

Interaction between Dietary Fat Intake and Metabolic Genetic Risk Score on 25-Hydroxyvitamin D Concentrations in a Turkish Adult Population

Item Type	Article
Authors	Isgin-Atici, Kubra;Alathari, Buthaina E.;Turan-Demirci, Busra;Sendur, Suleyman Nahit;Incilay, Lay;Ellahi, Basma;Alikasifoglu, Mehmet;Erbas, Tomris;Buyuktuncer, Zehra;Santhanakrishnan, Vimalleswaran Karani
Citation	Isgin-Atici, K., Alathari, B. E., Turan-Demirci, B., Sendur, S. N., Incilay, L., Ellahi, B., Alikasifoglu, M., Erbas, T., Buyuktuncer, Z., & Vimalleswaran, K. S. (2022). Interaction between dietary fat intake and metabolic genetic risk score on 25-Hydroxyvitamin D Concentrations in a Turkish adult population. <i>Nutrients</i> , 14(2), 382. https://doi.org/10.3390/nu14020382
DOI	10.3390/nu14020382
Publisher	MDPI
Journal	Nutrients
Download date	2026-04-18 07:40:31
Item License	https://creativecommons.org/licenses/by/4.0/
Link to Item	http://hdl.handle.net/10034/626800

Interaction between Dietary Fat Intake and Metabolic Genetic Risk Score on 25-Hydroxyvitamin D Concentrations in a Turkish Adult Population

Kubra Isgin-Atici^{1,2,†}, Buthaina E. Alathari^{3,4,†}, Busra Turan-Demirci¹, Suleyman Nahit Sendur⁵, Incilay Lay⁶, Basma Ellahi⁷, Mehmet Alikasifoglu⁸, Tomris Erbas⁵, Zehra Buyuktuncer^{1, †,*} and Vimalleswaran Karani Santhanakrishnan^{3, 9, †,*}

¹Department of Nutrition and Dietetics, Faculty of Health Sciences, Hacettepe University, 06230, Ankara, Turkey; zbtuncer@hacettepe.edu.tr (Z.B.); k.isginatici@gmail.com (K.I.A.); busraturan@hacettepe.edu.tr (B.T.D.)

²Department of Nutrition and Dietetics, Faculty of Health Sciences, Amasya University, 05000, Amasya, Turkey

³Hugh Sinclair Unit of Human Nutrition, University of Reading, Reading RG6 6DZ, UK; b.e.a.a.alathari@pgr.reading.ac.uk (B.A.); v.karani@reading.ac.uk (V.K.S.)

⁴Department of Food Science and Nutrition, Faculty of Health Sciences, The Public Authority for Applied Education and Training, AlFaiha 72853, Kuwait

⁵Department of Endocrinology and Metabolism, School of Medicine, Hacettepe University, 06230, Ankara, Turkey; erbast@hacettepe.edu.tr (T.E.); snahitsendur@hotmail.com (S.N.S.)

⁶Department of Medical Biochemistry, Faculty of Medicine, Hacettepe University, Ankara, Turkey; Clinical Pathology Laboratory, Hacettepe University Hospitals, 06230, Ankara, Turkey; lincilay@gmail.com (I.L.)

⁷Faculty of Health and Social Care, University of Chester, Chester CH1 4DS, UK; b.ellahi@chester.ac.uk (B.E.)

⁸Department of Medical Genetics, School of Medicine, Hacettepe University 06230, Ankara, Turkey; Genetics Diagnostic Centre, DAMAGEN, Ankara, Turkey; kasif@hacettepe.edu.tr (M.A.)

⁹Institute for Food, Nutrition, and Health, University of Reading, Reading RG6 6AP, UK

* Correspondence: zbtuncer@hacettepe.edu.tr; Tel.: +90-312-305-1094 (Z.B.); v.karani@reading.ac.uk; Tel.: +44 -0118 -378 -8702 (V.K.S.)

† These authors contributed equally to this work.

