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Role of *FADS1* and *FADS2* polymorphisms in polyunsaturated fatty acid metabolism

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Abstract

Tissue availability of polyunsaturated fatty acids (PUFAs) depends on dietary intake and metabolic turnover and has a major impact on human health. Strong associations between variants in the human genes fatty acid desaturase 1 (*FADS1*, encoding Δ-5 desaturase) and fatty acid desaturase 2 (*FADS2*, encoding Δ-6 desaturase) and blood levels of PUFAs and long-chain PUFAs (LC-PUFAs) have been reported. The most significant associations and the highest proportion of genetically explained variability (28%) were found for arachidonic acid (20:4n-6), the main precursor of eicosanoids. Subjects carrying the minor alleles of several single nucleotide polymorphisms had a lower prevalence of allergic rhinitis and atopic eczema. Therefore, blood levels of PUFAs and LC-PUFAs are influenced not only by diet, but to a large extent also by genetic variants common in a European population. These findings have been replicated in independent populations. Depending on genetic variants, requirements of dietary PUFA or LC-PUFA intakes to achieve comparable biological effects may differ. We recommend including analyses of *FADS1* and *FADS2* polymorphism in future cohort and intervention studies addressing biological effects of PUFAs and LC-PUFAs.

1. Introduction

The polyunsaturated fatty acid (PUFA) status has a major impact on human health and has been shown to be associated with outcomes such as early visual, cognitive, and motor development [1,2]; mental health and psychiatric disorders [3]; cardiovascular disease mortality [4]; immunologic and inflammatory responses; as well as related diseases such as allergies [5,6]. These and other biological effects of PUFAs are suggested to be mediated to a large extent by the availability of the n-6 long-chain PUFA (LC-PUFA) arachidonic acid (AA, 20:4n-6) and the n-3 LC-PUFAs eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3).

Long-chain PUFAs are precursors of eicosanoids and similar mediators (eg, docosanoids) and hence can influence inflammatory processes (Fig. 1) [7-9]. The key link between PUFAs and inflammatory processes are the eicosanoids, which are derived from 20-carbon PUFAs. The main precursor of eicosanoids is AA. Arachidonic acid–derived eicosanoids have important roles in sensitization to allergens and in allergic inflammation. It has been hypothesized that there is a link between high dietary intake of n-6 PUFAs and atopic disease [9]. The n-3 LC-PUFAs inhibit AA incorporation into cell membranes and AA metabolism to eicosanoids. The n-3 LC-PUFA EPA acts as a substrate for the generation of alternative eicosanoids. Thus, it is hypothesized that inflammatory diseases (eg, atopy and obesity) are associated with a higher ratio of n-6 PUFAs to n-3 PUFAs [10]. Individual eicosanoids have different biological effects and can act in different ways depending upon their specific action. In general, AA-derived eicosanoids have mainly proinflammatory effects, whereas EPA-derived eicosanoids are rather less inflammatory. Furthermore, recent studies have identified a novel group of mediators termed *E*- and *D-series resolvins* formed from

