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Nutritional Genomics of Cardiovascular Disease

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Abstract

Purpose—Cardiovascular disease (CVD) is the leading cause of death in the United States and globally. There is significant evidence implicating genetic and dietary factors in the development and progression of CVD and its risk factors. Nutritional genomics is a comparatively new field of science that focuses on the relationship of individual genetic variation with response to nutrition. The purpose of this review is to summarize recent progress, in the field of nutritional genomics as it relates to cardiovascular disease.

Recent findings—Evidence from recent studies has shown significant effects of gene-diet interactions on CVD biomarkers and the development and progression of CVD. The cardiovascular effects of gene-nutrient interactions with respect to macronutrients and genes such as *FTO*, *ACE*, *PPARs*, *TCF7L2*, *BDNF*, *MC4R*, *APOAs*, *FADS*, etc. have shown consistent results across age groups and populations whereas gene-nutrient interaction effects of other genes have only been limited to specific ages, genders or populations and need to be validated and confirmed.

Summary—The identification of individual genetic variation influencing diet-related CVD risk is important and may inform future nutritional intervention studies. Although there is ample scientific evidence indicating that the genetic susceptibility to CVD can be modified by diet, we are still not at a stage where this information is easily translated into dietary plans. Thus, there is a need for better approaches to achieve precision in dietary data collection and streamline computational approaches for meaningful and effective nutritional interventions.

Keywords

Nutrients; diet; genetics; genomics; transcriptomics; precision nutrition

Introduction

Cardiovascular disease (CVD) refers to a group of disorders including coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart diseases, congenital heart disease, deep vein thrombosis and pulmonary embolism (1,2). CVD is the

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Compliance with Ethics Guidelines

Conflict of Interest

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Human and Animal Rights and Informed Consent

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number one cause of death globally, accounting for about one-third of deaths (3). Although over three quarters of deaths take place in low and middle income countries, the United States is not far behind. In the United States, one in 4 deaths are attributed to CVD (3,4). Cardiovascular diseases are highly influenced by genetic factors (5,6), and there is also significant evidence implicating diet and lifestyle factors (e.g., obesity, sedentary behavior) in the development and progression of CVD and its risk factors (7,8). It is also known that diet and lifestyle at younger ages can influence the risk for disease risk at a later age. Differences in susceptibility to CVD based on genotypes, ethnicities and environments have long intrigued people; more recently, there has been a growing interest in the role of individual genetic variation in response to nutrition in human populations (9,10) and an increasing recognition that the interaction between genes and environment (e.g. diet/nutrition) can have a major impact on metabolic alterations. Thus, understanding the biological mechanisms underlying CVD and applying this knowledge to are key components for management of CVD

The discipline of nutritional genomics, focusing on the effects of nutrients or dietary constituents on the expression of genes (nutrigenomics) and the effects of genetic variation on the metabolic response of nutrients (nutrigenetics) (11*–15), is being increasingly recognized as a major player in disease risk. Obesity, type 2 diabetes/insulin resistance/glucose intolerance, hypertension and dyslipidemia represent four modifiable CVD risk factors where there has been considerable progress related to nutritional genomics. Other CVD risk factors where nutritional genomics can be important to understand the etiological underpinnings include elevated oxidative stress and inflammation. Since genes, diet and their interactions can have significant effect on disease risk, translating this science to practice is crucial for disease prevention and management. Most modifiable among the CVD risk factors are diet/nutrients (16, 17), highlighting the importance of understanding the interaction between genes and diet in modulating CVD risk. However, key questions remain, e.g.: Is there enough scientific evidence to implicate genes, nutrients and their interactions as significant contributing factors in CVD risk? And where are we in the field with respect to disseminating this information to patients or public, e.g., precision health (precision medicine and precision nutrition) (12*)? The purpose of this review is to summarize recent progress in the field of nutritional genomics related to cardiovascular disease research.

