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FADS1 and *FADS2* Polymorphisms Modulate Fatty Acid Metabolism and Dietary Impact on Health

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Abstract

Variants in the *FADS* gene cluster modify the activity of polyunsaturated fatty acid (PUFA) desaturation and the lipid composition in human blood and tissue. *FADS* variants have been associated with plasma lipid concentrations, risk of cardiovascular diseases, overweight, eczema, pregnancy outcomes, and cognitive function. Studies on variations in the *FADS* gene

cluster provided some of the first examples for marked gene–diet interactions in modulating complex phenotypes, such as eczema, asthma, and cognition. Genotype distribution differs markedly among ethnicities, apparently reflecting an evolutionary advantage of genotypes enabling active long-chain PUFA synthesis when the introduction of agriculture provided diets rich in linoleic acid but with little arachidonic and eicosapentaenoic acids. Discovering differential effects of PUFA supply that depend on variation of *FADS* genotypes could open new opportunities for developing precision nutrition strategies based either on an individual's genotype or on genotype distributions in specific populations.

Contents

INTRODUCTION

PUFAs: polyunsaturated fatty acids

LA: linoleic acid

ALA: α-linolenic acid

DGLA: dihomo-γ-linolenic acid

ARA: arachidonic acid

EPA: eicosapentaenoic acid

Polyunsaturated fatty acids (PUFAs) with double bonds in the omega-6 position (n-6 position; linoleic acid, or LA; 18:2n-6 and its metabolites) and in the omega-3 position (n-3; α-linolenic acid, or ALA; 18:3n-3 and its metabolites) cannot be synthesized de novo by humans and other animal species because higher organisms insert new double bonds or elongate fatty acid chains only at the carboxyl end (the alpha end), but not at the omega end of the molecule. Therefore, n-6 and n-3 PUFAs are essential nutrients that must be regularly provided to support normal body functions and health.

Many of the biological functions of PUFAs are not induced by the essential fatty acids LA and ALA, but by their longer-chain, highly unsaturated metabolites, including dihomo-γ-linolenic acid (20:3n-6, or DGLA), arachidonic acid (20:4n-6, or ARA), eicosapentaenoic acid (20:5n-3, or EPA), and docosahexaenoic acid (22:6n-3, or DHA). Such longer-chain omega-6 and omega-3 PUFAs are designated long-chain PUFAs (LC-PUFAs). It is predominantly the LC-PUFAs, and not the precursor essential fatty acids, that are incorporated into membrane lipids and influence

membrane and tissue functions, such as membrane fluidity, the activities of membrane-bound receptors and transport proteins, the release and binding of transmitter substances, and electrical excitation and signal transmission (48, 66, 77). In addition, LC-PUFAs serve as the precursors of potent eicosanoids and docosanoids, such as prostaglandins, leukotrienes, thromboxanes, and resolvins, that mediate physiological functions, such as platelet aggregation, inflammation, and the resolution thereof. These actions of LC-PUFAs may to some extent explain the observed linkage between LC-PUFA status and a variety health outcomes, including cardiovascular health (17, 20); metabolic syndrome (80); immune-related diseases, such as pulmonary disease, osteoarthritis, and allergies (19, 26, 55, 56, 81); mental health (9, 60); and visual and neurological development in early life (16, 41).

DHA: docosahexaenoic acid

SNPs: single nucleotide polymorphisms

LC-PUFAs can be endogenously derived from LA and ALA by a consecutive series of desaturation and chain elongation steps mediated by enzymes that convert both n-6 and n-3 PUFAs (**Figure 1**). The rate regulating conversion steps are mediated by the enzymes Δ-6 desaturase, encoded by the *FADS2* gene, and Δ-5 desaturase, encoded by the *FADS1* gene (25, 71). The *FADS* gene cluster is located on human chromosome 11 in the region 11q12–11q13.1, a region that has been associated with atopy and other complex diseases. In addition to *FADS1* and *FADS2*, it also comprises a *FADS3* gene, for which a great degree of uncertainty remains with regard to the function of its gene product (83). Numerous single nucleotide polymorphisms (SNPs) have been described in the human *FADS*-gene cluster (e.g., see **http://grch37.ensembl.org/Homo_sapiens/Gene/Variation_Gene/Table?db=core;g=ENSG00000134824;r=11:61560452-61634826**, Ensembl GRCh37, release 96).

The LC-PUFA content in human blood and tissue is modulated not only by endogenous formation from precursor PUFAs but also by the supply of preformed LC-PUFAs in the diet (and from supplements). For example, sources of ARA include a variety of animal-derived foods, such as meat, liver, and egg, whereas EPA and DHA are found primarily in marine fish and other seafood. The questions of whether preformed LC-PUFAs should be provided with the human diet to support optimal health and, if so, in which quantities, have received considerable attention

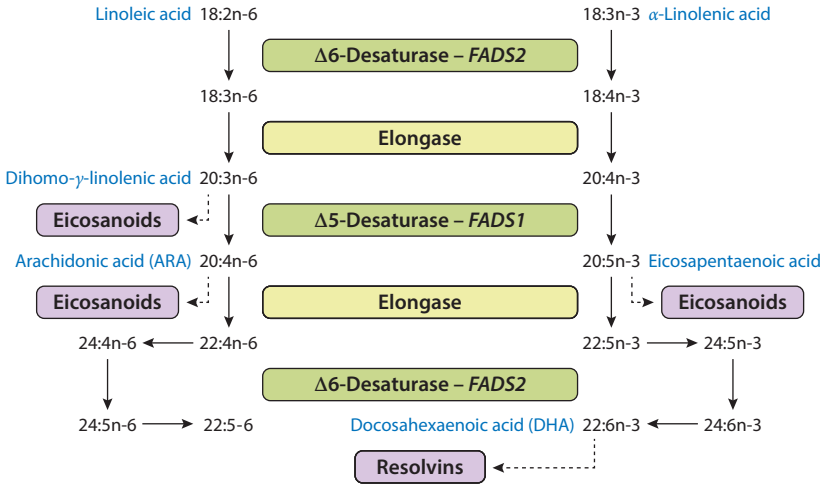

Figure 1

Pathway of conversion of omega-6 and omega-3 precursor polyunsaturated fatty acids (PUFAs) into long-chain PUFAs. Data from Reference 64.

(22, 23). Of particular interest is the provision of LC-PUFAs during early growth and development. During the period of rapid body and brain growth in early life, relatively large amounts of ARA and DHA are incorporated into the membrane lipids of growing tissues, such as the liver, immune cells, and the brain. In utero the fetus receives preformed LC-PUFAs in amounts considered to match the needs for tissue growth; this is achieved through an active and preferential maternofetal transfer of ARA and DHA that is facilitated by specific transport proteins (45, 61). After birth, breastfed infants receive preformed ARA and DHA, which are important components of human breast milk (36). Throughout the first months of exclusive or full breastfeeding, the supply of ARA and DHA from human breast milk remains constant, with a mean daily supply of about 100 mg ARA and about 50 mg DHA (29).

During most of the twentieth century, conventional infant formula containing lipids based on vegetable oils did not provide ARA and DHA, which led to lower blood LC-PUFA levels among formula-fed infants compared with those who were breastfed (43). The effects of adding ARA and DHA to infant formula has been explored since the 1980s (38). Adding ARA and DHA to formula was shown to have beneficial effects on clinical outcomes in prematurely born infants, for whom the provision of ARA and DHA is now considered standard nutritional care (42). However, the benefits of adding ARA and DHA to formula for healthy, term infants remain controversial. Some recommendations advise adding both ARA and DHA at levels similar to those usually found in human breast milk to all infant formula for infants born at term (23, 37). However, European legislation adopted in 2016 stipulates that by 2020, when the legislation will be implemented throughout European Union Member States, all infant and follow-on formula must contain 20–50 mg DHA/100 kcal (equivalent to ≈0.5–1% of fatty acids), but there is no requirement to add ARA (21). Adding high amounts of DHA without ARA has never been evaluated in clinical trials in healthy babies (39). Moreover, the suitability and safety of this approach appear questionable, given that formula with very high ratios of DHA to ARA induced lowered ARA in some brain regions in nonhuman primates (33) and attenuated developmental outcomes in human infants born at term (13). A study in preterm infants with high ratios of DHA to ARA reported adverse effects on chronic lung disease (12). In contrast to the new European Union requirements, the global standards for infant formula in the Codex Alimentarius of the World Health Organization and the Food and Agriculture Organization of the United Nations support the optional addition of DHA provided that ARA is also added in equivalent or higher amounts.

