Review

Associations of delta fatty acid desaturase gene polymorphisms with lipid metabolism disorders

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Abstract: Overweight, obesity, type 2 diabetes mellitus, metabolic syndrome, cardiovascular diseases, and non-alcoholic fatty liver disease are common chronic ailments associated with lipid metabolism disorders. One of the mechanisms of these disorders is related to the deficiency and/or change in the balance of essential fatty acids (FAs). At the same time, the provision of ω3 and ω6 polyunsaturated fatty acids (PUFAs) depends, besides sufficient dietary intake, on efficiency of their endogenous biosynthesis by desaturation and elongation processes regulated by FA elongases and FA desaturases. Desaturases are encoded by PUFA desaturase genes (FADSs): FADS1 and FADS2. Alteration of FA desaturase activity and single nucleotide polymorphisms (SNPs) in the FADS1 and FADS2 gene cluster are associated with lipid metabolism dysfunction and may affect the pathogenesis of lipid-related diseases. People of different ages, from different ethnic backgrounds and countries may exhibit varying degrees of response to dietary supplements of ω3 and ω6 PUFAs. The study of the relationship between lipid metabolism disorders and genetic factors controlling FA metabolism is an important research area since the health effects of alimentary ω3 and ω6 PUFAs can depend on genetic variants of the FADS genes. This review summarizes the literature data on the association of FADS gene polymorphisms with lipid metabolism disorders and their role in the development of chronic non-communicable pathologies associated with changes in lipid metabolism.

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Introduction

Polyunsaturated fatty acids (PUFAs) are components of the diet and are endogenously produced by the elongation and desaturation from essential fatty acids (FAs), such as α-linolenic (18:3ω3) and linoleic (18:2ω6) acids [1]. The effect of PUFAs is associated with their activation via specific receptors, ability to modulate the function of membrane lipid rafts and activity of many signaling pathways, as well as with genetic and epigenetic mechanisms [2-4]. The study of ω3 and ω6 PUFA metabolites is of interest due to their involvement in immunometabolic responses and the pathogenesis of chronic diseases associated with lipid metabolism disorders [5, 6]. The lack of essential FAs impairs the resolution of inflammation and results in the development of a slow chronic low-grade inflammation [7, 8]. This type of inflammation underlies many non-communicable chronic diseases and conditions accompanied by lipid metabolism dysfunction, in particular obesity, cardiovascular diseases (CVDs), type 2 diabetes mellitus (DM2), metabolic syndrome (MS), non-alcoholic fatty liver disease (NAFLD) [1, 8-11]. Obesity, overweight, MS, CVDs, and NAFLD are common in both adults and children [12, 13]. Childhood obesity is a risk factor for developing CVDs and DM2 in adulthood [14]. Their relationships with lipid metabolism disorders in pregnant and breast-feeding women is studied as well [15].

PUFAs are widely used as dietary supplements for the prevention and treatment of lipid metabolism pathologies [16-18]. Despite this, there are contradictory results regarding their effectiveness [17, 19, 20]. In the course of analyzing the available data, it is necessary to consider such factors as variable bioavailability of dietary ω3 PUFAs, background levels of ω3 and ω6 PUFAs, functional state of gut microbiota, and experimental conditions used in animal studies that are more homogeneous and controlled compared with studies involving humans [8, 21, 22]. Some studies confirm the metabolic and anti-inflammatory properties of ω6 PUFA, especially linoleic acid, while other publications emphasize that the conversion of this FA into arachidonic acid is accompanied by the formation of its pro-inflammatory metabolites – eicosanoids [23]. Such contradictory views and fragmented results can be explained by the fact that people of different ages, from different ethnic groups and countries, may exhibit different degrees of response to dietary PUFAs [24, 25]. Children, pregnant and breast-feeding women have their own features of responding to the dietary PUFA supplementation [26-29].

The heterogeneity of the response to treatment may be associated with genetic variability among individuals [20, 30]. Endogenous processing of PUFAs is controlled by FA elongases and FA desaturases encoded by PUFA desaturase (delta fatty acid

desaturases, *FADSs*) genes [31]. Changes in the activity of FA desaturases and polymorphisms of their genes are observed in a significant number of diseases related to lipid metabolism dysregulation [32-34]. At the same time, the genetic regulation of endogenous lipid metabolism is poorly understood [35, 36]. Investigating the association of genetic factors controlling FA metabolism with lipid metabolism disorders and development of the low-grade inflammation in chronic non-communicable diseases can be considered as a promising study field. The health effects of dietary ω3 and ω6 PUFAs may vary with genetic variants within the *FADS* genes.

We carried out bibliographic searches in PubMed for reports of randomized controlled trials published between 2010 and 2020. In our search for relevant publications, the following keyword combinations were used: *fatty acids*, *fatty acid desaturase*, *fatty acid desaturase genes*, and *lipid metabolism*. Only articles in English were considered. Hence, 481 publications were identified, of which 19 were the reviews.