Obesity

Obesity, particularly abdominal obesity, is a key risk factor for CVD. According to a recently released report by the CDC, the prevalence of obesity, in 2015–2016, was 39.8% among adults and 18.5% among youth (cdc.gov accessed on Feb 1, 2018). It is well known that obesity is influenced by genetic and environmental factors. To date, more than 300 common single nucleotide polymorphisms (SNPs) affecting obesity and related phenotypes have been identified from genome-wide association and candidate gene studies (18). The key genes that have been implicated in obesity and related phenotypes are fat mass-and obesity-associated gene (*FTO*), melanocortin 4 receptor (*MC4R*), peroxisome proliferator activated receptor gamma (*PPAR γ*), transmembrane protein 18 (*TMEM18*), brain derived neurotrophic factor (*BDNF*), pro-opiomelanocortin (*POMC*), neuronal growth regulator1 (*NEGR1*), proprotein convertase subtilisin/kexin type 1 (*PCSK1*), SH2B adaptor

protein1 (*SH2B1*), leptin receptor (*LEPR*) and neurotrophic receptor tyrosine kinase 2 (*NTRK2*) with *FTO* showing the strongest and consistent signal across age groups, genders and ethnicities (18–29, 24*). In a recent study of more than 339,000 individuals (23), 97 loci were identified as associated with BMI, 56 of which were novel. However, all these 97 loci jointly explain only about 2.7% of the variation in BMI. This indicates that many more SNPs and other factors such as gene $\times$ gene and gene $\times$ environment interactions may explain the missing variance.

Epidemiological studies have shown that environment can exacerbate the effects of genes on obesity. Evidence has consistently pointed to the role of gene $\times$ diet interaction in the risk of obesity (19). Most of the studies have focused on the interaction between genes and consumption of macronutrients as they relate to the development and/or progression of obesity. The best-characterized gene variants known to interact with dietary nutrients and affect obesity have been mostly identified using candidate gene approaches. These candidate variants are usually the top ranked in genome-wide association studies using some data reduction strategies. Of these genetic loci, *FTO*, *BDNF*, apolipoprotein A2 and A5 (*APOA2* and *APOA5*), *PPAR γ* , *NEGR1*, *TMEM18* and *LEPR* have been extensively studied with respect to their interaction with diet (26–30). In about 26,000 individuals from a cohort in Southern Sweden, *NEGR1* SNP was associated with dietary intake (low fat and high carbohydrate intake) and the interaction of rs4923461 of *BDNF* with protein intake was significantly associated with BMI (26). Protein intake was also found to affect the association between *FTO* and BMI in children and adolescents where the association between *FTO* variant and BMI was much weaker in low-protein intake groups compared to high-protein intake groups (27). Similarly, the association between *FTO* and BMI was found to be stronger in individuals with high fat intake than those with low fat intake (28,29) which was replicated in three cohorts comprising of more than 9000 women from Nurses' Health study, 6000 men from the Health Professionals Follow-up study and 21000 women from Women's Genome Health study (30,31). Additionally, studies in children have shown the modification of the association between SNPs in *APOA2*, *APOA5* and *LEPR* and obesity by dietary fat (32). Most of the studies shown above have been conducted in individuals of European ancestry. However, the effects of *FTO* and its interaction with either protein or fat intake on BMI seems to expand across ethnicities to Asian Indians (33).

Since single variants may not explain the complete phenotypic variation, taking into account multiple variants by computing a comprehensive genetic risk score (GRS) may be better to detect a significant portion of genetic variance affecting a phenotype. Following this approach, Qi et al. (30) found that an association between BMI and a multi-SNP GRS was stronger in individuals who consumed more fried foods than those with who didn't. This specific GRS included 32 SNPs near genes related to central nervous system such as *FTO*, *BDNF*, neurexin 3 (*NRXN3*), and *TMEM18*. The SNPs included in the GRS were selected based on previous genetic association results of BMI and/or obesity traits. The same group also showed the pronounced effects of sugar-sweetened beverages consumption on the association between a 32 SNP GRS and BMI (31). In contrast, the CHARGE consortium (Cohorts for Heart and Aging Research in Genomic Epidemiology) reported the same 32 SNP GRS to be strongly associated with BMI in subjects eating a healthier diet that included self-reported intake of whole grains, fish, fruits, vegetables, nuts, etc (20*).