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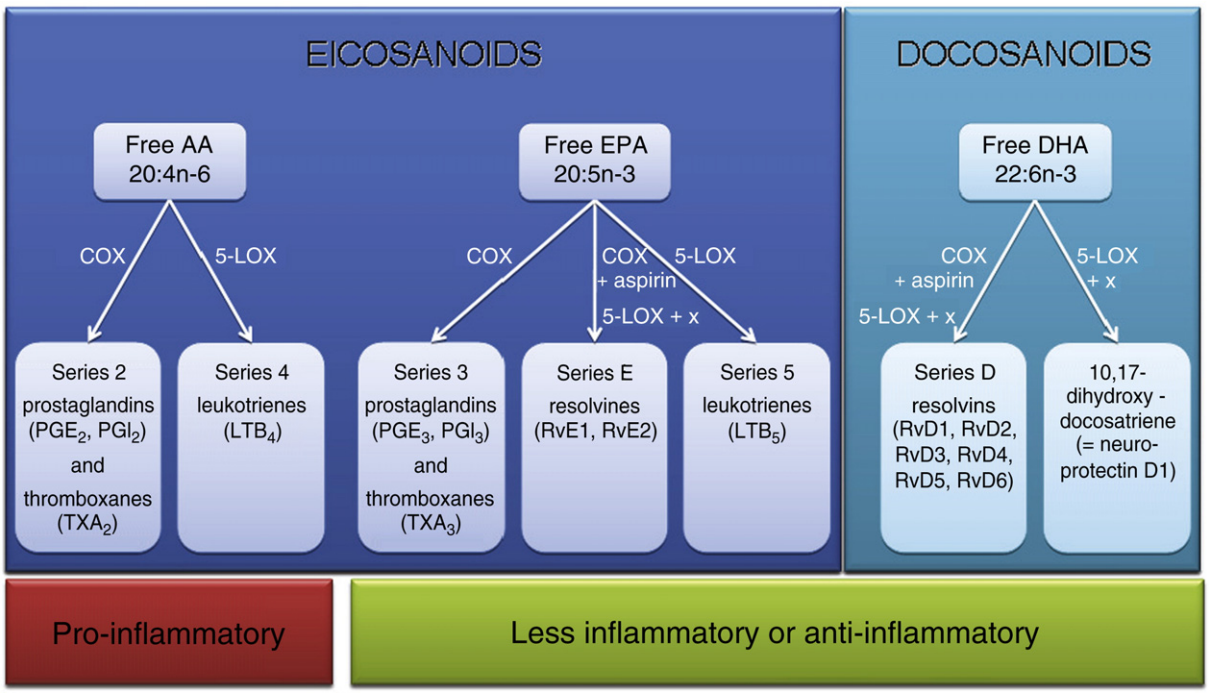

Fig. 1. Outline of eicosanoid and docosanoid pathways with free AA, EPA, and DHA, released from cell membranes by phospholipase A_2, as substrates for cyclooxygenase (COX), 5-lipoxygenase (5-LOX), and other reactions (x). Free AA is a substrate for potent inflammatory eicosanoids such as prostaglandin (PG) E_2, thromboxane (TX) A_2, and leukotriene (LT) B_4. Free EPA may compete with AA as a substrate and lead to less potent inflammatory eicosanoids such as PGE_3, TXA_3, and LTB_5. Anti-inflammatory E-series resolvins (RvE) and D-series resolvins (RvD) are formed by a series of reactions involving COX (acting in the presence of aspirin) and 5-LOX from EPA and DHA, respectively. A further potent anti-inflammatory mediator, termed *neuroprotectin D1*, is synthesized from DHA by several steps including 5-LOX.

EPA and DHA, respectively. Together with neuroprotectin D1, a mediator formed from DHA via several reactions, these mediators appear to exert strong inflammation resolving effects [9,10].

Long-chain PUFAs are provided by the diet, but can also be synthesized in human metabolism from the precursor essential fatty acids, linoleic acid (LA, 18:2n-6) and α-linolenic acid (ALA, 18:3n-3), by the action of desaturases and elongases (Fig. 2). The Δ-5 and Δ-6 desaturases are considered the rate-limiting enzymes in the formation of LC-PUFAs [11-13]. It is hypothesized that both desaturases play a key role in inflammatory diseases. This is strengthened by functional studies in mice, where selective Δ-5 and Δ-6 desaturase inhibitors showed marked anti-inflammatory effects [14,15].

Regulatory mechanisms of Δ-5 and Δ-6 desaturases have been scarcely examined in human tissue. The human desaturase complementary DNAs were first cloned in 1999 [16,17]. In 2000, they were identified as *FADS1* and *FADS2* in the human genome [18]. Both genes, *FADS1* and *FADS2*, are oriented head-to-head and localized in a cluster on chromosome 11 (11q12-13.1). Linkage was previously reported between or nearby the human chromosomal region 11q12-13.1 and complex diseases such as asthma [19], atopy [20,21], bipolar disorders [22], osteoarthritis [23], and type 1 diabetes mellitus [24].

2. PUFA metabolism and dietary intake

Fatty acids are aliphatic compounds comprising a carboxyl group and a hydrocarbon chain of varying length and degree of saturation. Natural fatty acids commonly have straight chains of an even number of 4 to 28 carbon atoms. Saturated fatty acids have no double bonds in the acyl chain, whereas unsaturated fatty acids contain at least one double bond. Fatty acids containing 2 or more double bonds are referred to as *PUFAs*. Polyunsaturated fatty acids are classified in 2 principal families, the n-6 (or ω-6) and the n-3 (or ω-3) families, according to the position of the terminal double bond. The parent fatty acids of these families, LA and ALA, cannot be synthesized in mammals; they must be provided by the diet and are therefore defined as essential fatty acids.