Abstract: Previous studies have pointed out a link between vitamin D status and metabolic traits, however, the consistent evidence has not been provided yet. This cross-sectional study has used a nutrigenetic approach to investigate the interaction between metabolic-genetic risk score (GRS) and dietary intake on serum 25-hydroxyvitamin D [25(OH)D] concentrations in 396 unrelated Turkish adults, aged 24-50 years. Serum 25(OH)D concentration was significantly lower in those with a metabolic-GRS \geq 1 risk allele than those with a metabolic-GRS $<$ 1 risk allele ($p=0.020$). A significant interaction between metabolic-GRS and dietary fat intake (energy%) on serum 25(OH)D levels was identified ($P_{\text{interaction}}=0.040$). Participants carrying a metabolic-GRS \geq 1 risk allele and consuming a high fat diet ($\geq 38\%$ of energy= 122.3 ± 52.51 g/d) had significantly lower serum 25(OH)D concentration ($p=0.006$) in comparison with those consuming a low-fat diet ($<38\%$ of energy= 82.5 ± 37.36 g/d). In conclusion, our study suggests a novel interaction between metabolic-GRS and dietary fat intake on serum 25(OH)D level, which emphasises that following the current dietary fat intake recommendation ($<35\%$ total fat) could be important in reducing the prevalence of vitamin D deficiency in this Turkish population. Nevertheless, further larger studies are needed to verify this interaction, before implementing personalized dietary recommendations for the maintenance of optimal vitamin D status.

Keywords: Vitamin D; *TCF7L2*; *MC4R*; genetic risk score; fat intake; metabolic traits

1. Introduction

Nearly one billion people suffer from vitamin D deficiency (VDD) globally [1]. The prevalence of VDD among adults has been reported as $\sim 40\%$ in Europe [2] and 44-96% in the Asia, Middle East, North Africa, and 30-90% in West Asia [3-7]. Despite having high levels of sun exposure, VDD remains a significant problem in Turkey [8,9]. A meta-analysis of data from 111,582 Turkish participants reported that the prevalence of VDD was 63.5% (58.9-66.6%) in adults, 76% in pregnant women, 39.8% in children and 86.6% in infants [8]. In addition to the genetic determinants of vitamin D status, personal characteristics such as age, gender, skin colour,

race, religious beliefs and clothing style, and lifestyle factors including physical activity level have been suggested as potential factors which can affect the levels of vitamin D in the Turkish population [8,10,11].

As a member of secosteroid hormones, vitamin D plays essential roles in both calcium and phosphorus metabolism, cell proliferation and differentiation, muscle contraction, nerve transmission, and function of the immune system [12]. Due to the immunomodulatory, anti-inflammatory, antifibrotic and antioxidant roles of vitamin D, its deficiency has associations with several diseases including obesity, diabetes, cardiovascular diseases, bone metabolic disorders, cancers, neuropsychiatric disorders and autoimmune diseases, and more recently with increased risk of SARS-CoV-2 infection [12-14]. The link between VDD and the risk of cardiometabolic diseases has been extensively studied [15-17], and it has been shown that vitamin D exhibits anti-adipogenic activity in 3T3-L1 preadipocytes [18,19] and has potential roles in inducing the expression of the insulin receptor, in regulation of insulin secretion, glucose homeostasis, and inflammation [20,21].

Despite the current evidence for the link between VDD and cardiometabolic diseases, a causal effect has not been established [22]. Furthermore, previous studies investigating this link are inconsistent due to the unmeasured confounding factors [23,24]. A genetic approach may provide a better understanding to the potential association between VDD and metabolic diseases by eliminating any unclear confounding factors [25]. The heritability of circulating vitamin D levels has been reported between 20-85%, and a number of genetic variants in genes for vitamin D pathways have been associated with metabolic diseases [12,26]. Furthermore, several genetic variants associated with cardiometabolic health have also been linked to vitamin D level status. Melanocortin 4 Receptor (*MC4R*) and Transcription Factor 7-Like 2 (*TCF7L2*) genes are commonly studied candidate genes for obesity and diabetes [25,27-39], and the interactions of *MC4R* and *TCF7L2* genotypes with dietary intakes on obesity [35,36] and diabetes related traits [25,30,37] have been investigated in multiple ethnic groups. However, to our knowledge, the potential effects of the interaction between metabolic-genetic risk score (GRS) and dietary intake on vitamin D status have not been investigated in a Turkish population. Hence, in the present study, we have explored the association of the metabolic-GRS with metabolic traits and vitamin D status and explored the interaction between metabolic-GRS and dietary intake on vitamin D status in a Turkish population.