The considerable differences in recommendations and regulatory concepts related to providing ARA and DHA during infancy are due to inconsistent results from randomized controlled trials assessing the effects of their addition to infant formula on children's development (67). A Cochrane Review reported that four of the included randomized controlled trials showed neurodevelopmental benefits, while seven reported no difference; and four trials revealed improved visual development, but five found no difference (34). Part of the inconsistency in the studies' results might be due to differences in design, the populations included and their baseline ARA and DHA statuses, the choice and timing of interventions, and the use of different forms and dosages of ARA and DHA, as well as considerable differences in the outcome measures and their assessment (67). Also, concentrations of LC-PUFAs in blood and tissue, which may mediate functional outcomes, not only depend on dietary supply and the disappearance of LC-PUFAs for tissue incorporation and further metabolism but also are modified by genetically determined variation in the conversion between precursor PUFA and LC-PUFA (**Figure 2**). We aimed to study the impact of variations in *FADS* SNPs on PUFA metabolism and their possible nutrigenetic interactions with diet on health-related outcomes.

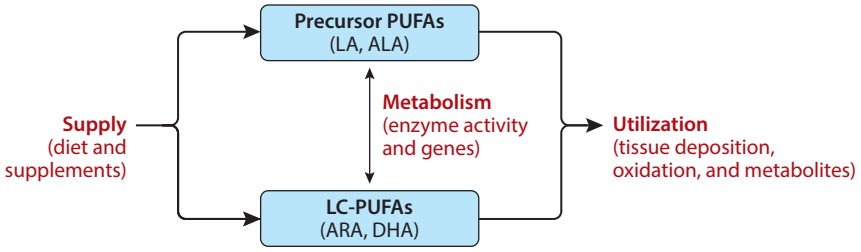

Figure 2

Key modulators of polyunsaturated fatty acid (PUFA) levels in blood and tissue include dietary supply, as well as utilization via tissue incorporation, oxidation, and conversion to other metabolites, such as prostaglandins, thromboxanes, and resolvins. In addition, the rate of conversion from precursor PUFA to long-chain PUFA (LC-PUFA) matters, and it is mediated by the gene-dependent activity of desaturating enzymes.

HUMAN *FADS* GENE VARIANTS AND PUFA METABOLISM

In the first candidate gene study looking at the potential role of genotype in modifying LC-PUFA status, we explored the effects of common genetic variants of the *FADS1* and *FADS2* gene cluster and their reconstructed haplotypes on the fatty acid composition of serum phospholipids. We included a group of 727 generally healthy Caucasian adults [mean (SD) age 31.6 (±12.3) years; 58% males] who participated in the European Community Respiratory Health Survey and consumed self-selected diets (64). After extraction of serum lipids and isolation of the phospholipid fraction by thin-layer chromatography, we analyzed the serum phospholipid fatty acid composition by capillary gas liquid chromatography. To enhance the chance of detecting associations, the selection of SNPs included in genotyping was based on their positional and functional aspects. Genomic DNA was extracted from whole blood by a standard salt precipitation method, and genotyping was performed using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. The associations between SNPs and reconstructed haplotypes were analyzed with linear models (64). Genotyping confirmed the 18 analyzed *FADS* SNPs as polymorphic. Participants carrying the minor alleles of the SNPs rs174544, rs174553, rs174556, rs174561, rs174568, rs968567, rs99780, rs174570, rs2072114, rs174583, and rs174589 exhibited higher levels of LA (18:2n-6), eicosadienoic acid (20:2n-6), and DGLA (20:3n-6), but decreased levels of γ-linolenic acid (18:3n-6), ARA (20:4n-6), adrenic acid (22:4n-6), n-3 eicosapentaenoic acid (20:5n-3) and n-3 docosapentaenoic acid (22:5n-3). There was no significant effect on DHA (22:6n-3). The reconstructed five-locus haplotype was the most common haplotype, with the major alleles at all loci in 68% of the participants, while 26% of participants had the next most frequent haplotype, which carries only minor alleles. Association analysis indicated highly significant associations between the haplotypes and PUFA levels (**Table 1**). Overall, the more common alleles were associated with higher blood levels of the products of PUFA desaturation, indicating more active conversion. In contrast, the less common alleles predicted higher blood levels of the substrates of desaturation, reflecting inactive conversion (**Figure 3**). The most marked effect was found for ARA, with close to 30% of the variation in serum phospholipid levels predicted by genotype, an effect size that is much larger than the variation achieved in dietary intervention studies.

Carriers of the less common alleles of several SNPs and their respective haplotypes also had a much lower prevalence of allergic rhinitis and atopic eczema than those with the common SNPs. For example, carriers of the five-locus haplotype consisting only of minor alleles had significantly reduced odds ratios (ORs) for allergic rhinitis [OR = 0.46, 95% confidence interval (CI) = 0.26

Table 1 Significant associations between *FADS* 5-locus and 11-locus haplotypes with percentage of maximum variations (r^2) in serum phospholipid fatty acids in Caucasian adults consuming self-selected diets[a]

Fatty acid	r^2 for 5 SNPs (%)	r^2 for 11 SNPs (%)
Omega-6 PUFAs		
Linoleic acid (18:2n-6)	8.6	9.2
γ-Linolenic acid (18:3n-6)	7.9	7.9
Eicosadienoic acid (20:2n-6)	10.1	12.3
Dihomo-γ-linolenic acid (20:3n-6)	7.4	10.8
Arachidonic acid (20:4n-6)	27.7	28.5
Omega-3 PUFAs		
α-Linolenic acid (18:3n-3)	3.9	5.4
Eicosapentaenoic acid (20:5n-3)	5.2	6.9

Data from Reference 64.
Abbreviations: PUFAs, polyunsaturated fatty acids; SNPs, single nucleotide polymorphisms.
[a]There was no significant association with docosahexaenoic acid.

to 0.83] and atopic eczema (OR = 0.46, 95% CI = 0.22 to 0.94) (64). There was no association with total and specific immunoglobulin E levels.

Since this first observation, the association of *FADS* genotypes with PUFA levels in blood and tissue has been replicated in numerous candidate gene and genome-wide studies. Consistently, the minor alleles in Caucasian populations have been linked to higher precursor PUFA levels and lower levels of ARA and EPA, as well as less inflammation and lower risks of cardiovascular diseases (50, 59). However, most studies did not find an appreciable effect of genotype variation on DHA levels (59).

We first detected an effect of the *FADS* genotype on blood DHA levels in a large study in pregnant women who joined the ALSPAC (Avon Longitudinal Study of Parents And Children) birth cohort study in the area of Bristol, United Kingdom, in the early 1990s (40). *FADS* genotypes were related to the fatty acid composition of red blood cell phospholipids in 6,711 samples obtained from 4,457 women. The blood samples were obtained when diagnostic venipunctures were performed between the fourth and forty-fourth weeks of pregnancy [at mean (SD) 26.8 (±8.2) weeks]. Most samples were taken during the third (64%) or second (33%) trimester of

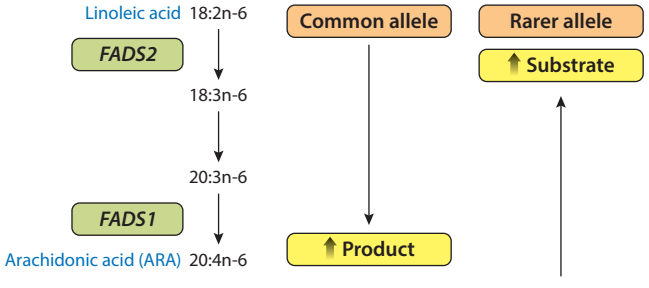

Figure 3

In Caucasians, the more common alleles of the *FADS* genes are associated with higher serum levels of products of the desaturating enzymes, such as arachidonic acid, indicating more active conversion of the precursors. The less common alleles predict higher levels of substrates of desaturation, such as linoleic acid, indicating less active conversion.