Our analysis of available literature established that international databases contained a sufficient number of the articles dedicated to studying the relationships between FA synthesis disorders and chronic diseases [1, 5-7, 21, 24, etc.], as well as enough publications highlighting the effects of alimentary PUFAs intake in various pathological conditions [8-10, 16-20, 22, 23, 25, etc.]. The articles discussing genetic regulation of endogenous lipid metabolism were less abundant [4, 11, 24-29, etc.]. There were just a few studies aimed at establishing the health effects of alimentary PUFAs depending on FADS genetic variants [26, 35, 36, etc.]. Finally, only a small number of the relevant literary sources were reviews, which implied the urgent need to systematize current accumulated data. It should be noted that there were some reviews summarizing the data on association of FADS gene polymorphisms with the development of diseases related to altered lipid metabolism [2].

In our review, we analyze literary sources of the last decade on the relationships between FADS gene polymorphisms, FA synthesis disorders and the development of socially significant chronic diseases associated with changes in lipid metabolism (overweight, obesity, DM2, MS, CVD, and NAFLD). The features of FADS genotype in adults, children, along with pregnant and breast-feeding women are described. The link between genetic factors controlling FA metabolism and lipid metabolism disorders in adults and children is defined. The therapeutic prospects of alimentary PUFA supplementation are discussed as well.

Metabolism of ω-3 and ω-6 PUFAs
The ω-3 and ω-6 PUFAs

Fatty acids are carboxylic acids with a carbon chain containing carboxyl and methyl groups at its ends [31]. Natural FAs are classified into saturated and unsaturated. In contrast to unsaturated FAs, saturated FAs do not have double bonds. If unsaturated FAs contain one double bond, they are called monoenic (monounsaturated) FAs; if they have from two to six double bonds, they are polyunsaturated fatty acids (PUFAs). PUFAs are classified into ω9, ω7, ω6, and ω3 FAs by the position of the first double bond closest to the methyl end of the carbon chain. Additionally, according to the length of the carbon chain (C), FAs are grouped into long-chain (C12-C22), medium-chain (C7-C12) and short-chain (C2-C6) categories. Medium- and short-chain FAs are synthesized *de novo* or are a result of fat consumption [37].

Short-chain FAs can be produced in the intestine during partial digestion of soluble fiber and then enter the circulatory system [38]. Some ω3 and ω6 PUFAs are essential and cannot be synthesized by the human organism; their sufficient intake is critical for its normal functioning [39, 40].

Synthesis of saturated FAs occurs in the cytoplasm of cells of the liver, kidneys, intestines, brain, lung, mammary glands, as well as in adipose tissue (with the participation of acetyl-CoA, NADPH, ATP, Mn^{2+} and HCO^{3-}), while the lengthening of the carbon chain of FAs (both endogenous FAs synthesized in the cytoplasm, and exogenous FAs coming from the intestine) takes place in the mitochondria and involves β-oxidation reactions. Other FAs are formed from palmitic acid synthesized in the cell cytoplasm by elongation of the carbon chain (lengthening) and desaturation (formation of double bonds) with the participation of malonyl-CoA [41]. The processes of elongation and desaturation are repeated and combined with each other.

Enzymes involved in the biosynthesis of monounsaturated and polyunsaturated FAs are called FA desaturases. The transformation of saturated FAs into monounsaturated FAs is catalyzed by stearoyl-CoA-desaturase-1. In mammals, there are no enzymes catalyzing the introduction of double bonds into the FA carbon chain after the 9th carbon atom. Therefore, essential FAs (α-linolenic and linoleic) can be obtained exclusively with food [42, 43]. Linoleic acid is converted into FAs of the ω6 family: γ-linolenic (18:3ω6), dihomo-γ-linolenic (20:3ω6), arachidonic (20:4ω6), adrenic (docosotetraenoic) (22:4ω6), tetracosatetraenoic (24:4ω6), tetracosapentaenoic (24:5ω6), and ω6 docosapentaenoic (22:5ω6) acids. In turn, α-linolenic acid is transformed into FAs of the ω3 family: stearidonic (18:4ω3), eicosatetraenoic (20:4ω3), eicosapentaenoic (20:5ω3), ω3 docosapentaenoic (22:5ω3), tetracosapentaenoic (24:5ω3), tetracosahexaenoic (24:6ω3), and docosahexaenoic (22:6ω3) (*Table* 1).