Linoleic acid and ALA serve as substrates for other important fatty acids (Fig. 2). By insertion of additional double bonds into the acyl chain and by elongation of the acyl chain, LC-PUFAs are synthesized endogenously from LA and ALA. Both fatty acids have analogous reaction pathways catalyzed by the same enzymes. Therefore, a competition exists between both fatty acid families for metabolism. Linoleic acid and ALA can be converted by Δ-6 desaturation to γ-linolenic acid (GLA, 18:3n-6) and stearidonic acid (SA, 18:4n-3), respectively. This step is

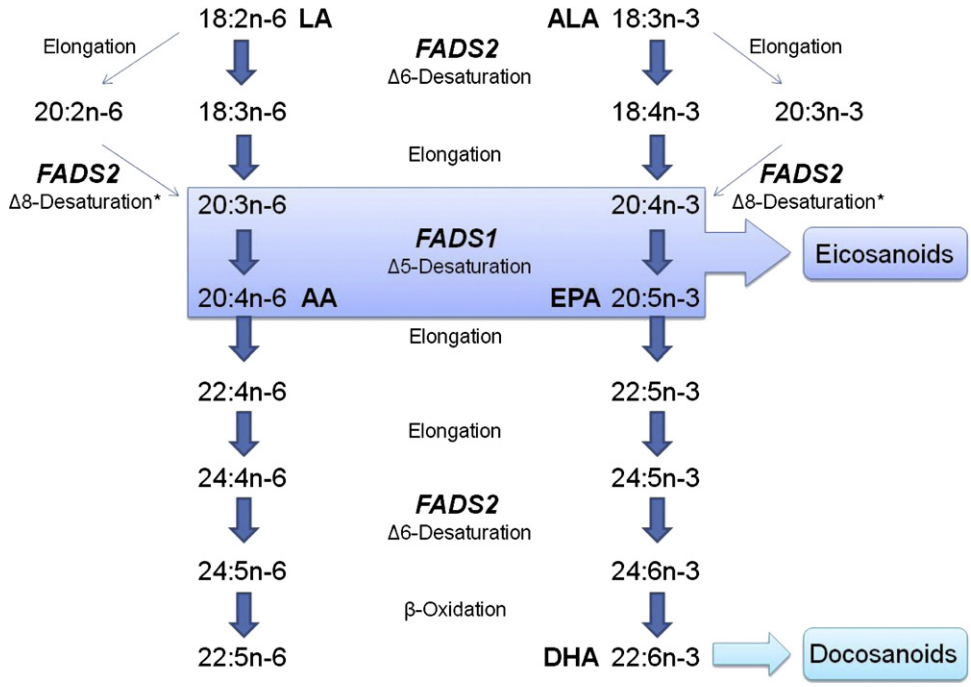

Fig. 2. Pathways for LC-PUFA synthesis from n-6 (left) and n-3 (right) essential fatty acids by enzymatic desaturation and chain elongation (*alternative pathways via Δ-8 desaturase demonstrated in mammals by Park et al 2009 [25]).

rate limiting and is followed by elongation of GLA to dihomo-γ-linolenic acid (DGLA, 20:3n-6) and of SA to eicosatetraenoic acid (ETA, 20:4n-3). In addition to these common pathways, Park et al [25] reported an alternative pathway via elongation of LA and ALA to n-6 eicosadienoic acid (EDA, 20:2n-6) and n-3 eicosatrienoic acid (20:3n-3), followed by a Δ-8 desaturation of these PUFAs to DGLA and ETA, respectively. Both PUFAs can be further elongated, leading to the production of AA and EPA.

A further important LC-PUFA is DHA, the end-product of the n-3 family. The conversion of ALA to DHA requires several elongation and desaturation steps, all taking place in the endoplasmatic reticulum. However, the last step requires a compartmental translocation to peroxisomes, the unique place for β-oxidation of LC-PUFAs [26,27]. This restriction may explain why the conversion rate of docosapentaenoic acid (DPA, 22:5n-3), the elongation product of EPA, to DHA is low, as shown in humans using ^{13}C-labeled precursors [28].