In addition to macronutrient intake, dietary fiber intake was also found to modify the association between *FTO* and BMI. Using individual *FTO* SNPs and GRS created with *FTO* SNPs, the authors found that the association of *FTO* variants with BMI was stronger in individuals who consumed high levels of dietary fiber. Individuals with AA of rs11076023 (33) and TT and AT of rs3751812 (34) had lower abdominal obesity or waist circumference in those who had the highest fiber intake (33,34). A member of the superfamily of non-haem-Fe(II) and 2-oxoglutarate (2OG)-dependent dioxygenases, FTO is believed to be involved in regulation of energy intake with a key role in nervous and cardiovascular system (35,36).

Type 2 diabetes, insulin resistance and glucose intolerance

Type 2 diabetes (T2D) is defined as hyperglycemia resulting from insufficient insulin secretion and/or utilization (37). T2D is an independent risk factor for CVD. Similar to other CVD risk factors, T2D is under significant nutritional and genetic influence. Over 70 genes and 100 SNPs have been identified so far that are associated with T2D (38*). Gene-nutrient interaction studies have identified interactions between western dietary patterns and variants in *PPAR* γ , transcription factor 7 –like 2 (*TCF7L2*) and *FTO* in influencing T2D. Mainly, rs1801282 (Pro12Ala) of *PPAR* γ has been positively associated with insulin sensitivity (39, 40*). Individuals with the ProPro were more responsive to increased polyunsaturated fatty acids (PUFA) intake than those with the ProAla or AlaAla genotypes(39). The same group also showed the association between G protein-coupled receptor 120 (*GPR120*) loss-of-function variant (R270H) and the risk of T2D was higher with higher fat intake, particularly in H-carriers (40*). Similarly, rs12573128 of transcription factor 7 like 2 (*TCF7L2*) interacts with fat intake to affect insulin sensitivity as measured by HOMA-IR index and rs9939609 of *FTO* interacts with carbohydrate intake to affect T2D risk (41). The role of BDNF in diabetes and Alzheimer's disease is known (42). In a Korean study, the interaction between *BDNF* variants and energy and protein intake had significant effects on T2D and glucose intolerance. Individuals with rs6265 Val/Met and Met/Met variants had lower risk for T2D on high-carbohydrate and low energy intake (42).

Hypertension

Hypertension, characterized by high systolic blood pressure and/or high diastolic blood pressure, is associated with heart failure, renal disease, stroke and cardiovascular death, and is highly modified by lifestyle changes (43). It has been reported that, for individuals between the ages of 40–69 years, every 20 mmHg increase in systolic blood pressure and 10 mmHg increased in diastolic blood pressure doubles the risk for CVD (44,45). Weight loss, increased physical activity and a healthy diet with decreased salt intake are some of the lifestyle modifications advocated for management of hypertension. Blood pressure is also influenced by genetic factors with its heritable component being 30–50% (46). The renin-angiotensin system (RAS) and its components play a major role in the regulation of hypertension (47). The angiotensin-converting enzyme (ACE) is the key enzyme in controlling blood pressure and polymorphisms in *ACE*, the gene encoding this enzyme, have been implicated in the risk for hypertension and CVD. In the Nutrigenomic analysis in Twins (NUGAT) study, GG genotype of rs4343 of *ACE* was associated with increased risk for hypertension and CVD in individuals on high saturated fat diet (48**). The proposed

mechanisms seem to involve high-fat in activating RAS in adipocytes through toll-like 4 receptors and NFkB signaling (49). The association of salt with hypertension is well-known and there have been some efforts to elucidate the genetic contribution to salt-sensitive blood pressure (SSBP) changes. In a recent study, variants in estrogen receptor (*ESR2*) were implicated in SSBP. Estrogen-replete women with *ESR2* rs10144225 minor allele were more salt-sensitive than men or postmenopausal women (50). The Genetic Epidemiology Network of Salt-sensitivity (GenSalt) study was designed to understand the basis of salt-sensitivity in ~ 2000 individuals administered a 7-day low-sodium diet followed by a 7-day high-sodium diet. This study found SSBP to be associated with rare variants in three genes of a group of renal epithelial sodium channels (ENaC) (51). Using a blood pressure GRS, the same group found that a blood pressure GRS to be inversely related to SSBP (52).