2. Materials and Methods

2.1. Study population

This cross-sectional study was performed with 396 Turkish adults, aged 24-50 years. The study participants were enrolled following a physical examination by the research endocrinologists at the outpatient clinic of the Department of Endocrinology and Metabolism at the Hacettepe University Hospitals between June and November 2017. Criteria for inclusion required a routine visit to the outpatient clinic, being 24-50 years old and having a Body Mass Index (BMI) of ≥ 18.50 kg/m². Those who had diagnosed liver and kidney diseases, mental and psychological disorders, cancers and severe endocrine abnormalities (hypothyroidism, hyperthyroidism, hypopituitarism, etc.), as well as those who were pregnant or breastfeeding, using drugs or dietary supplements that affect the body weight or having a history of bariatric surgery were excluded from the study. Following the physical examination, all participants underwent a nutritional assessment and biochemical and genetic analysis. The study was approved by the Non-interventional Clinical Research Ethics Board of Hacettepe University (GO 15/612-11) in compliance with the Declaration of Helsinki, and written informed confirmation was obtained from all the participants. The details of the study including procedure for taking blood samples and transport to laboratory have been previously published [40]. The study was performed as a part of the GeNuIne (Gene-Nutrient Interactions) Collaboration [41,42].

2.2. Anthropometrical measurements

Height and body weight were assessed using standardized methods with digital scale (Seca 220 Scale). BMI was calculated with the formula: "body weight (in kilograms) divided by the square of height (in meters)" [43]. Waist circumference (WC) and hip circumference (HC) were measured by standard methods, and the waist-to-hip ratio was calculated by dividing WC (cm) to HC (cm) [44]. Body composition was determined by bioelectrical impedance (Tanita MC- 980 MA). Fat mass index (FMI) was estimated as fat mass (kg) / height squared (m²) [45].

2.3. Biochemical and Clinical Measures

Fasting lipid profile including triglyceride, total cholesterol, high-density lipoprotein cholesterol (HDL-cholesterol), low-density lipoprotein cholesterol (LDL-cholesterol), and both fasting and postprandial plasma

glucose and insulin concentrations were analysed by routine methods at Hacettepe University (Biochemistry Laboratory). Plasma adiponectin and serum 25(OH)D concentrations were analysed in Hacettepe University (Clinical Pathology Laboratory) using ELISA kits (Ebioscience, Austria; and Dia Source, Belgium, respectively). According to the Institute of Medicine recommendation (IOM) [46], ≥ 20 ng/mL was considered as an optimal concentration for serum 25(OH)D concentration. Insulin resistance (HOMA-IR) was calculated using the formula: 'Fasting insulin level ($\mu\text{U} / \text{L}$) x fasting glucose level (nmol / L) / 22.5 [47]. Systolic (SBP) and diastolic (DBP) blood pressure was measured as a part of the physical examination [48].

2.4. Dietary Assessment

Two trained research dietitians assessed the dietary intake using the 24-h-dietary recall method. The amount of food items consumed by the participants were confirmed using the food portion size photographic atlas [49], replicas of food items and household measurement tools. Dietary energy and nutrient intakes were estimated using a dietary analysis computer program (BeBIS, Nutrition Information System, Version 8).

2.5. Assessment of Physical Activity Level

Turkish version of the International Physical Activity Questionnaire (IPAQ) was used to determine physical activity level of the participants [50]. The physical activity level was categorized into three groups based on metabolic equivalent of task (MET) values suggested by IPAQ protocol: sedentary (< 600 MET/min/w), moderate (600-3000 MET/min/w), and vigorous (> 3000 MET/min/w) [51].

2.6. Single Nucleotide Polymorphism (SNP) Selection and Genotyping

SNPs, *TCF7L2* rs7903146 and *MC4R* rs571312, were selected because of their associations with metabolic diseases which have been suggested previously in different populations [25,27-39]. The genomic DNA was isolated from the whole blood in K2EDTA containing tubes by the salting-out method. The details of this method have been described previously [40]. The genotypes of the *TCF7L2* rs7903146 and *MC4R* rs571312 SNPs were in Hardy-Weinberg equilibrium ($p=0.101$ and $p=0.176$, respectively). Genotype distributions and MAFs for the SNPs of *TCF7L2* and *MC4R* are given in Table S1.