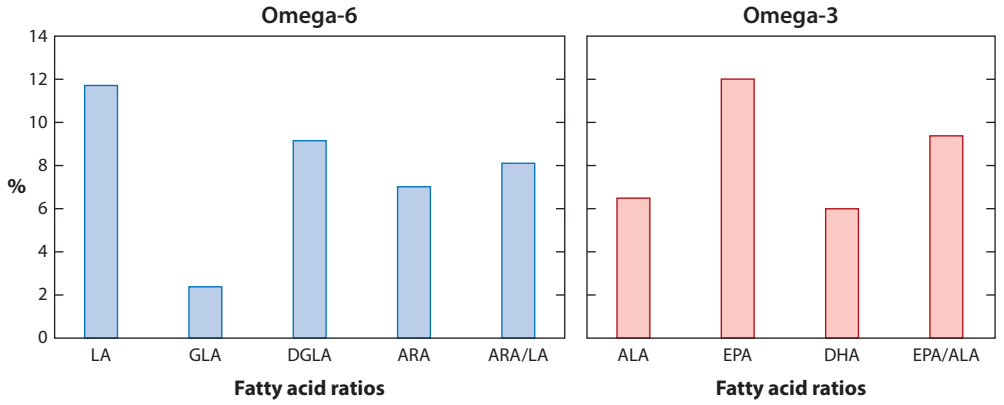

Figure 4

Maximum variation (r^2) of red blood cell phospholipid fatty acids and ratios of product to substrate for the n-6 (ARA/LA) and n-3 (EPA/ALA) conversion pathways, which are explained by 17 genetic *FADS* variants in analyses adjusted for confounders. Data from Reference 40. Abbreviations: ALA, α-linolenic acid; ARA, arachidonic acid; DGLA, dihomo-γ-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LA, linoleic acid.

pregnancy, and 3% were obtained during the first trimester. Genotyping determined 12 tagging SNPs located in the genomic region spanning *FADS1*, *FADS2*, and *FADS3* (rs174576, rs174579, rs174448, rs2727271, rs174634, rs174449, rs968567, rs526126, rs174455, rs174602, rs498793, and rs174570).

In this large cohort, minor alleles of *FADS* gene variants were positively associated with the precursor PUFAs that have two or three double bonds, while they were negatively associated with LC-PUFAs and with the product-to-substrate ratios of the n-6 (ARA/LA) and the n-3 (EPA/ALA) pathways (**Figure 4**). Associations between *FADS* and intergenic SNPs were strongest for the n-6 metabolite DGLA (20:3n-6), followed by ARA (20:4n-6), 20:2n-6, and LA (18:2n-6). Associations were weaker for n-3 PUFAs, with lower regression coefficients for DHA than for ARA, and with lower regression coefficients for ALA than for LA. The closest association for any n-3 PUFA was found for DHA.

The consistent association of rare *FADS* SNP alleles with DHA that we found, in contrast to preceding studies, might partly be due to the fact that we studied women during pregnancy who are exposed to high estrogen levels. Estrogen has been reported to stimulate PUFA desaturation, which was almost threefold greater in women taking oral contraceptives containing 17-ethynylestradiol than in those who were not taking these contraceptives (8).

In the ALSPAC cohort there was a high prevalence of the less common, or minor, alleles linked to low PUFA conversion activity, which were found in 11% to 40% of the population. There was a high prevalence of women with reduced DHA formation, which modulates DHA blood levels during pregnancy, and this reduced DHA formation might have an impact on the risk of preterm birth, fetal and child development, and the risk of allergic disease in offspring, and, thus, might be of considerable relevance for maternal and child health (25, 35, 37).

We also noted associations of the *FADS3* SNP rs174455 with precursor and product PUFAs acting in the same direction as the *FADS1* and *FADS2* SNPs, although the associations were weaker. These observations, which were recently replicated in Indonesian infants (78), lead us to speculate that the gene product of *FADS3* may also have desaturating enzyme activity.

IMPACT OF MATERNAL AND FETAL GENOTYPES ON CORD BLOOD FATTY ACIDS

In a subgroup of 2,035 mother–child pairs from the same study, we explored whether maternal and fetal *FADS* genotypes modulate the LC-PUFA content in neonatal cord blood, which reflects both placental transfer and fetal metabolism of PUFA. We explored the association of 11 cord plasma n-6 and n-3 PUFAs with 17 *FADS* SNPs in a multivariable analysis. The maternal genotype effect was adjusted for the child genotype and vice versa to estimate which of the two has a stronger influence on cord plasma fatty acid composition. The results showed that both maternal and child *FADS* genotypes and haplotypes influence the amounts of cord plasma LC-PUFAs and fatty acid ratios. In the multivariable analysis, most of the maternal SNPs were associated with cord plasma levels of the precursor n-6 PUFAs, whereas the child genotypes mainly were associated with more highly desaturated n-6 LC-PUFAs, including ARA. Maternal and child genotypes were equally associated with DHA.

It has often been assumed that the fetus does not synthesize LC-PUFAs from essential fatty acid precursors. In contrast to this assumption, this first association study of fetal *FADS* genotypes and cord plasma fatty acids demonstrates that fetal fatty acid conversion does contribute to fetal LC-PUFA status, and, thus, it provides evidence for the ability of the fetus to endogenously synthesize LC-PUFAs from precursors.

FADS VARIANTS AND HUMAN BREAST MILK FATTY ACIDS

After birth, breastfed infants continue to obtain preformed LC-PUFAs from human breast milk, which always provides LC-PUFAs. Worldwide, human breast milk has relatively stable ARA levels at approximately 0.5% of total fatty acids, whereas DHA levels (median: approximately 0.3%) are more variable and are markedly influenced by maternal dietary DHA intake (24, 29, 36). In addition, *FADS* gene variants also modify human breast milk PUFA levels, particularly n-6 PUFAs. We analyzed maternal *FADS* SNPs and fatty acid contents in breast milk collected at 1.5 months after birth in 772 women who participated in the prospective Ulm Birth Cohort study. A subgroup of 463 mothers who continued to breastfeed at 6 months after birth provided a second breast milk sample at this time (47). We determined the fatty acid composition of total milk lipids as well as eight tagging *FADS* SNPs in the genomic region spanning *FADS1*, *FADS2*, and *FADS3*. Linear regression analyses using fatty acid levels were conducted at both time points separately, and the genotype effects over time were assessed in a longitudinal analysis by using a generalized estimating equation regression model. The results indicated there are significant associations of *FADS* genotypes with breast milk ARA contents and with the ARA (20:4n-6):DGLA (20:3n-6) ratio at both 1.5 and 6 months of lactation. A longitudinal analysis of fatty acids other than LC-PUFAs by genotype also demonstrated associations with the saturated fatty acids dodecanoic acid (12:0) and tetradecanoic acid (14:0), intermediate-chain fatty acids that can be synthesized in the mammary gland, and the monounsaturated fatty acids *cis*-15-tetracosenoic acid (24:1n-9) and *trans*-9-octadecenoic acid (18:1n-9*tr*). The metabolic mechanisms leading to these effects of *FADS* variants on nonessential fatty acids remain to be determined.

These results indicate that maternal *FADS* genotypes modulate human breast milk ARA content and, hence, the ARA supply to breastfed infants. They also point to potential metabolic relationships between the LC-PUFA pathway and saturated and monounsaturated fatty acids. More recent studies in Chinese breastfeeding women confirmed the effects of *FADS* variants on human milk n-6 but not on n-3 PUFA levels (18).