Dyslipidemia

Elevated circulating triglycerides and LDL cholesterol levels and lower HDL cholesterol increase the risk for CVD. Studies have shown that polymorphisms in genes associated with fatty acid metabolism interact with glucokinase dietary fat intake to affect circulating lipid concentrations (53–56). In a study where 208 participants were given fish oil supplementation for 6 weeks, plasma triglycerides levels decreased in individuals with retinoid $\times$ receptor alpha (*RXR α*) SNPs. They found that individuals with CT or TT genotypes of *RXR α* SNP rs11185660 had decreased plasma triglycerides as compared to those with CC genotypes following fish oil intake (53). They also found significant increase in the expression of carnitine palmitoyl transferase 1 A (*CPT1A*) gene following the intake of fish oil. Similarly, people with the E4 allele of apolipoprotein E (*APOE*) were less responsive in their plasma PUFA concentrations to dietary fat manipulation and more so if they were overweight (54,55). PUFAs such as ω 3 and ω 6 fatty acids are essential fatty acids that need to be provided through diet. They are part of membrane structure and have roles in lipid metabolism, blood clotting, blood pressure and inflammation (56). They have also been shown to interact with fatty acid desaturase (FADS) variants to affect low-density lipoprotein (LDL) cholesterol concentrations and obesity phenotype (85,86). Additionally, carbohydrate intake has also been reported to interact with glucokinase genetic variation to affect plasma triglycerides (57).

Inflammation, oxidative stress and other CVD risk factors

Diet $\times$ gene interactions are believed to affect inflammation and oxidative stress, which contribute significantly to the development and progression of CVD (58–61). However, nutrigenetics/nutrigenomics studies in humans are very limited. In elderly women, vitamin D3 supplementation reduced inflammatory markers and increased total antioxidant capacity in those with vitamin D insufficiency. Those with the BB/Bb genotype of vitamin D receptor (*VDR*) gene were more responsive to the supplementation compared to those with bb genotype (58). In a Japanese study, genetic variation in oxidative risk-related genes carnosine dipeptidase (*CNDP1*) and carnosine cellular non-specific dipeptidase (*CNDP2*) were correlated with obesity risk but only in individuals with high carbohydrate intake and low carotene intake (59). Although it is believed that diet can modify the relationship between oxidative stress and gene polymorphisms, very few studies have been conducted in this regard. There have been some studies related to the supplementation of zinc, copper and

selenium and their interaction with gene polymorphisms on oxidative stress, particularly interleukin 6 (*IL6*) and metallothionein 1A (*MT1A*) genes (60,61). Elderly people carrying GG genotypes may need zinc supplementation to improve their stress response because GC/CC genotypes display better stress response than GG carriers (60). Similarly, *MT1A* +647A/C is associated with zinc deficiency. Thus, *IL6* and *MT1A* polymorphisms can be used to identify old people for dietary intervention (61).

There has been much interest in studying the effects of dietary patterns in addition to individual nutrients. Several dietary patterns have been shown to be beneficial for cardiovascular health. Some of these, such as Mediterranean, Prudent and Dietary Approaches to Stop Hypertension (DASH) diets, have been extensively researched. All of them emphasize the beneficial effects of whole grains and fruits and vegetables and deleterious effects of sodium, saturated fats and sugars. One of the prominent trials highlighting the beneficial effects of the Mediterranean diet is PREDIMED (Prevencion con Dieta Mediterranea) trial (62,63). The PREDIMED trial was conducted to determine the effect the type of fat on CVD mortality. Spanish individuals at high risk for CVD were asked to partake Mediterranean diet supplemented with olive oil or nuts or low fat (62). The intervention was based on provision of olive oil or nuts and education. The primary endpoint was the rate of major CV events (63). Ortega-Azorin and colleagues have found that the association between *FTO*-rs9939609 and *MC4R*-rs17782313 and T2D was stronger when the adherence to a Mediterranean diet was low (64). In fact, several studies from the PREDIMED trial have demonstrated the effectiveness of a Mediterranean meal in modulating genetic association of obesity, diabetes and other CVD risk factors (65–67). Individuals on Mediterranean diet and G-carriers of rs382316 of Max-like protein X interacting protein-like (*MLXIPL*) reduced their triglycerides and their risk for myocardial infarction as compared to CC carriers (68*). The Dietary Approaches to Stop Hypertension (DASH) was a multi-center study to test the effects of healthy dietary patterns on hypertension (69). A comparison between individuals on Western diet and DASH diet showed that the effect of sodium intake on blood pressure differed based in their genotypes mainly in angiotensinogen, beta2-adrenergic receptor and kallikrein loci (70). In addition, interaction between low fat and hypocaloric diets have been shown to interact with circadian locomotor cycles kaput (*CLOCK*) and BDNF SNPs to affect obesity, inflammation and diabetes phenotypes (Table 1) [81,82, 87,88].