In Western diets, PUFAs comprise up to 20% of dietary fat. In most cases, LA and ALA contribute more than 95% of dietary PUFA intake [7,9]. Linoleic acid is the primary PUFA, found in significant quantities in many vegetable oils (eg, corn, safflower, soybean, and sunflower oil) and in products made from such oils (eg, margarines). α-Linolenic acid is found in green plant tissues, in some common oils (eg, flaxseed, rapeseed, and soybean oil) and in nuts [7,9]. Over the last 40 years, LA intake increased markedly in Western countries because of an increased popularity of cooking oils and margarines in these countries. Although ALA intake changed rather slightly over this time, consumption of both PUFAs exceeds minimal requirements needed to prevent essential fatty acid deficiency. The increased LA intake has changed the ratio of n-6 to n-3 PUFAs in the diet. This ratio increased markedly and is today estimated at 5 to 20 in Western countries [7,9].

In contrast to consumption of LA and ALA, dietary intake of LC-PUFAs is markedly lower. Arachidonic acid is typically provided by meat, eggs, and offal. Intakes of AA are typically in the range of 50 to 500 mg/d [7,9]. Eicosapentaenoic acid and DHA are found in marine foods, especially in fatty sea fish (eg, herring, mackerel, salmon, and tuna). One oily sea fish meal can provide 1.5 to 3.5 g of n-3 LC-PUFAs. In the absence of oily sea fish consumption, intakes of n-3 LC-PUFAs are very low, at approximately less than 100 mg/d [7,9].

3. Indications for interindividual variations in PUFA metabolism

Several studies indicate interindividual variations in the capacity for endogenous formation of LC-PUFAs. In 1988, Koletzko et al [29] found a significant correlation between n-6 and n-3 LC-PUFA contents in mature breast milk of 15 German women. Because n-6 and n-3 LC-PUFAs originate from different dietary sources, it was assumed that some women had a higher ability to synthesize and secret milk n-6 and n-3 LC-PUFAs than others.

Innis et al [30] observed a positive correlation of DHA and n-6 DPA in erythrocyte phosphatidylethanolamine of 84 Canadian preschool children. This was in contrast to results

obtained in animals, where DHA and n-6 DPA were inversely correlated. The authors concluded that the positive relationship obtained in children may reflect different activity levels of desaturases between individuals affecting the conversion of n-6 and n-3 fatty acids.

Guerra et al [31] studied the tracking of different plasma phospholipid fatty acids over 3 years of 28 children at 24, 36, and 60 months of age. They found a marked change of dietary fatty acid intake over time; and intakes of saturated fatty acid, monounsaturated fatty acid, and PUFAs showed no correlation for the 3 time points. In contrast, significant correlations were obtained for n-6 LC-PUFAs, n-6/n-3 LC-PUFA ratio, AA/LA ratio, and DHA/ALA ratio over time. This significant tracking points to an influence of individual endogenous fatty acid metabolism on plasma concentrations of LC-PUFAs. Similar findings were observed by Moilanen et al [32,33] in serum cholesteryl ester fatty acid compositions of Finnish youth.

4. Evaluation of the effects of *FADS1* and *FADS2* polymorphisms on LC-PUFA status in humans

Some 7 years after the human desaturases were first cloned in 1999 [16,17], Schaeffer et al [34] performed an analysis of 18 single nucleotide polymorphisms (SNPs) of the *FADS1 FADS2* gene cluster in 727 white subjects participating in the European Community Respiratory Health Survey I. To explore genetic determinants of PUFA metabolism, the fatty acid composition in serum phospholipids of these 727 participants was analyzed.

Association analysis of SNPs with fatty acids showed that the *FADS1 FADS2* cluster and the n-6 and n-3 fatty acids were highly associated except for n-6 DPA and DHA. Carriers of the minor alleles of 11 SNPs (rs174544, rs174553, rs174556, rs174561, rs3834458, rs968567, rs99780, rs174570, rs2072114, rs174583, and rs174589) showed enhanced levels of the n-6 fatty acids LA, EDA, and DGLA and of the n-3 fatty acid ALA, and decreased levels of the n-6 fatty acids GLA, AA, and adrenic acid (22:4n-6) and of the n-3 fatty acids EPA and DPA [34].