The enzymes involved in metabolism of ω-3 and ω-6 PUFAs

The synthesis of ω6 and ω3 PUFAs is regulated by the elongation and desaturation enzymes: elongase 2 (ELOVL2) and elongase 5 (ELOVL5), Δ5 desaturase (delta-5 desaturase (D5D) or FADS1) and Δ6 desaturase (delta-6 desaturase (D6D) or FADS2) [44, 45]. Elongases are responsible for the lengthening of the carbon chain in PUFAs. Desaturases catalyze the conversion of a single bond between carbon atoms into a double bond (C=C) called unsaturated bonds. The biosynthesis of docosahexaenoic (22:6ω3) and ω6 docosapentaenoic (22:5ω6) acids includes the formation of FAs with 24 carbon atoms in the endoplasmic reticulum and their further movement to the center of β-oxidation. Considering that FAs can be a substrate for peroxisomal oxidation, they are involved in the regulation of FA composition of membrane lipids [3, 15].

PUFAs of the ω6 and ω3 families are synthesized under the influence of the same enzymes. Thus, as a result of the synthesis of long-chain ω3 PUFAs with the participation of FADS2, stearidonic acid (18:4ω3) is formed from α-linolenic acid (18:3ω3) that is converted into eicosatetraenoic acid (20:4ω3). FADS1 catalyzes the formation of eicosapentaenoic acid (20:5ω3). Then, with the participation of ELOVL2, microsomal elongation of the ω3 chain of docosapentaenoic acid (22:5ω3) to tetracosapentaenoic acid (24:5ω3) occurs followed by desaturation at the position-6 by FADS2 to tetracosahexaenoic acid (24:6ω3). Further, this PUFA is

metabolized through β-oxidation in peroxisomes to docosahexaenoic acid (22:6ω3). Both α-linolenic (18:3ω3) and tetracosapentaenoic (24:5ω3) acids can serve a substrate for desaturation at position-6 of FAs by FADS2 [46].

The sequential synthesis of long-chain ω6 PUFAs begins with desaturation of linoleic acid (18:2ω6) to γ-linolenic acid (18:3ω6) under the impact of FADS2. The resulting acid is metabolized by ELOVL5 into dihomo-γ-linolenic acid (20:3ω6) that, in turn, is converted into arachidonic acid (20:4ω6) by FADS1. Further elongation of arachidonic acid (20:4ω6) by the enzymes ELOVL5 and ELOVL2 leads to the formation of adrenic (docosotetraenoic) (22:4ω6) and tetracosatetraenoic (24:4ω6) acids. At this stage, FADS2 lead to the transformation of tetracosatetraenoic acid (24:4ω6) into tetracosapentaenoic (24:5ω6), and then, as a result of β-oxidation, ω6 docosapentaenoic acid (22:5ω6) is synthesized. Therefore, adrenic (docosotetraenoic) acid (22:4ω6) is a progenitor of ω6 docosapentaenoic acid (22:5ω6), but this pathway does not depend on acyl-CoA-dependent Δ4 desaturase and requires moving between the endoplasmic reticulum and the center of β-oxidation.

The activity of FA desaturases is controlled by the level of dietary PUFAs intake, which can affect the FADS gene expression [47-49].

An impact of polymorphisms of the *FADS1* and *FADS2* genes on the plasma lipid profile

FA desaturases are encoded by genes *FADS1* and *FADS2,* located on the long arm of the human chromosome 11 and on mouse chromosome 19 [45]. In addition to *FADS1* and *FADS2*, other genes that can also affect the plasma level of ω6 PUFAs have been reported: genes on chromosome 10 associated with linoleic acid (18:2ω6) (rs10740118), genes on chromosome 16 associated with linoleic acid, γ-linolenic (18:3ω6), dihomo-γ-linolenic (20:3ω6), and arachidonic (20:3ω6) acids (rs16966952), as well as the genes on chromosome 6 associated with adrenic acid (22:4ω6) (rs3134950) [50]. It has been shown that single nucleotide polymorphisms (SNPs) – i.e., a single base change (A, T, G, C) in a DNA sequence of the *FADS* gene cluster – alter the activity of FA desaturases, plasma lipid profile and glucose homeostasis [51]. Close relationships between *FADS1* and *FADS2* gene polymorphisms, and the plasma levels of ω3 PUFAs, ω6 PUFAs, high-density lipoproteins (HDL), low-density lipoproteins (LDL), and triglycerides have been established [4, 52]. Polymorphisms of the *FADS1* and *FADS2* genes have a different effect on the plasma lipid profile in adults, children, as well as pregnant and breast-feeding women (*Table* 2).