2.7. Statistical analysis

The statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) software (version 24). Descriptive data for continuous variables were given as mean and standard deviation, and groups were compared using the independent sample t test. Allele and genotype frequencies of two SNPs were computed by gene counting, and the chi-squared test was used to calculate the percentages of alleles/genotypes. The SNPs of *TCF7L2* rs7903146 and *MC4R* rs571312 were used to create the GRS. A value varying from zero to two was given to each SNP, indicating the number of metabolic disease-associated risk alleles. The GRS was determined via the addition of the number of risk alleles through each SNP. The median value (1 risk allele) was used to classify the participants into two groups: those with < 1 risk allele and ≥ 1 risk allele. The association analysis between the GRS and categorical and continuous variables was performed using logistic regression and general linear models, respectively. Logistic and linear regression analyses were performed to examine the interaction between lifestyle factors and SNPs. The models were adjusted for age, gender, obesity status, energy intake and months of measurement, wherever appropriate. The variable 'month of measurement' was created based on the months (June - November) in which the participants were enrolled in the study. The participants included in June, July and August were coded as 'Summer' ($n=192$ for this group) while the participants included in September, October and November were coded as 'Autumn' ($n=204$ for this group). P value < 0.05 was considered to be statistically significant. The dietary factors and metabolic traits were assessed according to the vitamin D status classified by the IOM recommendation [46]. A power calculation was not conducted given that there are no available effect sizes from studies focusing on metabolic GRS and vitamin D levels in the Turkish population.

3. Results

3.1. Characteristics of the study participants

The mean of serum 25(OH)D concentration was 24.6 ± 1.66 ng/mL in the study population, and the prevalence of VDD was 25% (Table 1). The general characteristics of the study participants including anthropometric measurements, biochemical parameters, dietary intake and physical activity level are given in Table 1 stratified based on serum vitamin D levels (deficient/insufficient < 20 ng/ml and optimal ≥ 20 ng/ml). No significant

difference in clinical, anthropometric and biochemical parameters was obtained between the groups ($p>0.05$, for each).

Table 1. Basic characteristics of the study participants according to serum vitamin D levels.

	Serum 25(OH)D Concentration*		P value
	Deficient/Insufficient (n=182)	Optimal (n=214)	
Anthropometric measurements			
Body mass index (kg/m ²)	25.7±4.21	25.8±4.11	0.271 ^a
Waist circumference (cm)	87.0±10.79	88.8±12.04	0.938 ^a
Hip circumference (cm)	101.7±8.27	101.8±7.41	0.127 ^a
Waist-to-hip ratio	0.86±0.09	0.87±0.08	0.404 ^a
Fat mass index	6.84±2.96	6.94±2.85	0.559 ^a
Body fat mass (%)	25.7±7.90	26.0±7.29	0.890 ^a
Body fat mass (kg)	19.1±7.55	19.6±7.48	0.556 ^a
Visceral fat percentage	5.59±3.15	5.89±3.25	0.628 ^a
Biochemical parameters			
Glucose (mg/dl)	88.1±8.21	87.5±8.48	0.305 ^a
Insulin (μIU/ml)	8.1±0.39	7.3±0.29	0.055 ^a
Postprandial glucose (mg/dl)	84.9±17.21	84.7±15.72	0.408 ^a
Postprandial insulin (μIU/ml)	29.3±2.69	24.9±1.95	0.091 ^a
VLDL cholesterol (mg/dl)	24.1±15.25	23.1±13.76	0.453 ^a
Total cholesterol (mg/dl)	190.2±40.12	188.0±37.12	0.977 ^a
HDL cholesterol (mg/dl)	48.6±11.55	48.8±11.57	0.440 ^a
LDL cholesterol (mg/dl)	123.9±31.20	122.2±28.72	0.913 ^a
Triglyceride (mg/dl)	120.7±76.35	115.7±68.74	0.440 ^a
Adiponectin (ng/ml)	10480.1±6217.49	10626±6692.54	0.556 ^a
HOMA-IR	1.8±0.09	1.6±0.07	0.058 ^a
Dietary intake			
Total energy (kcal)	2429.3±1093.98	2368.0±992.98	0.675 ^a
Carbohydrate (%)	46.7±8.90	45.3±9.73	0.073 ^a
Protein (%)	15.5±3.68	15.7±4.83	0.207 ^a
Fat (%)	37.5±7.66	38.9±8.41	0.098 ^a
Total fiber (g)	23.9±10.95	23.7±11.31	0.382 ^a
Physical activity level, n (%)			
Sedentary	68 (37.4)	84 (39.3)	0.306 ^b
Moderate	90 (49.5)	112 (52.3)	
Vigorous	24 (13.1)	18 (8.4)	

Data are represented as means ± SD for anthropometric measurements, biochemical parameters and dietary intake; and as number (percentage) for physical activity level. ^aIndependent Sample t test, ^bPearson chi-square test. * Cut-off point for serum vitamin D level was based on the recommendation of Institute of Medicine.