Analysis of reconstructed haplotypes indicated highly significant associations between the haplotypes and the fatty acid levels, which remained also significant after correction for multiple testing. Virtually all haplotypes carrying minor alleles were associated with increased levels of LA, EDA, DGLA, and ALA and with decreased levels of GLA, AA, adrenic acid, EPA, and n-3 DPA. These findings were in line with the findings of the SNP analysis. For n-6 DPA and n-3 DHA, no significant associations were achieved, probably because the effect of desaturation activity on their serum concentration was diminished by the indirect synthesis via peroxisomal β-oxidation. The most significant associations and the highest proportion of genetically explained variability (28%) were found for AA, the main precursor of eicosanoids [34].

Subjects carrying the minor alleles of several SNPs had a lower prevalence of allergic rhinitis and atopic eczema, whereas no association were found for genotypes or haplotypes with total or specific immunoglobulin E levels [34].

Further evidence for the role of *FADS* polymorphisms was provided by Rzehak et al [35], who studied a subgroup of Bavarian adults participating in the Bavarian Nutrition Survey II (163 subjects for plasma and 535 subjects for erythrocyte fatty acids). They confirmed the associations between *FADS1 FADS2* haplotypes and serum phospholipid PUFA levels. In addition, associations of haplotypes with PUFAs in erythrocyte membranes were established, particularly for the n-6 fatty acids AA and DGLA [35].

Malerba et al [36] analyzed 13 SNPs located in the *FADS1 FADS2* gene cluster and reported associations between SNPs and serum phospholipid and erythrocyte total fatty acids in 658 Italian adults participating in the Verona Heart Project. Minor allele homozygotes and heterozygotes of the studied Italian adults were associated with higher levels of LA, EDA, and ALA and lower levels of AA. No significant association were observed for SA, EPA, and DHA [36].

Analogous results were reported by Xie and Innis [37] in a cohort of 69 pregnant women from Canada. They analyzed 4 SNPs in the *FADS1 FADS2* gene cluster and associated them with plasma phospholipid and erythrocyte membrane fatty acids compositions. They showed that carriers of the minor alleles of the 4 analyzed SNPs had higher LA and lower AA levels in plasma phospholipids and erythrocyte membranes. Furthermore, they showed that genetic variants of *FADS1* and *FADS2* influenced breast milk essential fatty acids in pregnancy and lactation [37].

A study that aimed at identifying a common *FADS2* gene promoter polymorphism as potential modulator of the effect of ALA on myocardial infarction was performed by Baylin et al [38]. They evaluated the effect of the polymorphism on adipose tissue PUFA concentrations in 1820 control subjects of their Costa Rican study population.

A common deletion in the *FADS2* promoter was found to be associated with GLA, AA, EPA, ETA, and EDA. In agreement with previous findings [34], carriers of the minor deletion allele showed enhanced desaturase substrate levels and decreased desaturase product levels. Furthermore, they analyzed plasma fatty acids in a subsample of 196 controls and found analogous associations as reported before [34].

5. Genomewide association studies identified *FADS* polymorphisms as genetic contributors to PUFA concentrations

Gieger et al [39] determined associations between the genotype of 284 men (55-79 years old) from Augsburg who participated in the KORA study (Cooperative Health Research in the Region of Augsburg, Southern Germany)

with 363 metabolites measured in serum samples of these participants. They found strong associations between the SNP rs174548, located on the *FADS1* gene, and a number of plasma glycerophospholipid concentrations. This SNP explained up to 10% of the observed variance of certain glycerophospholipid species in plasma. Carriers of the minor allele of rs174548 were shown to have the lowest levels of glycerophospholipid species containing PUFAs with 4 and more double bonds. Arachidonic acid was found to be significantly reduced with increasing copy number of the minor allele. Concentrations of glycerophospholipid species containing PUFAs with 3 or less double bonds showed a positive association with the *FASD1* genotype [39].

In the InCHIANTI study (Invecchiare in Chianti, aging in the Chianti area, Tuscany, Italy), 1075 Italian adults were genotyped [40]. The strongest evidence for association with plasma PUFA concentrations was observed in a region of chromosome 11. In the analysis of AA, the SNP with the most significant association was rs174537 near *FADS1*. Homozygotes carrying only the minor alleles had lower AA levels compared with the major allele homozygotes. The SNP rs174537 was found to account for 18.6% of the additive variance in AA concentrations. These effects were further confirmed in an independent sample of 1076 subjects participating in the GOLDN study (Genetics of Lipid Lowering Drugs and Diet Network, white men and women from the United States) in erythrocyte total fatty acids [40].