Table 1. The spectrum of ω3 and ω6 fatty acids synthesized from α-linolenic and linoleic acids

The ω6 FAs synthesized from linoleic acid (18:2ω6)		The ω3 FAs synthesized from α-linolenic acid (18:3ω3)	
Name	Formula	Name	Formula
γ-linolenic acid	18:3ω6	stearidonic acid	18:4ω3
dihomo-γ-linolenic acid	20:3ω6	eicosatetraenoic acid	20:4ω3
arachidonic acid	20:4ω6	eicosapentaenoic acid	20:5ω3
adrenic acid (docosotetraenoic) acid	22:4ω6	ω3 docosapentaenoic acid	22:5ω3
tetracosatetraenoic acid	24:4ω6	tetracosapentaenoic acid	24:5ω3
tetracosapentaenoic acid	24:5ω6	tetracosahexaenoic acid	24:6ω3
ω6 docosapentaenoic acid	22:5ω6	docosahexaenoic acid	22:6ω3

Table 2. Associations of FADS1 and FADS2 gene polymorphisms with PUFA levels in adults, children, pregnant and breast-feeding women

SNPs	Association with level of PUFAs	References
FADS1-rs174546	plasma level of ω3 PUFAs in adults	[53]
	plasma level of ω3 PUFAs in pregnant women	[54]
FADS1-rs174547	plasma level of ω3 PUFAs in adults	[53]
FADS1-rs174550	plasma level of ω3 PUFAs in adults	[53]
	plasma level of ω6 PUFAs in adults	[55]
FADS1-rs174556	plasma level of ω3 and ω6 PUFAs in pregnant women	[56]
	level of ω6 PUFAs in breast milk	[57]
FADS2-rs1535	plasma level of ω3 PUFAs in adults	[53]
	level of ω6 PUFAs in breast milk	[58]
FADS2-rs174546	plasma level of ω3 PUFAs in adults	[53]
FADS2-rs174576	plasma level of ω3 PUFAs in adults	[53]
FADS2-rs174575	plasma level of ω3 PUFAs in children (girls and boys)	[59]
	plasma level of ω6 PUFAs in boys	
FADS2-rs174577	plasma level of ω3 PUFAs in adults	[53]
FADS2-rs174602	plasma level of ω3 and ω6 PUFAs in pregnant women	[56]
FADS-rs174537		
FADS-rs174561	plasma level of ω3 PUFAs in adults	[50]
FADS-rs3834458		
Haplotypes		
FADS2-rs1535-rs3834458	level of ω6 PUFAs in breast milk	[58]
FADS2-rs1535-rs174575	level of ω6 PUFAs in breast milk	[58]
FADS1-rs174547-rs174553	level of ω6 PUFAs in breast milk	[58]
FADS2 rs3834458-rs1535-rs174575	level of ω6 PUFAs in breast milk	[58]

SNP, single nucleotide polymorphism; PUFA, polyunsaturated fatty acid.

Table 3. Associations of FADS1 and FADS2 gene polymorphisms with lipid metabolism-related diseases

SNPs	Association with parameters	Pathology	References
FADS1-rs174547	waist circumference, fasting blood glucose, plasma HDL level, BMI	MS, DM2	[32, 71, 72]
FADS2-rs2727270	fasting blood glucose	DM2	[32]
FADS2-rs174575	high birth weight	risk of developing metabolic disorders	[28]
FADS2-rs174601	serum lipid level	risk of developing IHD and IS	[73]
FADS2-rs174602	high birth weight	risk of developing metabolic disorders	[56]
FADS1-rs174545 FADS1-rs174548 FADS1-rs174553 FADS2-rs1535 FADS2-rs174583	BMI	risk of developing obesity in pregnancy	[29]
FADS1-rs174546	BMI, serum lipid level	risk of developing obesity in pregnancy, risk of developing IHD and IS	[29, 73, 74]
FADS2-rs174601 T/T	serum lipid level	risk of developing IHD and IS	[73]
FADS-rs174537G/T	-	high risk of developing IHD	[75, 76]
FADS-rs174537T	-	low risk of developing IHD	[75, 76]
FADS-rs174537 GG	DM2	high risk of developing IHD	[75, 76]
Haplotypes			
FADS1-rs174546 -FADS2-rs174601 T/T)	serum lipid level	high risk of developing IS	[73]
FADS1-rs174546 -FADS2-rs174601 C/C)	serum lipid level	low risk of developing IHD	[73]

SNP, single nucleotide polymorphism; MS, metabolic syndrome; IHD, ischemic heart disease; IS, ischemic stroke; DM2, type 2 diabetes mellitus; BMI, body mass index; HDL, high-density lipoproteins.

An impact of polymorphisms in the FADS1 and FADS2 genes on levels of ω3 and ω6 PUFAs