3.2. Association of vitamin D status with metabolic traits

After adjusting for potential confounders, There were significant inverse associations of serum 25(OH)D concentration was significantly associated with fasting insulin ($p=0.011$) and HOMA-IR ($p=0.010$) (Figure S1) and, none of the other phenotypic associations were statistically significant (Table S2).

3.3. Genetic association of metabolic-GRS with metabolic traits and serum 25(OH)D concentrations

Metabolic-GRS was significantly associated with serum 25(OH)D concentration ($p=0.020$), where participants carrying ≥ 1 risk allele had lower serum 25(OH)D levels (23.5±0.89 ng/mL) compared to those carrying <1 risk allele (27.9±1.96 ng/mL) (Figure 1). None of the other characteristics differed significantly between the two GRS groups (<1 risk allele vs. ≥ 1 risk allele) ($p>0.05$, for all associations) (Table S3).

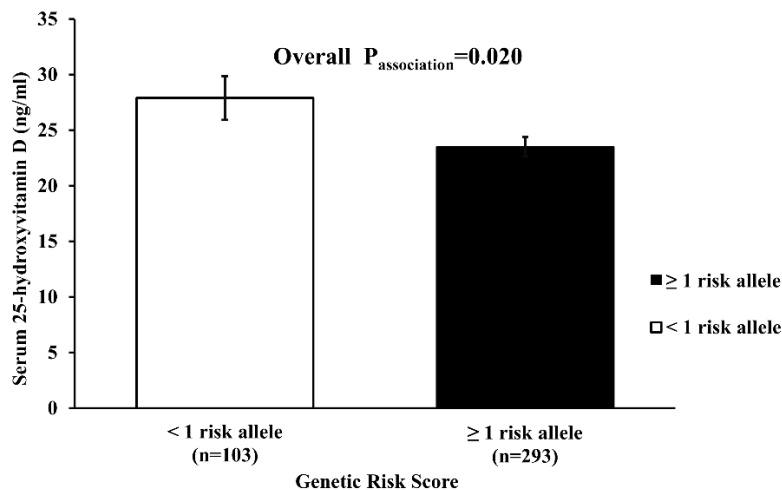


Figure 1. Association between serum 25-Hydroxy-Vitamin D level and metabolic-GRS. Individuals having 1 or more risk allele had lower serum 25(OH)D concentrations compared to participants with <1 risk allele. The mean and standard deviation for serum 25(OH)D level was 27.9 ± 1.96 ng/mL in participants with <1 risk allele, while it was 23.5 ± 0.89 ng/mL in participants with ≥ 1 risk allele. P value was calculated using linear regression analysis after adjusting for age, gender, obesity status and months of measurement.

3.4. Interaction between metabolic-GRS and serum 25(OH)D concentration on clinical and biochemical outcomes

There was no significant interaction between metabolic-GRS and vitamin D concentrations on metabolic traits ($p > 0.05$) (Table S4).

3.5. Interaction between metabolic-GRS and dietary intake on serum vitamin D concentration

There was a significant interaction between metabolic-GRS and dietary energy from fat intake on serum 25(OH)D concentrations after adjusting for age, gender, and obesity status, and months of measurement ($p = 0.04027$, **Figure 2**). Participants in the highest tertile of fat intake (122.3 ± 52.51 g/d) and carrying ≥ 1 risk allele had significantly lower serum 25(OH)D concentrations compared to the participants having highest tertile of fat intake and carrying <1 risk allele ($p = 0.006$) (Figure 2). No significant interactions between metabolic-GRS and dietary intakes of other macronutrients on serum 25(OH)D were obtained ($p > 0.05$, for each) (Table S5).