GENETIC VARIABILITY OF LC-PUFA SYNTHESIS WITHIN AND ACROSS POPULATIONS

The variation of *FADS* genotypes was explored in a large study by Ameur et al. (1) that performed genome-wide genotyping in 5,652 individuals from five European populations. There were two common *FADS* haplotypes: The more common haplotype D predicted more active LC-PUFA conversion than the less common haplotype A. People homozygous for haplotype D showed 24% higher DHA and 43% higher ARA levels than those homozygous for haplotype A (1). Calculated product-to-substrate ratios were in line with effects on both Δ-5 and Δ-6 desaturation (**Figure 1**). Haplotype D was also associated with higher plasma lipid levels than haplotype A.

Ameur et al. (1) also reported major differences in haplotype distribution across human populations, based on data from the Human Genome Diversity Project. In African people, slow converters (haplotype A) are almost absent (1% of chromosomes), whereas they comprise 25% to 50% of populations in Europe, Asia, and Oceania and >95% of Native Americans (1). The marked variation in the distribution of genotypes predicting active and inactive PUFA conversion in different populations is also illustrated by the substantially different frequency of alleles associated with active PUFA conversion in our own studies, with a prevalence of about one-quarter of the population in Indonesia and Mexico but two-thirds to three-quarters of the Caucasian population in Europe and Australia (**Table 2**). Therefore, caution is warranted when the effects of PUFA supply in a specific population are extrapolated to another population with a different genotype distribution.

Ameur et al. (1) concluded that the high frequency of haplotype D in African people and the high linkage disequilibrium in the *FADS* region indicate strong genetic selection. Haplotype A is the ancestral haplotype in mammals, whereas haplotype D, predicting more active LC-PUFA synthesis, is specific to humans (1, 52). Mathieson & Mathieson (53) showed that almost all of the inhabitants of Europe carried the ancestral allele until the derived allele was introduced only about 8,500 years ago through early Neolithic farming populations. This allele appears to have

Table 2 ***FADS*** **alleles associated with rapid conversion of polyunsaturated fatty acids are the minor alleles in studies of populations in Indonesia (78) and Mexico (27), but the major alleles in Europe (64) and Australia (54)**

SNP	Location of study (reference) and % of population with SNP				
	Indonesia (78)	Mexico (27)	Germany (64)	United Kingdom (64)	Australia (54)
FADS1					
rs174548	27	22	ND	70	67
rs174556	27	24	73	70	72
rs174561	27	24	72	70	ND
FADS2					
rs174570	23	27	87	87	77
rs174574	22	20	ND	66	53
rs174576	22	21	ND	66	64
rs174578	22	21	ND	66	61
rs174579	28	38	ND	79	87
rs174602	41	37	82	66	58
rs498793	15	35	ND	60	69

Abbreviations: ND, not determined; SNP, single nucleotide polymorphism.

been preferentially selected only much later, presumably during the Bronze Age (7, 53). One would assume that this genetic selection resulted from the considerable advantage provided by haplotype D when a change occurred to diets that were low in preformed LC-PUFA. This change resulted from the transition from a hunter–gatherer diet to a diet based on agriculture, with the cultivation of grains, which provided a major portion of the human energy and supplied high dietary intakes of LA but low amounts of ARA and EPA (7, 82). Under these conditions, people with genetic variants supporting the active conversion of LA to ARA could metabolically compensate, in part, for the change in dietary PUFA supply, which must have provided a major biological advantage in support of the effective preferential selection of this genetic variant. In contrast, humans who moved from Asia to the Americas more than 18,000 years ago were confronted with different dietary conditions. The selection of *FADS* genes in Inuit populations appears to have resulted from adaptation to the cold Greenland and Arctic climate, with a protein-rich and marine-food-rich diet providing ample amounts of LC-PUFA, which may explain the persisting dominance of haplotype A genotypes mediating inactive LC-PUFA formation in Native Americans (2).

POTENTIAL IMPACT OF HUMAN *FADS* GENE VARIANTS ON SELECTED HEALTH OUTCOMES

Given that *FADS* genotypes predicting active PUFA conversion have been associated with higher plasma lipid levels in several studies in human adults (1, 59), we explored this relationship in children. In a sample of 2,006 children participating in the German prospective birth cohort studies known as GINI (German Infant Nutrition Intervention) and LISA (Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood), serum lipid concentrations measured at the age of 10 years were significantly associated with *FADS* genotype (72). Individuals homozygous for a minor allele predicting slow PUFA conversion had lower levels of total and low-density lipoprotein (LDL) cholesterol compared with carriers homozygous for a major allele. Recently, links between *FADS* variants and hypertriglyceridemia were also reported in Iranian children (32) and in young people in Mexico (79).

A pregnancy cohort study in Spain comprising 180 women reported that carriers of the minor alleles of the *FADS1* SNPs rs174545, rs174546, rs174548, and rs174553 and carriers of the *FADS2* SNPs rs1535 and rs174583 had an increased risk of overweight (body mass index $\geq$25 kg/m^2) (15).

Several studies have explored the relationship between *FADS* variants and risk of cardiovascular disease, the results of which have been summarized in a systematic review (59). The authors concluded that *FADS1* and *FADS2* alleles predicting inactive PUFA conversion are associated with reduced inflammation, total cholesterol, LDL cholesterol, and risk of coronary artery disease in the majority of published studies. For example, a study performed within the framework of the Verona Heart Study found a large difference in the incidence of coronary artery disease of 84% versus 66% for people who carried 6–7 versus 2–3 *FADS* alleles, and it also identified a higher ratio of ARA to LA as an independent risk predictor for coronary artery disease (51). The authors suggest that better understanding of the underlying metabolic mechanisms could lead to refined and targeted strategies for supplying a specific PUFA, such as EPA or DHA, to attenuate risk.

A recent systematic review explored whether *FADS* polymorphisms and dietary fatty acid intake also influence the risk of type 2 diabetes mellitus (6). A systematic search identified five studies indicating that *FADS* polymorphisms influence plasma and erythrocyte fatty acid composition, as well as influencing risk markers for type 2 diabetes, such as homeostatic model assessment–insulin resistance and fasting glucose, but no firm conclusions on the potential impact on diabetes risk could be drawn.

There is no conclusive evidence that *FADS* variants are associated with gastric cancer (49), mild cognitive impairment (65), or depression (14).

FADS GENES AND ECZEMA

While the first study on the human effects of *FADS* SNPs showed that the haplotype predicting inactive PUFA conversion was associated with about a halving of the risk for allergic rhinitis and atopic eczema (OR = 0.46, 95% CI = 0.22, 0.94) (64), no association between *FADS* SNPs and several atopic outcomes, such as asthma and hay fever up to the age of 6 years, was found in a cohort of 2,718 German children (68). The potential impact of the *FADS* genotype on childhood eczema at the age of 2 years was studied in two European prospective birth cohort studies, the Dutch KOALA study (Kind, Ouders en gezondheid: Aandacht voor Leefstijl en Aanleg), and the German LISA study (63). In the total cohort of 879 children, all *FADS* SNPs were significantly associated with all PUFAs except for ALA and EPA. All tested SNPs were associated with eczema in the LISA study ($N = 333$), with an approximately fourfold higher risk in children carrying minor alleles, whereas SNPs were not associated with eczema in the KOALA study ($N = 546$) (**Table 3**).

