Stores
(adipose tissue?/
membranes)
Lipolysis
↑ in PE
↓ in IUGR
VLDL
Synthesis
↓ in PE
↔ in IUGR
Maternal
LC-PUFA
Pool
Transport
↔ in PE
↔ in IUGR
Placenta
FADS2
? synthesis → LC-PUFA
pFABPpm (GOT2)
FABP7
Fetal
LC-PUFA
Pool
Membrane
synthesis &
brain
development

DHA mobilisation from the liver

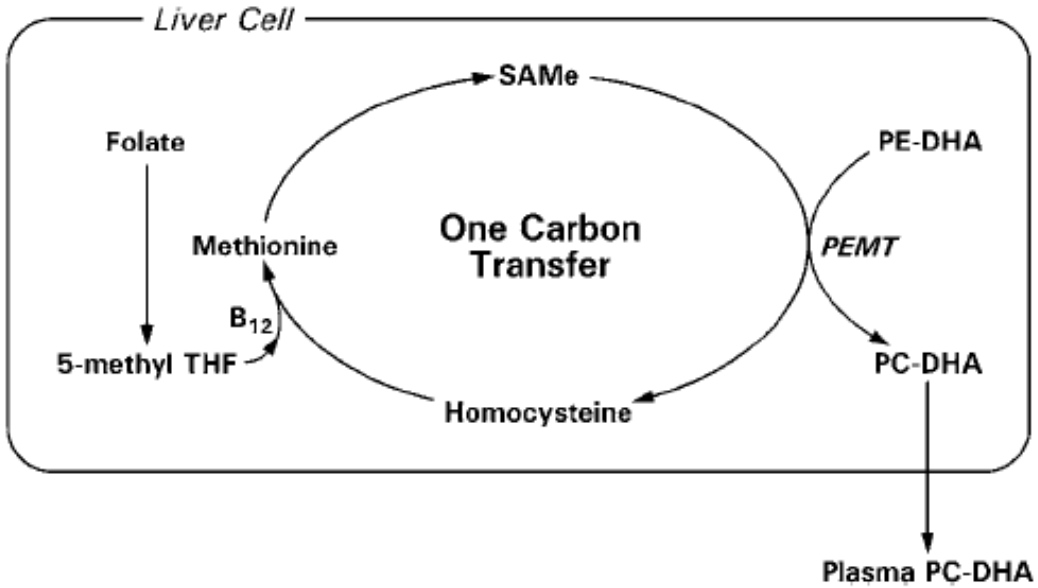


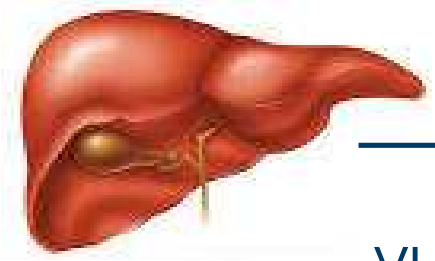
Figure 2 Methyl transfer in the liver producing phosphatidylcholine-DHA is critical for mobilization of DHA into the blood. Dietary folate is converted in the body to 5-methyl tetrahydrofolate (5-methyl THF). Methyl transfer from 5-methyl THF to homocysteine requires vitamin B_{12} and results in the synthesis of methionine. Methionine is converted into *S*-adenosyl-L-methionine (SAMe). Methyl groups from SAMe are transferred by phosphatidylethanolamine-*N*-methyltransferase (PEMT) to ethanolamine in a series of steps that convert it to choline and produce homocysteine. In this way, liver DHA incorporated into phosphatidylethanolamine is transformed into the nonpolar phosphatidylcholine-DHA. DHA which undergoes this process can be released from the liver into the plasma.

Folate and phosphatidylethanolamine-*N*-methyl transferase (PEMT) are involved in mobilising DHA from the liver into the plasma

Umhau et al EJCN 2006

Could this system exist in placenta?

Plasma DHA



VLDL particle number
with normal DHA composition

LPL

PEMT

PE-DHA
I
DHA
FATP4

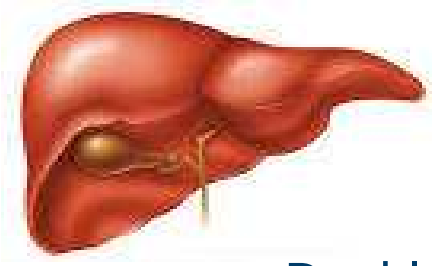
PC-DHA

DHA uptake
by fetus

healthy placenta

And fail in preeclampsia?

↓ DHA by 40%



Double VLDL particle number
with normal DHA composition

PEMT

↑PE-DHA ↑PC-DHA

LPL

DHA

FATP4

↓ DHA by 35%

PE placenta

University of Glasgow

Summary

- DHA is an important nutrient for neurodevelopment
- Humans do not synthesise DHA efficiently
- Maternal DHA plasma concentrations are increased during pregnancy as early as day 18 gestation
- DHA is selectively transported across the placenta
- Maternal and fetal DHA levels are lower in preeclampsia possibly due to decreased maternal synthesis and a defect in placental transfer

Glasgow

Ann Brown

Shahzya Huda

Fiona Jordan

Vanessa Mackay

Christopher Onyiaodike

Frances Stewart

Helen Lyall

Heather Murray

Scott Nelson

Rob Nibbs

Naveed Sattar

University of Wollongong

Barbara Meyer

Simon Brown

Sam Eather

Todd Mitchell