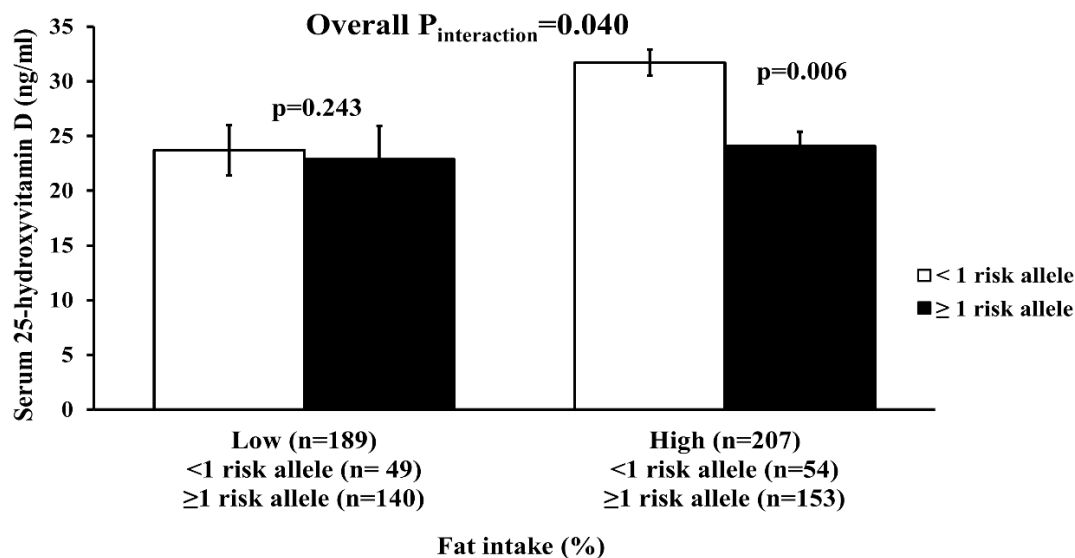


Figure 2. Interaction between metabolic-GRS and fat intake (%) on serum 25(OH)D concentration. There was a significant interaction of the GRS with dietary fat intake on serum 25-hydroxyvitamin D level. Among those with ≥ 1 risk alleles, individuals with high of fat intake had lower serum 25-hydroxyvitamin D level ($p=0.006$). Vitamin D level was 23.1 ± 1.06 ng/ml among those with low fat intake: (for individuals without risk allele: 23.7 ± 2.29 ; for individuals with risk allele: 22.9 ± 1.19 ng/ml). It was 26.1 ± 1.26 ng/ml among those with high fat intake (for < 1 risk allele: 31.7 ± 3.03 ; for ≥ 1 risk alleles: 24.1 ± 1.30 ng/ml). 38 %: median value of dietary fat intake. The mean intake of low fat intake was $31.6 \pm 4.61\%$ (for individuals without risk allele: $31.7 \pm 4.89\%$; for individuals having ≥ 1 risk alleles: $31.6 \pm 4.52\%$). The mean intake of high fat intake was $44.4 \pm 5.32\%$ (for < 1 risk allele: $45.1 \pm 5.46\%$; for ≥ 1 risk alleles: $44.1 \pm 5.26\%$). P values were derived from linear regression analysis and adjusted for age, gender, obesity status and months of measurement.

180
181
182
183
184
185
186
187
188
189

4. Discussion

190

To date,, our study is the first to use a nutrigenetic approach to investigate the interaction between metabolic-GRS and dietary intakes on serum 25(OH)D levels in a Turkish population. This study has proposed a novel interaction between metabolic-GRS and dietary fat intake on serum 25(OH)D concentrations by demonstrating that participants with high metabolic-GRS and higher dietary fat intake had significantly lower serum 25(OH)D levels compared to the participants with high metabolic-GRS but lower dietary fat intake. Given the high prevalence of VDD in Turkey [8,9], these results might have public health significance in preventing VDD in those with high metabolic genetic risk. Therefore, following the current dietary fat intake recommendations ($< 35\%$) [52,53] might be important to maintain the optimal vitamin D status, especially in individuals who have a genetic risk of VDD.