These apparently inconsistent results, with a significant association of *FADS* variants and eczema occurring only in the German but not in the Dutch children, could be a chance finding, but they might also be related to considerable differences in the two populations. The German children had a far lower reported prevalence of eczema at up to 2 years of age than the Dutch children (14.1% versus 30.6%), which could reflect a true difference in prevalence or different diagnostic criteria, or both. In addition, the German children also differed in variables that can

Table 3 Odds ratios of indicator-coded single nucleotide polymorphisms (SNPs) (the reference is a homozygous major allele genotype) for eczema in the Dutch KOALA study and the German prospective birth cohort LISA study as estimated by logistic regression and adjusted for sex, maternal education level, maternal smoking during pregnancy, and exclusive breastfeeding for at least 3 months

		KOALA study (The Netherlands)				LISA study (Germany)			
SNP	Allele	*N*	OR	95% CI	*P* value trend	*N*	OR	95% CI	*P* value trend
rs174545	C/C	237	1.00		0.950	155	1.00		0.003
	C/G	219	1.17	0.79 to 1.75	NS	138	2.00	0.96 to 4.17	
	G/G	59	0.88	0.46 to 1.66	NS	33	4.12	1.58 to 10.77	
rs174546	C/C	238	1.00		0.998	156	1.00		0.005
	C/T	218	1.16	0.78 to 1.73	NS	138	1.87	0.91 to 3.84	
	T/T	60	0.86	0.46 to 1.63	NS	33	3.84	1.48 to 9.93	
rs174556	C/C	253	1.00		0.843	164	1.00		0.004
	C/T	214	1.12	0.75 to 1.67	NS	137	2.33	1.15 to 4.71	
	T/T	51	0.96	0.49 to 1.86	NS	24	3.74	1.26 to 11.09	
rs174561	T/T	256	1.00		0.953	164	1.00		0.004
	T/C	212	1.09	0.73 to 1.62	NS	137	2.33	1.15 to 4.71	
	C/C	52	0.93	0.48 to 1.80	NS	24	3.74	1.26 to 11.09	
rs3834458	T/T	237	1.00		0.818	152	1.00		0.004
	T/Z	222	1.17	0.78 to 1.74	NS	141	1.77	0.86 to 3.63	
	Z/Z	60	0.95	0.51 to 1.78	NS	30	4.32	1.65 to 11.35	

Data from Reference 63.

Abbreviations: CI, confidence interval; NS, not significant; OR, odds ratio; SNP, single nucleotide polymorphism.

potentially modulate eczema risk, such as having lower plasma EPA levels (0.55% versus 1%), presumably reflecting lower fish consumption than in the Netherlands, and more frequently being exclusively breastfed at the age of 3 months (71.6% versus 50%).

In line with our results, Barman et al. (4) reported a close to twofold greater risk of eczema in carriers of the minor alleles of the *FADS* gene variants rs102275 and rs174448 in a small sample of 211 children aged 13 years from a Swedish prospective birth cohort study of children born in 1996–1997. In contrast, variants in the *ELOVL* genes that encode the chain elongation enzymes (**Figure 1**) did not affect eczema, and neither type of polymorphism was related to respiratory allergies. The synthesis of ARA, as assessed by the ratio of ARA to DGLA, was significantly affected by *FADS* but not by *ELOVL*.

Based on these results, we consider it plausible that *FADS* genes and the related PUFA availability may modulate eczema risk.

FADS GENE VARIANTS AND COGNITIVE FUNCTION

In view of the interest in the potential relevance of LC-PUFA availability to brain development and function, we studied the relationship between maternal red blood cell PUFA levels during pregnancy, *FADS* gene variants, and child intelligence at school age in 2,839 mother–child pairs from the population-based ALSPAC birth cohort study in the United Kingdom (76). We found low levels of maternal erythrocyte ARA were associated with lower performance intelligence quotient (IQ) at the age of approximately 8 years (−2.0 points, 95% CI = −3.5 to −0.6 points, $P = 0.007$, $r^2 = 0.27\%$), whereas lower verbal IQ was associated with high levels of n-6 docosapentaenoic acid (22:5n-6) (−1.8 points, 95% CI = −3.2 to −0.4 points, $P = 0.014$, $r^2 = 0.20\%$) and high levels of n-6 adrenic acid (22:4n-6) (−1.7 points, 95% CI = −3.1 to −0.3 points, $P = 0.016$, $r^2 = 0.19\%$), two fatty acids whose levels increase if DHA supply is low.

In multivariable analyses, a number of *FADS* variants were associated with IQ. Most notably rs3834458 showed a beneficial association with the minor allele for all IQ measures (**Table 4**). Other SNPs were generally associated with a negative effect for the minor alleles, with the exception of rs968567.

The gene locus of rs968567 is proximal to rs3834458, with both SNPs located in the intergenic promoter region on chromosome 11. A first functional study on SNPs in the *FADS* gene cluster showed that rs968567 influences gene transcription and transcription factor binding in in vitro assays (46). A regulatory effect of this SNP on gene expression is therefore likely, but the exact mechanisms and interactions of the effects of additional regulatory variants in the *FADS* gene cluster await further investigation.

Some care needs to be taken when interpreting the effect sizes of *FADS* SNPs because of the high linkage disequilibrium between variants, so greater emphasis must be placed on the direction rather than the magnitude of effects. However, the data indicate that *FADS* gene variants show a modest but significant impact on cognitive development.

An association between *FADS* genotype and child development was also found in a smaller study in 166 children of obese mothers in Denmark (3). *FADS* SNPs that were associated with increased DHA levels in red blood cells were also consistently associated with improved personal and social skills as assessed by the Ages and Stages Questionnaire at the age of 3 years (3).

In the randomized controlled POSGRAD (Prenatal Omega-3 Fatty Acid Supplementation and Child Growth and Development) trial in Mexico, pregnant women received 400 mg/day of preformed DHA or a placebo from gestational week 18–22 through delivery. No differences in cognitive outcomes were found between the DHA and control groups in the intention-to-treat analysis. However, there was a significant effect of interaction between DHA supplementation and

Table 4 Effect on intelligence quotient points per copy of a minor allele on the basis of linear regression analyses[a]

Single nucleotide polymorphism	*B* statistic	95% confidence interval	*P* value
Verbal IQ			
rs3834458	3.91	0.89 to 6.93	0.011
rs174578	−3.29	−6.28 to −0.30	0.031
rs498793	0.81	0.07 to 1.55	0.032
Performance IQ			
rs174548	−2.03	−3.93 to −0.14	0.035
rs3834458	2.62	0.80 to 4.43	0.005
rs968567	1.57	0.25 to 2.89	0.020
rs174455	−1.49	−2.45 to −0.53	0.002
Full scale IQ			
rs3834458	4.24	1.50 to 6.98	0.002
rs174574	−3.67	−6.37 to −0.97	0.008

Data from Reference 76.

Abbreviation: IQ, intelligence quotient.

[a]The r^2 values for the models were 0.25% for verbal IQ, 0.38% for performance IQ, and 0.23% for the full scale.

maternal *FADS* SNP rs174602 on child development compared with controls as assessed by the McCarthy Scales of Children's Abilities at age 5 years with regards to the verbal (23 ± 7 versus control $= 19 \pm 6$, $P = 0.01$) and memory scales (DHA $= 28 \pm 8$ versus control $= 24 \pm 8$, $P = 0.01$) (28). Thus, maternal *FADS* SNPs modified the impact of prenatal DHA on cognitive development outcomes at 5 years, and these differential responses to prenatal DHA supplementation based on genetic makeup could help to elucidate results from previous supplementation trials.

NUTRIGENETICS: INTERACTIONS BETWEEN *FADS* VARIANTS AND DIET AND RISK OF ASTHMA

Compared with gene effects alone, the impact of *FADS* gene variants on health appears to be even more pronounced when considering nutrigenetic interactions.

The first study to explore the interaction of *FADS* genotypes and diet on allergic sensitization and atopic diseases was published by Standl et al. (73), who studied children from the GINI and LISA birth cohorts at the age of 10 years. No direct association between *FADS* genotypes and allergic diseases or atopic sensitization was detected. Also, dietary fatty acid intake was not associated with allergy in the crude analysis. However, when the analysis was stratified by *FADS* genotype, it showed a higher asthma risk in children with higher daily margarine intake in the subgroup homozygous for two major alleles. Thus, in this population the combination of a higher dietary intake of LA with margarine together with an active endogenous conversion of LA to n-6 LC-PUFA predisposed to asthma.