6. *FADS2* polymorphism and breastfeeding effects on cognitive development

Caspi et al [41] studied the association between breastfeeding and later intelligence quotient (IQ) development in 2 independent birth cohorts: the Dunedin Multidisciplinary Health and Development Study (1037 children from Dunedin, New Zealand) and the Environmental Risk Longitudinal Twin Study (2232 children from England and Wales). They found that the effect of breastfeeding had a significant effect on cognitive development in both cohorts, whereas genetic polymorphism in the *FADS2* gene (rs174575) had no significant effect in the 2 total study populations. Further analyses revealed that rs174575 polymorphisms interacted with breastfeeding in predicting the IQ in both cohorts (Fig. 3). In both cohorts, breastfed children carrying the C allele had a marked IQ advantage over children not breastfed, whereas breastfeeding had no influence on the IQ in GG homozygotes. Caspi et al [41] were able to rule out potential confounding of the gene-environment interaction due to gene-exposure correlation, intrauterine growth differences, social class differences, and maternal cognitive ability. These observations raise the hypothesis that breastfeeding might have beneficial effects on later cognitive achievements due to its supply of LC-PUFAs, which were not contained in conventional infant formulas in the past, in subpopulations of infants with genetically determined metabolic conversion activity of LC-PUFA synthesis. This question deserves further exploration.

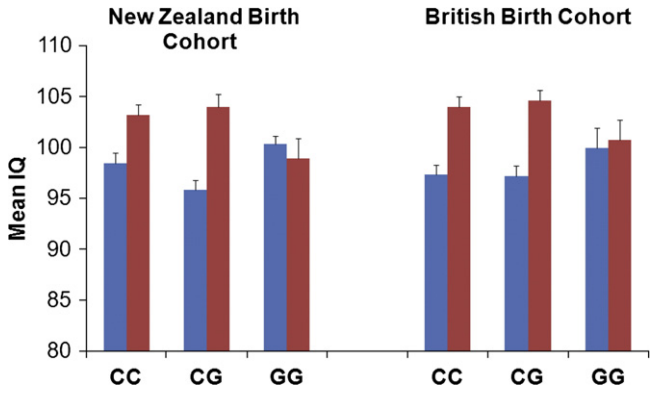

Fig. 3. Association between breastfeeding and IQ moderated by a genetic polymorphism (rs174575) in the *FADS2* gene studied by Caspi et al [41] in 2 independent birth cohorts. Breastfed children (■) carrying the C allele showed an IQ-point advantage relative to children not breastfed (■). Breastfeeding had no effect on IQ of GG homozygotes (adapted from Caspi et al 2007 [41]).

7. Conclusion

FADS1 and *FADS2* gene polymorphisms are likely to be important factors contributing to the variability in PUFA levels in serum phospholipids as well as in erythrocyte membranes [34-37,39,40]. The n-6 LC-PUFA AA as well as its precursors LA, GLA, and DGLA showed strong associations with polymorphisms and statistically reconstructed haplotypes of *FADS1* and *FADS2* [34,35]. In free-living individuals with self-selected diets, the reconstructed haplotypes explain a major proportion of the variation in serum phospholipid and erythrocyte membrane contents. Up to 28% of variation of blood level AA is due to genetic variation, whereas the value is in the order of 10% for the precursor fatty acids of AA [34]. For n-3 fatty acids, smaller percentage values are found. This could be due to a larger degree of variation in dietary intakes of the precursor ALA primarily from vegetable oils as well as of the products EPA and DHA primarily from marine foods.

These data demonstrate that blood and tissue levels of the essential fatty acids LA and ALA, as well as their biologically active LC-PUFA derivatives, are influenced not only by diet, but to a large extent also by genetic variants common in European and Canadian populations. Thus, in relation to genetic variants, population subgroups may have different requirements of dietary PUFA or LC-PUFA intakes to achieve comparable biological effects.