191
192
193
194
195
196
197
198
199

Studies that examined the link between metabolic disease associated gene variants and vitamin D status are limited and the findings have been conflicting [25,35]. A recent study conducted in 545 Asian Indians showed no significant association between metabolic-GRS and serum 25(OH)D concentration [25]. On the other hand, Alathari et al. [35] found that Southeast Asian women carrying < 4 metabolic risk alleles had higher serum 25(OH)D concentration compared to the individuals carrying four or more risk alleles. Similarly, our study has shown that individuals having ≥ 1 metabolic risk allele had lower serum 25(OH)D concentrations than the individuals not having any risk allele. Despite the limited evidence on the link between metabolic disease-associated gene variants and vitamin D level, many genetic association studies investigated the associations of vitamin D-related SNPs that can modify the activation, catabolism and transport of vitamin D, with metabolic traits. However, the findings of these studies were also inconsistent [22,54-56]. For instance, a couple of studies conducted in European populations showed no association between the gene variants of vitamin D binding protein/group-specific component (DBP/GC) and the risk of diabetes [54,55], while significant associations have been demonstrated in Asian populations [56]. The discrepancies in the findings of different studies could be explained by the diversity in the number of SNPs, ethnicity, culture and socioeconomic status.

200
201
202
203
204
205
206
207
208
209
210
211
212
213

The present study examined whether the genetic risk of metabolic diseases has been affected by VDD and found no significant interaction between metabolic-GRS and serum 25(OH)D level on metabolic traits. Similarly, a study that examined the interactions between vitamin D receptor SNPs and serum vitamin D level on metabolic disease related traits in 5,160 Europeans failed to show any evidence of vitamin D-related gene variations modifying the interaction between 25(OH)D concentrations and metabolic traits [57]. Other studies also confirmed the lack of any associations between genetically instrumented serum 25(OH)D concentrations and metabolic traits, such as BMI [35,58,59], waist circumference [35,58-60], glycated hemoglobin [35,61], fasting insulin [35,61], and glucose levels [35,61,62].

The World Health Organization Noncommunicable Diseases Progress Monitor (2017) declared that non-communicable diseases (NCDs) have been responsible for 88% of deaths in the Turkish population [63]. Targeting modifiable risk factors for NCDs including the dietary modifications for obesity could prevent mortality [36,64,65]. The present study found that dietary fat intake and metabolic-GRS had an interaction on vitamin D concentrations, and the level of serum 25(OH)D was lower in those carrying risk allele and consuming high amount of dietary fat. The high amount ($\geq 38\%$ = 122.3 \pm 52.51 g/d) was defined according to the median of total dietary fat intake in the study population. This cut off value also meets the high dietary fat intake as defined by the recommendations of WHO (15-30%), IOM (20-35%) and Turkish Dietary Guidelines (20-35%) [52,53,66]. Vitamin D is a fat-soluble vitamin and absorbed with dietary fat by passive diffusion; therefore, dietary fat can have a potential to modify the interaction between genetic risk of metabolic disease and vitamin D status [67]. Similar to current findings, it was shown that high fat diet-induced obesity resulted in lower serum 25(OH)D levels in an animal study [68]. To date, there have been only two studies that have examined the metabolic-GRS-diet interactions on serum 25(OH)D concentrations [25,35]. The first study examined whether any dietary factor could modify the relationship between serum 25(OH)D concentration and metabolic traits in 545 Asian Indians. In discordance with the findings of our study, they showed that individuals with low GRS ($GRS \leq 1$) and lower dietary carbohydrate intake ($\leq 62\%$) had higher serum 25(OH)D concentrations [25]. Furthermore, the study generated the GRS using five SNPs from three genes (*FTO*, *TCF7L2* and *MC4R*), and the energy from carbohydrate, protein and fat was 64%, 11% and 23%, respectively. The second study tested a similar hypothesis in Southeast Asian Minangkabau women using two GRSs constructed based on 15 SNPs from vitamin D and metabolic disease associated genes, respectively, and showed no significant interaction between metabolic-GRS and dietary intake on vitamin D status [35]. Some of the reasons for the discrepancy in the findings across the studies might be the number of SNPs that were used in the GRS, ethnicity, and the diversity in the dietary macronutrient intake patterns. Given these ethnic-specific findings, meeting the current dietary recommendations for macronutrient intake might be more essential in individuals with a known genetic risk to help maintain a healthy vitamin D status [52,53,66].