Nutrigenomics of CVD risk factors

Nutrigenomics is another aspect of nutritional genomics and refers to the study of effects of nutrients on the expression of individual genes (7). Nutrigenomics studies in humans typically use either whole blood or peripheral blood mononuclear cells (PBMCs) and focus on changes in PBMC gene expression after intervention with nutrients or meals (71–73). Vedin et al (71) found inflammation-related genes to be down regulated in Alzheimer's patients with ω 3 PUFA supplementation. Likewise, Rudkowska et al (72) found a positive change in CVD markers. The circulating levels of high-density lipoprotein (HDL) cholesterol increased with a parallel reduction in triglycerides and expression of genes related to oxidative stress and inflammation. Furthermore, positive changes were also observed in inflammation-related miRNA and cytokines gene expression with a one-year

supplementation with grape extract (73). A study comparing the effects of Mediterranean with Western meal on inflammation and oxidative stress found that the Mediterranean diet significantly reduced ox-LDL and expression of inflammation and oxidative stress-related genes (74).

In 30 individuals participating in a study from the Quebec City Metropolitan area, distinct gene expression patterns were found between individuals on Western vs. Prudent diet. The Western diet was characterized by high intake of refined grains, desserts, sweets and processed meats, while the Prudent diet featured high intake of vegetables, fruits and whole grain products (75). Most of the genes that showed significant differences were related to inflammation and immune response, cancer and CVD. In another study in which individuals were on Mediterranean diet as part of the PREDIMED trial, the observed alterations in PBMC gene expressions were in cardiovascular pathways (76). Ellsworth et al. (77**) tested the short-term and long-term effects of lifestyle modifications in which 63 individuals underwent lifestyle modification (low-fat vegetarian diet, increased physical activity, 1 hour of stress management and weekly group support sessions) versus 63 matched controls. There were no changes in CVD related circulating biomarkers or gene expression in controls. In contrast, the group with lifestyle modification experienced reduction in expression of pro-inflammatory genes.

Conclusions

The view that diet influences health is an ancient notion but our understanding of the various mechanisms is still evolving. Nutrigenetics and nutrigenomics are two areas which are leading the way in addressing the questions of which components of diet most influence health, what are the underlying mechanisms, and which individuals are more/less susceptible to nutrient-associated disease (78,79*). The role of nutritional genomics is well established in monogenic diseases such as phenylketonuria, lactase deficiency and glucose-6-phosphate deficiency, however, the field is still developing with respect to complex diseases such as CVD.

Although there is ample scientific evidence indicating that the genetic susceptibility to CVD can be modified by diet (summarized in Table 1), we are still not at a stage where this information is easily translated into dietary plans. Most of the previous results are based on cohort studies that rely on self-reported data derived from 24-hr diet recalls and food frequency questionnaires. Thus, there is a need for better approaches to achieve precision in dietary data collection and update computational approaches. The selection of SNPs for gene $\times$ nutrient interaction analyses also need to be streamlined. Currently, variants to be tested are selected based on the statistical significance in genetic studies and not necessarily, on biologically meaningful SNPs in the process. Additionally, follow-up studies may not be sufficiently powered for replications, variation in dietary exposure may be too great and some of the results may be replicable only in a sub group because of their particular genetic patterns.

There is a need for more intervention studies, specifically randomized and controlled clinical trials, generating valid and precise information that can be utilized by dietitians in their

practice. Some nutritional interventions can be very effective, with the likely effect size of some genotype-specific nutritional interventions being as large as that of medical treatments. Secondly, misconceptions about this field (nutrigenetics and nutrigenomics) and misinterpretation of outcomes are major barriers to the translation or implementation of these results with respect to public health. Therefore, we need to create awareness and emphasize health education, taking into consideration the social and ethical implications. Overall, this is an exciting time for nutritional genomics. Consistency of significant results by replication studies in separate cohorts and emphasis on biologically relevant and statistically significant variants will eventually lead to CVD prevention measures and generate hypotheses for clinical trials for genotype-guided CVD management.