The reported effects of breastfeeding on children's allergy and asthma are inconsistent and are mostly based on observational studies; these are difficult to interpret because of considerable confounding by lifestyle variables that are related to allergy risk. A large cluster-randomized study in the Republic of Belarus randomized childbirth facilities to the usual standard of care or intensified breastfeeding promotion and achieved a considerable increase in the duration of any and exclusive breastfeeding. However, this longer duration of any and exclusive breastfeeding had no effect on

allergy, asthma, or eczema risk at the age of 6.5 years (44). A recent review on the potential modulation of allergy risk by breastfeeding also reported mixed results and little conclusive evidence for an allergy-protective effect of breastfeeding (30).

In a study designed to elucidate the role of genotype in modifying the impact of breastfeeding on asthma, we included children from the two German prospective birth cohort studies, GINI and LISA. Parents used questionnaires to report on breastfeeding during the first 6 months after a child's birth. Children were categorized into those who were not exclusively breastfed and those who were exclusively breastfed up to the age of 2 months, up to the age of 4 months, or for longer than 4 months. Whether an asthma diagnosis was made by a physician was assessed at the ages of 6, 12, 18, and 24 months, and at 4, 5, 6, and 10 years (74). Complete information on breastfeeding, *FADS1* and *FADS2* genotype, and asthma were available for 2,245 children. We used logistic regression modeling to analyze the association between exclusive breastfeeding and ever having asthma, stratified by genotype. In individuals carrying a homozygous major allele (active PUFA converters), breastfeeding had no significant effect on the development of asthma. In contrast, in heterozygous and homozygous carriers of a minor allele (inactive PUFA converters), breastfeeding for 3–4 months after birth had a strong protective effect against asthma [adjusted OR between 0.37 (95% CI = 0.18 to 0.80) and 0.42 (95% CI = 0.20 to 0.88)] (**Table 5**). Interaction terms of breastfeeding with genotype were significant and ranged from −1.17 ($P = 0.015$) to −1.33 ($P = 0.0066$). In the stratified analyses, heterozygous and homozygous carriers of the minor allele who were exclusively breastfed for 5 or 6 months after birth had a reduced risk of asthma [OR between 0.32 (95% CI = 0.18 to 0.57) and 0.47 (95% CI = 0.27 to 0.81)]. It is important to note that at the time of study recruitment, infant formula in Germany was not yet generally enriched with ARA and DHA. Thus, we interpret these results as indicating a benefit of breastfeeding, which always provides preformed ARA and DHA, on long-term asthma risk in those children whose genotype leads to a low synthesis of ARA and DHA from precursors. The parental decision to breastfeed is not related to the child's *FADS* genotype. Therefore, this study on the effects of variation in genes known to have an effect on PUFA metabolism provides evidence for a causal effect of breastfeeding on reducing asthma risk based on the concept of Mendelian randomization (69).

INTERACTION OF *FADS* VARIANTS AND BREASTFEEDING IN PREDICTING COGNITIVE OUTCOMES

When compared with formula feeding, breastfeeding is associated with a small but consistently observed benefit regarding cognitive function, with a reported mean difference of 2.2 IQ points after adjustment for maternal IQ (31). However, it remains controversial whether this effect can be attributed to the specific nutrients supplied through breastfeeding or whether it may be due to possible residual confounding and the documented non-nutritional effects of breastfeeding. For example, breastfeeding mothers were found to spend markedly longer time interacting with their infant than mothers of formula-fed infants, with a mean additional 8.5 hours/week invested in childcare activities (70). This more intense mother–infant interaction associated with breastfeeding may have important implications for child development.

However, nutrigenetics may shed some light on the question of whether the nutrients provided through breastfeeding have an impact on child development. Steer et al. (75) studied the interaction between breastfeeding as reported by mothers at 1 month after birth and two *FADS* variants, rs174575 and rs1535, in relation to children's IQ in 5,934 children of white European origin from the ALSPAC cohort. There was no detectable genetic main effect on IQ, and specific genotypes were not associated with breastfeeding or with confounders. Breastfeeding was compared with formulas without added LC-PUFAs, which were the formulas used in the United Kingdom in the

Table 5 Adjusted odds ratios for physician-diagnosed asthma in 2,245 children up to the age of 10 years by duration of breastfeeding, stratified by genotype, and adjusted for sex, study center, maternal education level, prospective birth cohort study in Germany (GINI intervention arm, GINI nonintervention arm, LISA study), and presence of older siblings[a] (the reference category was never exclusive breastfeeding)

Genotype	Duration of exclusive breastfeeding					
	1–2 months		3–4 months		5–6 months	
	aOR (95% CI)	*P*	aOR (95% CI)	*P*	aOR (95% CI)	*P*
rs174578						
Major allele, homozygous	1.33 (0.61 to 2.89)	NS	1.47 (0.75 to 2.92)	NS	1.07 (0.60 to 1.91)	NS
Minor allele, homo- or heterozygous	0.89 (0.48 to 1.66)	NS	0.38 (0.19 to 0.76)	0.0062	0.41 (0.24 to 0.69)	0.0007
rs174546						
Major allele, homozygous	1.33 (0.62 to 2.89)	NS	1.48 (0.75 to 2.92)	NS	1.09 (0.61 to 1.94)	NS
Minor allele, homo- or heterozygous	0.90 (0.48 to 1.68)	NS	0.38 (0.19 to 0.77)	0.0073	0.41 (0.24 to 0.68)	0.0006
rs174556						
Major allele, homozygous	1.16 (0.56 to 2.38)	NS	1.37 (0.73 to 2.57)	NS	0.95 (0.56 to 1.62)	NS
Minor allele, homo- or heterozygous	0.98 (0.51 to 1.87)	NS	0.37 (0.18 to 0.80)	0.0107	0.41 (0.24 to 0.72)	0.0018
rs174561						
Major allele, homozygous	1.14 (0.55 to 2.34)	NS	1.38 (0.73 to 2.59)	NS	0.94 (0.55 to 1.59)	NS
Minor allele, homo- or heterozygous	1.02 (0.53 to 1.95)	NS	0.39 (0.18 to 0.83)	0.0148	0.47 (0.27 to 0.81)	0.0065
rs174575						
Major allele, homozygous	1.44 (0.74 to 2.81)	NS	1.32 (0.72 to 2.41)	NS	1.17 (0.71 to 1.94)	NS
Minor allele, homo- or heterozygous	0.81 (0.41 to 1.59)	NS	0.42 (0.20 to 0.88)	0.0224	0.32 (0.18 to 0.57)	0.0001
rs3834458						
Major allele, homozygous	1.25 (0.59 to 2.68)	NS	1.44 (0.75 to 2.76)	NS	1.07 (0.61 to 1.86)	NS
Minor allele, homo- or heterozygous	0.94 (0.51 to 1.73)	NS	0.40 (0.20 to 0.81)	0.0104	0.42 (0.25 to 0.71)	0.0011

Data from Reference 74.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; NS, not significant.

[a]Breastfeeding for at least 3–4 months leads to markedly reduced asthma risk in children with a genetically low capacity for formation of long-chain polyunsaturated fatty acids.

early 1990s when infants in the study were born. Compared with no breastfeeding, breastfeeding was associated with an almost 8-IQ-point benefit, which was reduced to about 3 IQ points after adjusting for confounders (preterm birth, low birth weight, sex, paternal social class, maternal educational level, and measures of child stimulation, both in the home environment and through maternal interaction with the child). **Table 6** shows the unadjusted and adjusted analyses in a sample that was reduced to 4,411 children to ensure matching between the adjusted and unadjusted groups.