More needs to be known about the associations between fatty acid availability, PUFA metabolism, and genetic variants. Therefore, we recommend including analyses of *FADS1* and *FADS2* polymorphism in future cohort and intervention studies addressing biological effects of PUFAs and LC-PUFAs. We believe investigations in the generation

of specific eicosanoid and docosanoid mediators from PUFAs in association with PUFA status and genetic variants are of large interest and would help to understand more about the link between PUFAs and inflammation and the impact of PUFA metabolism on human health.

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References

[1] Beblo S, Reinhardt H, Demmelmair H, et al. Effect of fish oil supplementation on fatty acid status, coordination, and fine motor skills in children with phenylketonuria. J Pediatr 2007;150:479-84.
[2] Koletzko B, Cetin I, Brenna JT. Dietary fat intakes for pregnant and lactating women. Br J Nutr 2007;98:873-7.
[3] Muskiet FAJ, Kemperman RFJ. Folate and long-chain polyunsaturated fatty acids in psychiatric disease. J Nutr Biochem 2006;17:717-27.
[4] Leaf A. Prevention of sudden cardiac death by n-3 polyunsaturated fatty acids. Fundam Clin Pharmacol 2006;20:525-38.
[5] Kompauer I, Demmelmair H, Koletzko B, et al. Association of fatty acids in serum phospholipids with hay fever, specific and total immunoglobulin E. Br J Nutr 2005;93:529-35.
[6] Trak-Fellermeier MA, Brasche S, Winkler G, et al. Food and fatty acid intake and atopic disease in adults. Eur Respir J 2004;23:575-82.
[7] Sala-Vila A, Miles EA, Calder PC. Fatty acid composition abnormalities in atopic disease: evidence explored and role in the disease process examined. Clin Exp Allerg 2008;38:1432-50.
[8] Lagarde M. Docosahexaenoic acid: nutrient and precursor of bioactive lipids. Eur J Lipid Sci Technol 2008;110:673-8.
[9] Calder PC. Polyunsaturated fatty acids, inflammatory processes and inflammatory bowel diseases. Mol Nutr Food Res 2008;52:885-97.
[10] Schmitz G, Ecker J. The opposing effects of n-3 and n-6 fatty acids. Prog Lipid Res 2008;47:147-55.
[11] Innis SM. Perinatal biochemistry and physiology of long-chain polyunsaturated fatty acids. J Pediatr 2003;143:S1-8.
[12] Nakamura MT, Nara TY. Structure, function, and dietary regulation of delta6, delta5, and delta9 desaturases. Annu Rev Nutr 2004;24:345-76.
[13] Sprecher H, Luthria DL, Mohammed BS, et al. Reevaluation of the pathways for the biosynthesis of polyunsaturated fatty acids. J Lipid Res 1995;36:2471-7.
[14] Obukowicz MG, Raz A, Pyla PD, et al. Identification and characterization of a novel Delta 6/Delta 5 fatty acid desaturase inhibitor as a potential anti- inflammatory agent. Biochem Pharmacol 1998;55:1045-58.
[15] Obukowicz M, Welsch D, Salsgiver W, et al. Novel, selective Delta 6 or Delta 5 fatty acid desaturase inhibitors as antiinflammatory agents in mice. Lipids 1999;34:S149.
[16] Cho HP, Nakamura MT, Clarke SD. Cloning, expression, and nutritional regulation of the mammalian Delta-6 desaturase. J Biol Chem 1999;274:471-7.
[17] Cho HP, Nakamura M, Clarke SD. Cloning, expression, and fatty acid regulation of the human delta-5 desaturase. J Biol Chem 1999;274:37335-9.
[18] Marquardt A, Stohr H, White K, et al. cDNA cloning, genomic structure, and chromosomal localization of three members of the human fatty acid desaturase family. Genomics 2000;66:175-83.
[19] Huang JL, Gao PS, Mathias RA, et al. Sequence variants of the gene encoding chemoattractant receptor expressed on Th2 cells (CRTH2) are associated with asthma and differentially influence mRNA stability. Hum Mol Genet 2004;13:2691-7.
[20] Stafford AN, Rider SH, Hopkin JM, et al. A 2.8 Mb YAC contig in 11q12-q13 localizes candidate genes for atopy: Fc epsilon RI beta and CD20. Hum Mol Genet 1994;3:779-85.