O. Coltell et al. established correlations between SNPs in the *FADS* gene cluster (*FADS1*-rs174546; *FADS1*-rs174547; *FADS1*-rs174550; *FADS2*-rs1535; *FADS2*-rs174546; *FADS2*-rs174576; *FADS2*-rs174577) and plasma concentration of ω3 PUFAs [53]. M. Al-Hilal et al. discovered associations of SNPs in the *FADS* gene cluster (rs174537, rs174561, rs3834458) with PUFA level [60]. Possibly, different sites at the *FADS1-FADS2* locus affect the activity of the FADS1 and FADS2 enzymes. A randomized controlled study has demonstrated that an increase in the consumption of eicosapentaenoic (20:5ω3) and docosahexaenoic (22:6ω3) acids (doses of 0.45, 0.9 and 1.8 g/day for six months) lead to the elevation of FADS1 enzyme activity and the decrease in FADS2 activity in men and women 45-70 years old [60]. The authors of the study concluded that the rs174537 *FADS* variation influences FADS1 activity and the body response to the increased intake of these FAs. The study by M.A. Lankinen et al. demonstrated that *FADS1*-rs174550 gene polymorphism is associated with fasting blood glucose and the increased serum levels of ω6 lipid mediators synthesized from linoleic acid (18:2ω6) [55]. According to the available data, high linoleic acid (18:2ω6) diet causes an increase in the levels of arachidonic acid (20:4ω6) and other ω6 lipid mediators in blood, kidneys and liver in rats [61]. However, O. Coltell et al. revealed no correlations between SNPs in the *FADS* gene cluster and ω6 PUFA level [53].

J.Y. Bernard et al. showed that the presence of *FADS1*-rs174546 gene in pregnant women correlated positively with ω6 PUFA level, but not with ω3 PUFA level [54]. It was established that pregnant women, carrying the minor alleles of various *FADS* SNPs, have high blood concentrations of PUFA precursors and low level of arachidonic acid (20:4ω6) [28, 29]. *FADS2*-rs498793 and *FADS1*-rs174556 were demonstrated to correlate positively with the plasma levels of arachidonic (20:4ω6) and docosahexaenoic (22:6ω3) acids. At the same time, there is an evidence that *FADS2*-

rs174602 is positively associated with arachidonic acid (20:4ω6) level, but correlates inversely with docosahexaenoic acid (22:6ω3) level [56]. These findings have also confirmed the fact that carriers of the minor allele of SNP rs174602 had a deficiency of docosahexaenoic acid (22:6ω3).

It was also demonstrated that *FADS* gene polymorphisms affected breast milk concentration of PUFAs in breast-feeding women. It was discovered that *FADS1*-rs174556 was related to the fraction of arachidonic acid (20:4ω6) [57], maternal *FADS* genotype was associated with the increased concentrations of linoleic acid (18:2ω6) in umbilical blood, and reduced ratio of arachidonic (20:4ω6) and dihomo-γ-linolenic (20:3ω6) acids, as well as docosahexaenoic (22:6ω3) and α-linolenic (18:3ω3) acids [26, 27]. Minor allele carriage of various *FADS* SNPs was linked to a lower concentration of arachidonic acid (20:4ω6) in breast milk [58]. Hence, FADS SNPs (*FADS2*-rs1535) and haplotypes (*FADS2*-rs1535-rs3834458, *FADS2*-rs1535-rs174575) were associated with low concentrations of γ-linoleic (18:3ω6) and arachidonic (20:4ω6) acids. Similarly, the *FADS* haplotype (*FADS1*-rs174547-rs174553) was also related to declined concentrations of γ-linoleic (18:3ω6) and arachidonic (20:4ω6) acids in breast milk. However, the *FADS2* haplotype rs3834458-rs1535-rs174575 caused an impact solely on the concentration of γ-linoleic (18:3ω6), but not arachidonic (20:4ω6) acid.

The association between *FADS* gene polymorphisms and PUFA level was found not only in adults, pregnant and breast-feeding women, but also in children. We feel that genetic and epigenetic status of maternal *FADS2* gene may affect the PUFA metabolism in children. According to the published data, changes in *FADS2*-rs174575 in a mother in combination with DNA methylation correlated with α-linolenic acid (18:3ω3) level in blood plasma in girls and boys 16 months old, and with arachidonic (20:4ω6) acid level in the group of boys [59]. Generally, changes in the *FADS* genes in children were associated with low concentration of

arachidonic acid (20:4ω6) in their blood, and increased level of linoleic (18:2ω6) and α-linolenic (18:3ω3) acids. However, subjects with both increased and decreased content of docosahexaenoic acid (22:6ω3) were noted [62]. In other studies, the association between changes in the *FADS* genes and docosahexaenoic acid (22:6ω3) level was not observed in children above 8 years of age [63, 64]. Children 9 months old carrying the rs174448 allele exhibited reduced levels of total cholesterol and LDL [65].

The presented results confirm an important role of the *FADS* genes in the regulation of PUFA levels in blood serum, kidneys, and liver [53, 61]. Genetic variations in the *FADS1* and *FADS2* genes involved in the ω3 PUFA metabolism may explain why the activity of these FAs is detected only in some people [25]. For example, SNPs reflecting changes in a nucleotide in the *FADS1* gene alter the effectiveness of fish oil consumption in children [66].

Since polymorphisms in the FA desaturase genes affect the concentration of arachidonic (20:4ω6) and docosahexaenoic (22:6ω3) acids in blood plasma, subjects with certain genotypes may require different amounts of FAs [67]. Personalized prescription of alimentary PUFAs can influence the relationship between these gene variants and FA levels [33]. Modification of the PUFA content in the diet can prevent the adverse effects of *FADS* gene polymorphisms [68].