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Table 1

Consistent (replicated) gene by nutrient interaction effects on CVD biomarkers

Gene	SNP	Nutrient/diet	CVD outcome	Discussion	Reference
<i>ACE</i>	rs4343	High saturated fat diet	Blood pressure	GG carriers had higher systolic blood pressure than AA or AG carriers	Schuler et al. 2017
<i>ACE</i>	INDEL	Salt intake	Hypertension	An increase in hypertension was observed with a higher salt intake in ID/DD but not II genotype.	Wang et al. 2017
<i>CLOCK</i>	rs4580704	Mediterranean diet	Type 2 diabetes status	G carriers showed decreased incidence of type 2 diabetes compared to CC genotypes after ~5 year intervention.	Corella et al. 2016
<i>CLOCK</i>	rs4580704	Low fat diet	C-reactive protein	CC carriers showed a greater reduction in hs-CRP than CG or GG carriers after a 12 month intervention	Gomez-Delgado et al. 2015
<i>CLOCK</i>	rs1801260	Low fat diet	Insulin concentrations	TT carriers had lower plasma insulin, HOMA1R and higher insulin sensitivity compare to C carriers after a 12 month intervention	Garcia-Rios et al. 2014
<i>CLOCK</i>	rs3749474	Hypocaloric diet	BMI	T carriers increased their BMI with increase in dietary fat compared to CC carriers who showed no change after a 12-week calorie restriction program	Loria-Kohen et al. 2016
<i>FTO</i>	rs8050136	Carbohydrate intake	Obesity	A carriers had increased risk of obesity as than CC carriers in a cross-sectional study in Asian Indians	Vinlaeswaran et al. 2016
<i>FTO</i>	rs9939609	High protein intake	BMI	Association between BMI and rs9939609 was stronger in children with higher protein intake	Qi et al. 2015
<i>FTO</i>	rs1558902	Protein intake	BMI	AA carriers with lower protein intake had higher BMI compared to TT carriers	Merritt et al. 2018
<i>FTO</i>	rs9939609	Protein intake	BMI	Association between rs9939609 and BMI was weaker in low-protein intake group compared to high-protein intake group	
<i>FTO</i>	rs9939609	Dietary saturated fat intake	Obesity	A carriers had higher risk of obesity exacerbated by high dietary saturated fat intake compared to TT carriers in longitudinal study of 7.5 years	Phillips et al. 2012
<i>FTO</i>	rs9939609	Energy-adjusted fat intake	BMI	A carriers had higher BMI intake in high-fat diet group but not low-fat diet group	Sonestedt et al. 2009
<i>FTO</i>	rs1558902	Fried food consumption	BMI	The association between FTO variant and BMI was stronger in high fried food consumer compared to low or normal fried food consumers	Qi et al. 2014
<i>BDNF</i>	rs4923461	High protein intake	BMI	A carriers had higher BMI with higher protein intake as compared to GG carriers	Rukh et al. 2013
<i>BDNF</i>	rs10767664	Hypocaloric diet	BMI	AA carriers had a greater reduction in BMI compared to T carriers in obese subjects after a 3-month intervention	de Luis et al. 2018
<i>FADS1</i>	rs174547	Linoleic acid (LA) intake	BMI	Each copy of the minor allele was associated with lower BMI and waist circumference in the lower LA intake group and not the high LA intake group	Dumont et al. 2017
<i>FADS1</i>	rs174547	Polysaturated fat (PUFA) intake	LDLc	C carriers had lower LDL concentrations only in the lowest tertile of n-3 PUFA intakes compared to TT carriers in a cross-sectional study	Hellstrand et al., 2012

ACE-Angiotensin-converting enzyme; BDNF Brain-derived Neurotrophic factor; CLOCK Circadian Locomotor Output Cycles Kaput; FADS1 fatty acid desaturase 1; FTO Fat mass and obesity-associated BMI Body mass index; LDLc Low density lipoprotein cholesterol