[21] Wheatley AP, Bolland DJ, Hewitt JE, et al. Identification of the autoantigen SART-1 as a candidate gene for the development of atopy. Hum Mol Genet 2002;11:2143-6.
[22] Fallin MD, Lasseter VK, Wolyniec PS, et al. Genomewide linkage scan for bipolar-disorder susceptibility loci among Ashkenazi Jewish families. Am J Hum Genet 2004;75:204-19.
[23] Chapman K, Mustafa Z, Irven C, et al. Osteoarthritis-susceptibility locus on chromosome 11q, detected by linkage. Am J Hum Genet 1999;65:167-74.
[24] Nakagawa Y, Kawaguchi Y, Twells RC, et al. Fine mapping of the diabetes- susceptibility locus, IDDM4, on chromosome 11q13. Am J Hum Genet 1998;63:547-56.
[25] Park WJ, Kothapalli KS, Lawrence P, et al. An alternate pathway to long-chain polyunsaturates: the *FADS2* gene product Delta8-desaturates 20:2n-6 and 20:3n-3. J Lipid Res 2009;50:1195-202.
[26] Sprecher H. Metabolism of highly unsaturated n-3 and n-6 fatty acids. Biochim Biophys Acta 2000;1486:219-31.
[27] Diczfalusy U. Beta-oxidation of eicosanoids. Prog Lipid Res 1994;33:403-28.
[28] Burdge G. Alpha-linolenic acid metabolism in men and women: nutritional and biological implications. Curr Opin Clin Nutr Metab Care 2004;7:137-44.
[29] Koletzko B, Mrotzek M, Bremer HJ. Fatty acid composition of mature human milk in Germany. Am J Clin Nutr 1988;47:954-9.
[30] Innis SM, Vaghri Z, King DJ. n-6 Docosapentaenoic acid is not a predictor of low docosahexaenoic acid status in Canadian preschool children. Am J Clin Nutr 2004;80:768-73.
[31] Guerra A, Demmelmair H, Toschke AM, et al. Three-year tracking of fatty acid composition of plasma phospholipids in healthy children. Ann Nutr Metab 2007;51:433-8.
[32] Moilanen T, Rasanen L, Viikari J, et al. Tracking of serum fatty acid composition: a 6-year follow-up study in Finnish youths. Am J Epidemiol 1992;136:1487-92.
[33] Moilanen T, Viikari J, Rasanen L, et al. Three-year tracking of serum fatty acids in Finnish boys and girls. Atherosclerosis 1987;67:191-7.
[34] Schaeffer L, Gohlke H, Muller M, et al. Common genetic variants of the *FADS1 FADS2* gene cluster and their reconstructed haplotypes are associated with the fatty acid composition in phospholipids. Hum Mol Genet 2006;15:1745-56.
[35] Rzehak P, Heinrich J, Klopp N, et al. Evidence for an association between genetic variants of the fatty acid desaturase 1 fatty acid desaturase 2 (*FADS1 FADS2*) gene cluster and the fatty acid composition of erythrocyte membranes. Br J Nutr 2009;101:20-6.
[36] Malerba G, Schaeffer L, Xumerle L, et al. SNPs of the *FADS* gene cluster are associated with polyunsaturated fatty acids in a cohort of patients with cardiovascular disease. Lipids 2008;43:289-99.
[37] Xie L, Innis SM. Genetic variants of the *FADS1 FADS2* gene cluster are associated with altered (n-6) and (n-3) essential fatty acids in plasma and erythrocyte phospholipids in women during pregnancy and in breast milk during lactation. J Nutr 2008;138:2222-8.

[38] Baylin A, Ruiz-Narvaez E, Kraft P, et al. alpha-Linolenic acid, Delta (6)-desaturase gene polymorphism, and the risk of nonfatal myocardial infarction. Am J Clin Nutr 2007;85:554-60.

[39] Gieger C, Geistlinger L, Altmaier E, et al. Genetics meets metabolomics: a genome-wide association study of metabolite profiles in human serum. PLoS Genet 2008;4:e1000282.

[40] Tanaka T, Shen J, Abecasis GR, et al. Genome-wide association study of plasma polyunsaturated fatty acids in the InCHIANTI Study. PLoS Genet 2009;5:e1000338.

[41] Caspi A, Williams B, Kim-Cohen J, et al. Moderation of breastfeeding effects on the IQ by genetic variation in fatty acid metabolism. Proc Natl Acad Sci U S A 2007;104:18860-5.