The described findings suggest an important role of polymorphisms of these genes in lipid metabolism and the contribution of polymorphisms in the pathogenesis of ailments associated with lipid metabolism disorders (MS, CVDs, DM2).

Polymorphisms of the *FADS1* and *FADS2* genes versus metabolic disorders

FADS genes versus inflammation

Recently, it was shown that *FADS1* was a regulator of inflammation [69]. ω3 and ω6 PUFAs, as well as their derivatives, play the pivotal role in onset and resolution of inflammatory reaction. M.A. Lankinen et al. reported that the *FADS1* genotype influenced the relationship between the diet enriched with linoleic acid (18:2ω6) and the development of inflammation [55]. The supplementation of FAs, which are the substrates for ω3 and ω6 PUFAs, to the diet of *FADS1* knockout mice, was accompanied by the development of liver inflammation. The authors pointed out that inflammation was probably not linked to arachidonic acid (20:4ω6), since it was reduced both in *FADS1* knockout mice and in carriers of the genotype related to a reduced activity of the FADS1 enzyme. H. Hermant et al. established that *FADS1*-rs174547 was associated with a low level of arachidonic acid (20:4ω6) and high concentration of dihomo-γ-linolenic acid (20:3ω6), which indicated reduced FADS1 activity in carriers of this allele [70]. In addition, in *FADS1* knockout mice, along with the inflammatory process in the liver, an improvement in glucose tolerance was observed [69]. It was suggested that the association between PUFAs and inflammation was mediated by eicosanoids [5, 6], and that relationship was modified by the *FADS1* genotype. Obviously, subjects have different capacities for the synthesis of ω3 PUFAs from α-linolenic acid and for their accumulation in erythrocytes, or tissues; therefore, the genotype can determine both high and low risk of developing chronic inflammatory diseases [33, 69].

Associations of *FADS1* and *FADS2* gene polymorphisms with lipid-related diseases are presented in *Table* 3.

FADS genes versus metabolic syndrome

Metabolic syndrome (MS) is defined as a group of metabolic disorders that are the risk factors for developing cardiovascular pathologies and type 2 diabetes [1, 10, 77, 78]. The components of MS are arterial hypertension, abdominal obesity, disorders of carbohydrate metabolism, and dyslipidemia [10, 77]. Lipid changes can be both a cause and a consequence of impaired glucose metabolism and insulin resistance. Accordingly, MS and other metabolic diseases, characterized by defective glucose or lipid metabolism, are closely interrelated [79]. The association between MS and cardiovascular pathology, NAFLD, arthritis, chronic kidney disease, schizophrenia, and some types of cancer has been described [80-82].

The rs174547 polymorphism in the *FADS1* gene is associated with the development of MS and its markers, such as an increased visceral fat mass and fasting hyperglycemia. Vegetarians with the *FADS1*-rs174547 genotype had an enhanced risk of developing MS. Decreased intake of α-linolenic acid (18:3ω3) vs. linoleic acid (18:2ω6) may disrupt FA metabolism and block the formation of eicosapentaenoic (20:5ω3) and docosahexaenoic (22:6ω3) acids in vegetarians [71].

The results of the meta-analysis by J. Dumont et al. have also confirmed the association between *FADS1*-rs174547 and plasma HDL level, waist circumference and body mass index (BMI). These connections were modulated by increased consumption of linoleic acid [72]. Single nucleotide polymorphisms in genes encoding *FADS* were discovered to relate to BMI in pregnant women [29]. Consequently, carriers of minor *FADS* alleles (*FADS1*-rs174545, *FADS1*-rs174546, *FADS1*-rs174548, *FADS1*-rs174553, *FADS2*-rs1535, and *FADS2*-rs174583) caused a higher risk of developing obesity during pregnancy. However, women with BMI ≥25 kg before pregnancy were exposed to a lower risk of obesity in pregnancy associated with *FADS* polymorphisms. Overweight or obese women with SNPs in *FADS2* and *ELOVL2* genes had higher ω3 PUFA level than normal weight women. Carriers of minor alleles of *FADS1*-rs174545, *FADS1*-rs174537, *FADS1*-rs174546, and *FADS1*-rs174553 exhibited a low ratio of arachidonic acid (20:4ω6) to dihomo-γ-linolenic acid (20:3ω6), which implied a decrease in activity of FA desaturases [29]. A.J. Yeates et al. noted high birth weights in infants as risk factor of metabolic disorders, those infants born to mothers homozygous for *FADS2*-rs174575 [28]. The effect of prenatal maternal docosahexaenoic acid (22:6ω3) intake on infant birth weight was not unidirectional: women carrying the minor allele *FADS2*-rs174602 gave birth to neonates with a greater body weight than women who received placebo, which may be partly accounted for by an increase in gestational age; hence this effect requires further investigation [56].