The strongest effects on IQ were found for rs174575 and full scale IQ, but there were also similar effects for rs1535 and for other IQ measures. The largest IQ difference between those who had been breastfed and those fed with formula was found in children homozygous for the GG genotype of rs174575—that is, those who have only a limited synthesis of ARA and DHA; these children also had the lowest IQ scores of all those who were fed formula (**Figure 5**). Breastfed

Table 6 Hierarchical linear regression analyses of full scale intelligence quotient in 4,411 matched children of Caucasian ethnic origin at age 8 years with gene-times-environment effects, unadjusted and adjusted for confounders, and assuming a recessive genetic effect

Single nucleotide polymorphism	Gene		Breastfeeding		Interaction	
	B statistic (95% confidence interval)	*P*	*B* statistic (95% confidence interval)	*P*	*B* statistic (95% confidence interval)	P
rs174545						
Unadjusted	0.76 (−1.09 to 2.62)	NS	7.75 (6.44 to 9.07)	<0.0001	4.70 (−0.09 to 9.50)	0.055
Adjusted	0.76 (−0.96 to 2.49)	NS	3.5 (2.21 to 4.79)	<0.0001	4.26 (−0.26 to 8.77)	0.065
rs1535						
Unadjusted	0.59 (−0.90 to 2.09)	NS	7.72 (6.41 to 9.02)	<0.0001	3.44 (−0.50 to 7.49)	0.094
Adjusted	0.16 (−1.24 to 1.56)	NS	3.48 (2.2 to 4.76)	<0.0001	3.71 (−0.08 to 7.50)	0.055

Abbreviations: NS, not significant.

children had the biggest IQ benefit compared with formula-fed children when they carried the GG genotype of the rs174575 polymorphism, in which case they had an additional 5.8 point benefit compared with those who were formula fed (95% CI = 1.4 to 10.1, *P* for interaction = 0.0091). These interaction results were attenuated by approximately 10% after adjusting for seven variables.

In contrast to these findings, Caspi et al. (10), in an earlier study of two smaller cohorts of children, reported no breastfeeding interaction between the GG genotype rs174575 and cognition. However, Morales et al. (58) replicated the findings of Steer et al. (75) in two cohorts of children in Spain. In children homozygous for *FADS* variants predicting low *FADS1* activity, Morales

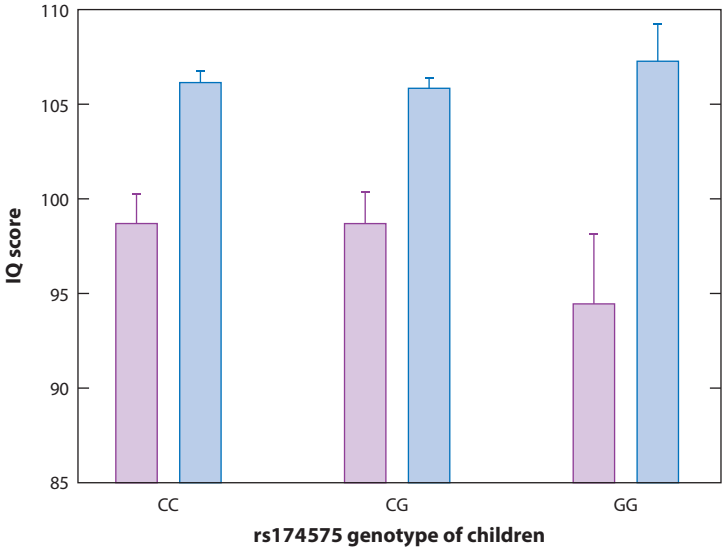

Figure 5

Unadjusted full scale intelligence quotient (IQ) scores of 5,045 children at about 8 years of age who were previously formula fed (*purple*) or breastfed (*blue*), stratified by the child's *FADS2* genotype rs174575. Formula-fed children had lower IQ scores. Formula-fed children with the GG genotype, predicting low long-chain polyunsaturated fatty acid synthesis, had particularly low IQ scores (*P* for interaction = 0.0091), and they had the biggest IQ benefit from breastfeeding (an additional 5.8 IQ points). Adapted from data in Reference 75.

et al. reported 8–9 point differences in cognitive development (Bayley Scales of Infant and Toddler Development) at the age of 14 months and the Cognitive Index of the McCarthy Scales of Children's Abilities at the age of 4 years) between previously breastfed and formula-fed children, whereas there was no significant difference for children with a genotype predicting active LC-PUFA synthesis. Similar to the study by Steer et al. (75), Morales et al. (58) documented poorer cognitive development in previously formula-fed children with alleles predicting lower compared with higher FADS1 activity.

Thus, in three cohorts in studies that applied the Mendelian randomization strategy, it was found that a genetically determined limitation of endogenous LC-PUFA synthesis results in poorer cognitive development in infants fed formula that did not provide ARA and DHA. This developmental deficit is completely eliminated when infants receive human breast milk that provides preformed ARA and DHA, which compensates for limited endogenous LC-PUFA synthesis. During infancy, ARA and DHA are the major LC-PUFAs incorporated into the growing human brain (41). Given that human endogenous synthesis forms primarily ARA and other n-6 LC-PUFAs, but very little DHA, it is tempting to speculate that the adequate availability of ARA during the first months of life may be important for the normal development of cognitive function. Therefore, it appears premature to suggest enriching infant formula only with high levels of DHA but not with ARA, as stipulated in recent European legislation, in the absence of reliable data on suitability and safety (21, 39).

INTERACTION OF *FADS* GENOTYPES AND EFFECTS OF LC-PUFA SUPPLEMENTATION

A few studies have reported results supporting the hypothesis that *FADS* variants may modify the response to sources of preformed n-3 LC-PUFAs. Molto-Puigmarti et al. (57) studied 309 pregnant women from the Dutch KOALA birth cohort study. Plasma samples were obtained at 36 weeks of gestation and human breast milk samples at 1 month after birth for analysis of fatty acids in milk total lipids and plasma phospholipids. Dietary habits were evaluated with a food frequency questionnaire. The *FADS1* rs174561, *FADS2* rs174575, and intergenic rs3834458 SNPs were genotyped. Women carrying minor alleles had lower levels of LC-PUFAs in plasma phospholipids and in their breast milk. Similar to the results of the study by Lattka et al. (47), the genetic effect was strongest on n-6 LC-PUFAs. As expected, Molto-Puigmarti et al. (57) found higher DHA levels in plasma phospholipids and in the breast milk of women who regularly ate fish or took fish oil supplements. DHA proportions in plasma phospholipids increased proportionally with higher DHA intake to similar extents for the three different genotypes (homozygous for the major alleles, heterozygous, or homozygous for the minor alleles), without any significant gene–diet interaction. In contrast, human breast milk DHA levels increased with maternal DHA supply only in women who carried the major alleles (active PUFA converters), but not in women homozygous for the minor allele ($P = 0.090$ for gene–diet interaction). Thus, the genetic differences in DHA levels in breast milk were further augmented at higher maternal DHA intakes. It remains unknown whether this is due to a link between *FADS* SNPs and differences in fatty acid transport from plasma to breast milk or to some scavenging of supplied DHA in more depleted maternal tissues in women who have inactive DHA synthesis.

An opposite effect of gene–diet interaction was reported by Meldrum et al. (54) with respect to the response of DHA in infants' red blood cells to fish oil supplementation. The authors studied 133 infants (93–94% Caucasian) at the age of 6 months who had participated in the randomized controlled Infant Fish Oil Supplementation Study. The study aimed to assess whether providing 650 mg/day of fish oil compared with olive oil altered the risk of allergic diseases, or altered

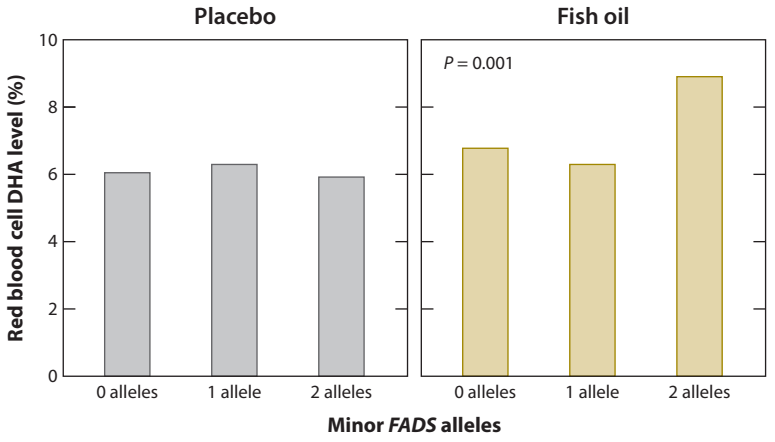

Figure 6

Supplementation with fish oil led to higher docosahexaenoic acid (DHA) levels in red blood cells in infants with two copies of the *FADS1* haplotype consisting only of minor alleles with single nucleotide polymorphisms (predicting less active conversion). There was no appreciable genotype effect in the placebo group. Adapted from data in Reference 54.

immune development and neurodevelopment. At the age of 6 months, blood was collected for analysis of fatty acids in plasma and red blood cell total lipids, and 22 *FADS* SNPs were analyzed and haplotypes constructed.