FADS genes versus type 2 diabetes mellitus

The prevalence and mortality from DM2 continue to rise worldwide, causing important medical and social implications for the health care system [83]. This pathology is accompanied by metabolic disorders, including hypertriglyceridemia, high LDL, and low HDL.

The genetically determined FA composition and their desaturation are associated not only with lipid metabolism, but also with glucose levels and insulin secretion [30, 32]. FA desaturases play an important role in the reduction of cytosolic nicotinamide adenine dinucleotide (NAD$^+$) to NADH. These reactions are related to glucose metabolism. A decreased

NAD⁺/NADH ratio in the cell cytosol correlates with an elevated activity of FA desaturases [84].

FADS polymorphisms can alter FA composition in plasma and modulate the development of DM2 [30, 46]. Huang M.C. et al. established that *FADS1*-rs174547 and *FADS2*-rs2727270 were associated with a decrease in the activity of FADS1/2 enzymes in patients with DM2 [32]. The effect of alimentary ω3 PUFAs in the associations between polymorphisms of the FADS genes and DM2 requires further investigation.

FADS genes versus cardiovascular pathology

The elevation of blood pressure (BP) and the prevalence of hypertension are associated with overweight and obesity in both adults and children/youth [14]. High activity of the FADS1 enzyme may protect against obesity and hypertension that are increasingly common in children and youth and tend to be observed in adulthood. In addition, the activity of this enzyme affects the content of eicosapentaenoic (20:5ω3), docosahexaenoic (22:6ω3), and arachidonic (20:4ω6) acids involved in the blood pressure regulation [34, 85]. An elevated level of arachidonic acid (20:4ω6) enhances blood pressure, while ω3 PUFAs reduces it [34]. FADS1 activity (assessed by the FADS1 index calculated as the ratio of arachidonic (20:4ω6) to dihomo-γ-linolenic (20:3ω6) acids) is inversely proportional to BMI [34] and blood pressure [86]. Since polymorphisms of the *FADS1* gene are associated with PUFA content in blood plasma, the genetic component may have a substantial effect on the relationship between PUFAs and blood pressure [87].

SNP rs174546 has been shown to affect serum PUFA content [74]. Carriers of the minor allele rs174546 exhibited reduced FADS1 activity, which led to an increase in the levels of linoleic (18:2ω6) and dihomo-γ-linolenic (20:3ω6) acids, while arachidonic (20:4ω6) and eicosapentaenoic (20:5ω3) acid concentrations were reduced [74]. All haplotypes carrying the minor allele were associated with a lower FADS1 activity [74].

Increased activity of FADS2 enzyme was demonstrated in patients with coronary artery disease (CAD). In both CAD and DM2 patients, along with high FADS2 activity, the content of arachidonic (20:4ω6) and dihomo-γ-linolenic (20:3ω6) acids in blood plasma is increased as a result of decline in stearidonic (18:4ω3) and α-linolenic (18:3ω3) acids. Simultaneously, the concentrations of eicosapentaenoic (20:5ω3) and docosahexaenoic (22:6ω3) acids are elevated in DM2 patients, but reduced in CAD patients [75].

The rs174537 G allele in the *FADS* gene is often detected in patients with CAD. At the same time, the rs174537 G/T alleles in the *FADS* gene are associated with an elevated risk of developing this disease, while the rs174537T allele is related to the reduced risk [76]. It should be noted that DM2 patients carrying the rs174537 GG allele in the *FADS* gene had an augmented risk of developing CAD [76]. The carriers of the rs174460 C allele also had a higher risk of CAD. These results imply that the *FADS* gene polymorphisms affect plasma FA concentration and FA desaturase activity. Q Yang et al. studied the relationship between SNPs *FADS1*-rs174546 and *FADS2*-rs174601, and the risk of CAD and ischemic stroke (IS). The haplotype of T/T nucleotides in the *FADS1* and *FADS2* genes (rs174546-rs174601) was associated with an increased risk of IS, and the haplotype of C/C nucleotides in these genes (rs174546-rs174601) was linked to a reduced risk of CAD

and IS [73]. The carriers of T/T SNPs in the *FADS2*-rs174601 gene had a decreased HDL and apolipoprotein (ApoAI) levels in serum in the groups of patients with CAD, IS and subjects with an elevated risk of these pathologies.

The study of *FADS* gene polymorphisms would allow establishing the efficacy of ω3 and ω6 PUFAs in the treatment of CVDs.

FADS genes versus NAFLD

NAFLD includes a wide range of liver disorders – such as steatosis, non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis [88, 89]. Clinical and preclinical studies showed that NAFLD was associated with severe lipid metabolism disorders and changed FA desaturase activity (increased FADS2 activity and decreased FADS1 activity). Currently, there is no doubt that disorder of FADS activity caused by polymorphisms of their genes are accompanied by dysregulation of FA biosynthesis, which contributes to the pathogenesis of NAFLD [4, 90]. Thus, the suppression of transcription of FADS1 genes in the liver results in an elevated risk of developing NAFLD in children [13]. Studying the relationship between *FADS* gene polymorphisms and the content of FADS enzymes could help in the development of personalized therapy for NAFLD. For example, children with NAFLD, who are carriers of low-functional alleles of the *FADS1* genes, exhibit a better response to alimentary ω3 PUFAs [13]. Adult carriers of alleles associated with reduced FADS1 activity also respond better to ω3 PUFA intake [90]. At the same time, FADS2 activity is significantly increased in patients with NAFLD combined with CAD, while this association is not observed regarding *FADS2*-rs3834458 polymorphism [46]. These results indicate the need for further studies of polymorphisms in genes encoding FADS for assessing the effectiveness of using ω3 PUFAs in the treatment of NAFLD and CVDs.

The *FADS1/2* gene polymorphism affects the activity of FA desaturases via DNA methylation [91]. High FADS2 activity in patients with NAFLD is associated with low DNA methylation at two sites: cg06781209 and cg07999042. The cg07999042 site is linked with the risk of developing DM2 in men with a low birth weight [92]. Altered DNA methylation of several genes, in turn, is related to obesity, DM2, and NASH [93]. At the same time, impaired DNA methylation in *FADS2* promotes, first of all, the change in the activity of FA desaturases and the development of hepatic steatosis, rather than inflammation or fibrosis [4, 94].

Therefore, polymorphisms of FA desaturase genes are closely linked to the disorders of lipid metabolism and diseases associated with them.

Conclusion

The literature data systematized in this review demonstrate that the impairment of the activity of FADS and their genes are accompanied by the dysregulation of the metabolic pathway involved in FA biosynthesis, which is an important component in the pathogenesis of many chronic non-communicable inflammatory diseases associated with lipid metabolism disorders. Obesity, overweight, MS, CVD, and NAFLD are typical not only for adults, but for children as well. Childhood obesity correlates with the development of CVD and DM2 in adulthood. The relationships between the risk of these pathologies and lipid metabolism disorders in pregnant and breast-feeding women are studied. The

modulation of epigenetic mechanisms in pregnant and breast-feeding women, children and youth via using fatty acids may improve metabolic health and reduce the risk of developing lipid metabolism-related diseases in adults.

The relationship between genetic factors controlling fatty acid biosynthesis, lipid metabolism disorders, and the development of common pathologies associated with those in adults and children, was described in this review. SNP in the *FADS1* gene cluster *FADS1*-rs174547 affect ω3 PUFA concentration in blood plasma and lead to the development of MS and DM2. *FADS1*-rs174546, *FADS2*-rs1535 SNPs also influence ω3 PUFA content in blood plasma and increase the risk of obesity during pregnancy, as well as the chance of developing CAD and IS. Correlations between *FADS*-rs174537 and PUFA level also relate to a higher risk of CAD. *FADS2*-rs174602 is associated with ω3, ω6 PUFA levels in blood plasma and an elevated risk of metabolic disorders. Changes in *FADS2*-rs174575 correlate with the levels of ω3 and ω6 PUFAs in blood plasma and enhance a risk of metabolic disorders in the mother. Thus, FAs can regulate gene expression by altering epigenetic mechanisms and, therefore, they have a positive or negative effect on metabolic outcomes. Additional research is needed to detail the role of FAs in the regulation of epigenetic mechanisms in metabolic diseases. The polymorphisms of *FADS1/2* genes affect the activity of FA desaturases via DNA methylation. However, it is important to investigate other epigenetic mechanisms, for example, acetylation or deacetylation of histones and miRNAs.

According to the literature, PUFAs are widely used as dietary supplements for the prevention and treatment of inflammatory diseases associated with lipid metabolism disorders. Disparities in the results of the studies assessing the benefits of PUFA supplementation may be explained by the fact that people of different ages and ethnic origins may exhibit different responses to PUFAs coming from food. Specific features of such metabolic response to the use of these FAs in adults, children, pregnant and breast-feeding women were established. Currently, many factors that may influence the ability to effectively react to alimentary PUFAs, in particular, variants of the genes involved in the PUFA metabolism, are under study.

Hence, the health effects of dietary ω-3 and ω-6 PUFAs may vary depending on FADS genetic variants. Further study of the genetic mechanisms regulating the metabolic pathways involved in the FA synthesis would contribute to a better understanding of the pathogenesis of many multifactorial diseases, as well as to predicting the effectiveness of their treatment via using ω3 PUFAs. Additional studies of the regulatory mechanisms of specific genes, their metabolic effects and the influence of other components (such as intestinal microbiota, methyl donors, polyphenols, etc.) on epigenetics are needed.

Conflict of interest
We declare that we have no conflicts of interest.

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