Infants who received fish oil supplements had higher EPA and DHA and lower ARA levels in erythrocytes and plasma lipids. Among these infants, erythrocyte DHA levels were significantly higher in those who carried two copies of the *FADS1* haplotype consisting only of SNP minor alleles (predicting less active conversion), whereas there was no appreciable genotype effect in the placebo group (**Figure 6**). Also, significantly higher erythrocyte DHA levels were found in infants who received fish oil supplements and were homozygous for the minor *FADS* SNPs rs174545, rs174546, rs174548, rs174553, rs174556, rs174537, rs174448, and rs174455 than were found in supplemented infants who had other genotypes, whereas there was no such genotype effect in the placebo group. Thus, the authors propose that providing fish oil supplements may significantly increase erythrocyte DHA only in carriers of minor alleles of *FADS1* SNPs.

A diet–gene interaction affecting infants' birth weight was observed in 654 mother–infant pairs who participated in the POSGRAD clinical trial in Mexico (27). Pregnant women were randomized to supplementation with either 400 mg DHA/day or placebo starting at 18–22 weeks of gestation and lasting until childbirth. Four SNPs (rs174455, rs174556, rs174602, and rs498793) in the *FADS* region were selected for analysis. *FADS* SNPs were associated with plasma ARA and DHA levels, and the four tagging SNPs together accounted for 24% of the variation in plasma ARA and for 11% of the variability in plasma DHA. The interaction of the *FADS* variants with the intervention was tested for infant birth weight, which reflects fetal growth. Analysis of variance modeling was used to test for heterogeneity of the effect on birth weight across each of the four SNPs. Mean (SD) birth weight [3,210 (±470) g] did not differ between the intervention and placebo groups (62). A significant interaction with SNP rs174602 was detected ($P < 0.01$). Neonates born to mothers who carried the alleles TT and TC (indicative of less active PUFA conversion) in the DHA-supplemented group were heavier than neonates in the placebo group [mean (SD) weight-for-age *Z* scores −0.13 (±0.14) g for the TT allele and −0.20 (±0.08) g for the TC allele in the intervention group and −0.55 (±0.15) g for the TT allele and −0.39 (±0.09) g

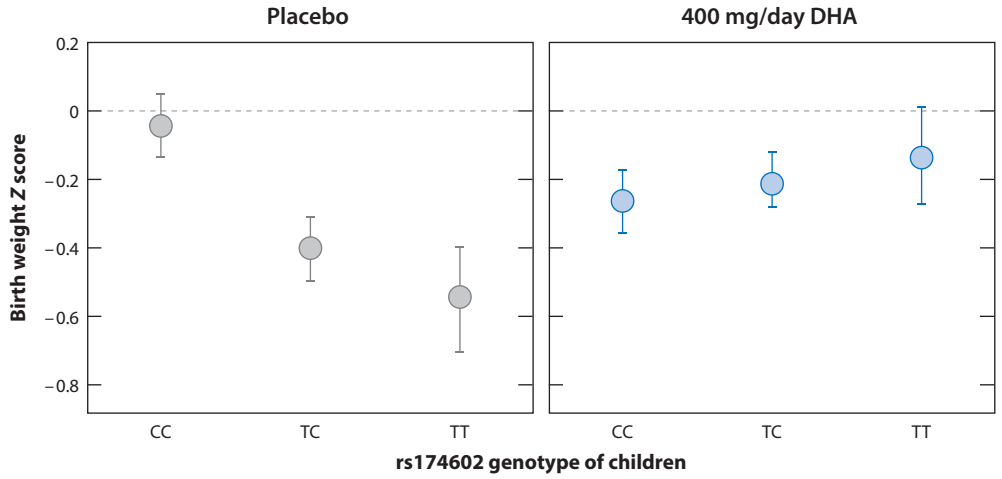

Figure 7

In a randomized trial on providing pregnant women with placebo or docosahexaenoic acid (DHA) supplementation, a significant interaction was found between the intervention and the *FADS* single nucleotide polymorphism rs174602. Neonates in the DHA-supplemented group born to mothers who carried the alleles TT and TC, indicating less long-chain polyunsaturated fatty acid formation, were significantly heavier than neonates in the placebo group. Adapted from data in Reference 27.

for the TC allele in the placebo group] (**Figure 7**). After adjusting for gestational age, the effects were somewhat attenuated but significance persisted; thus, the interaction was only partially explained by the duration of pregnancy. There was no heterogeneity across the other three *FADS* SNPs. These results demonstrate that maternal *FADS* genotypes modify the impact of DHA supplementation on an important biological outcome. This provides a potential explanation for the different and sometimes contrary results found in other randomized controlled trials of LC-PUFA supplementation.

The question of the impact of *FADS* variants on pregnancy outcomes was also explored in a recent tri-ethnic cohort study of mothers and infants in Singapore (5). The authors genotyped 35 genetic variants of *FADS1*, *FADS2*, and *FADS3* in 898 mothers and 1,103 infants and selected eight tagging SNPs for analysis that were associated with blood levels of n-6 but not n-3 LC-PUFAs. *FADS1* and *FADS3* gene variants were associated with weight and length at birth for infants born to women who had spontaneous labor, but the association was almost entirely removed after adjusting for pregnancy duration. *FADS3* variants both in offspring and mothers were associated with duration of pregnancy in women who had spontaneous labor: Each copy of the maternal rs174450 minor allele C was associated with 2.2 days' shorter gestation (95% CI = 0.9 to 3.4). This observation provides additional evidence for a role of LC-PUFAs in influencing gestation duration, as was previously observed in randomized controlled trials of n-3 LC-PUFA supplementation during pregnancy (35).

CONCLUDING REMARKS

Genetic variability in the *FADS* gene cluster has marked effects on PUFA levels, with particularly large effect sizes on n-6 LC-PUFA levels that exceed the effect sizes of most dietary interventions. *FADS* gene variants have been associated with important health consequences, such as the risk of cardiovascular diseases, eczema, and asthma; pregnancy outcomes; and cognition. Mendelian randomization studies exploring the interactions of *FADS* genes and diet and their

effects on eczema, asthma, and cognition represent powerful examples of the impact of the genome on dietary effects. Studies on the selection of different *FADS* genotypes in human populations exposed to different dietary conditions indicate marked evolutionary advantages of genotypes associated with more active LC-PUFA synthesis when the introduction of agriculture provided a diet rich in LA but with limited amounts of ARA and EPA. Considering the large effect sizes of *FADS* gene variants on PUFA metabolism and outcomes, it appears necessary to include genotyping in sizeable human observational and intervention studies that examine PUFA metabolism and its effects. The observed differential effects of dietary LC-PUFA supply according to specific *FADS* genotype may offer new opportunities for developing precision nutrition approaches that personalize the provision of LC-PUFAs for individuals or that target populations, depending on genotype frequencies in that population (11).

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AUTHOR CONTRIBUTIONS

B.K. wrote the manuscript, and all authors reviewed and contributed to the revision of the manuscript.

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Errata

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