Several hypotheses have been proposed to define the potential mechanisms of the associations between metabolic diseases including obesity and vitamin D status [69-78]. These include the volumetric dilution of serum vitamin D levels [68,73,74], adipocyte hypertrophy contributing to overexpression of proinflammatory cytokines [77,79], modifications of vitamin D related enzymes [75,76] affected by high fat diet-induced obesity, and lower endogenous vitamin D synthesis in the skin as a consequence of the less outdoor activity [75,80], less physical activity [71], and less exposure to sunlight in obese individuals [73-80]. In addition, the bi-directional Mendelian randomization analysis conducted in 42,024 Europeans showed a relationship between vitamin D status and obesity, suggesting that higher BMI leads to lower vitamin D levels where 4.2% decrease in serum 25(OH)D concentrations was observed for every 10% increase in BMI [22]. The Framingham Study also showed that the prevalence of VDD was higher among individuals with higher BMI [81]. Furthermore, a lifestyle intervention study conducted in obese individuals demonstrated that serum 25(OH)D concentrations were significantly increased as a consequence of weight loss [82]. Despite these findings, some studies failed to show any association between vitamin D status and metabolic traits [83-85]. For instance, Larsen et al. [83] showed no or marginal associations between serum 25(OH)D level and biomarkers of adiposity in 10,898 individuals comprising Danish, British and Finnish participants. Similarly, independent of the genetic associations, our study also has not shown either any difference in metabolic traits by vitamin D status, or any association between obesity related traits and serum 25(OH)D level. The inconsistencies among the studies might depend on the potential predisposition to bias and confounding factors (e.g. the time and amount of sunlight exposure, physical activity level, more clothing, skin colour, and ethnicity) in observational study designs conducted in different populations. Furthermore, the differences in the categorisation of vitamin D status and the measures of obesity including BMI, body weight, and waist circumference might be the other reason for the inconsistency [86]. Genetic

studies can provide more consistent findings in the exploration of the association between vitamin D status and metabolic traits, because the bias and confounding factors can be partly eliminated with this approach [26,87].

The main strengths of this study were the use of several biochemical markers related to metabolic traits and a well-characterized study cohort. In addition, the construction and use of GRS method rather than a single SNP approach enhances the statistical power and presents an efficient perspective for metabolic outcomes [88-90]. However, there are some limitations that need to be acknowledged. Firstly, the study did not measure exposure to sunlight, and data collection period only covered summer and autumn seasons. For overcoming this limitation, the months of measurement was adjusted as a confounding factor in all the analyses. Secondly, the small sample size might be considered as a further limitation of the study; however, our study has been able to confirm previously reported associations and identify gene-diet interactions. Thirdly, dietary intake was assessed using a 24-hour dietary recall method which is prone to self-reporting bias; however, this method is used commonly in nutrigenetic studies, and the method could be applied to diverse groups with a wide range of eating habits. Fourthly, we could not examine the causative effects due to limitations of the cross-sectional study design. Lastly, although analysis undertaken was adjusted for potential confounders, we cannot rule out the impact of residual confounders caused by unknown variables.

5. Conclusions

In summary, our study has provided evidence for a novel interaction between metabolic-GRS and dietary fat intake on serum vitamin D concentrations, suggesting that following current dietary fat intake recommendations (<35%) might be effective to prevent any consequences of the genetic risk of VDD. However, further larger studies are needed to endorse this interaction before generalizing the findings to the Turkish population and implementing any personalized dietary recommendations for the maintenance of optimal vitamin D status.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Figure S1: Association of 25(OH)D concentrations with metabolic traits, Table S1. Genotype frequencies of *TCF7L2* and *MC4R* SNPs, Table S2. Association between serum 25(OH)D concentration and metabolic traits, Table S3. Metabolic-GRS and baseline characteristics of the study participants, Table S4. The interaction between metabolic-GRS and serum 25(OH) D on metabolic traits, Table S5. The interaction between metabolic-GRS and macronutrient intake on serum 25(OH)D level.

Author Contributions: V.K.S. conceived the nutrigenetics study; V.K.S., K.I.A., B.A., and Z.B. drafted the manuscript; K.I.A. performed the statistical analysis; Z.B. and V.K.S. designed the study; K.I.A., B.T.D. and Z.B. conducted data collection and desk based analyses; S.N.S. and T.E. carried out the eligibility screening, physical examination and clinical evaluations; I.L. performed the biochemical analysis; M.A. carried out the genetic analysis; V.K.S., Z.B., B.A., and B.E. critically reviewed the manuscript. All authors contributed to and approved the final version of the manuscript.

Funding: This research was funded by the Scientific and Technological Research Council of Turkey (TUBITAK), grant number 216S272 and the APC was funded by the University of Reading, UK.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Hacettepe University (protocol code: GO 15/612-11 and date of approval: 16 September 2015).

Informed Consent Statement: Informed consent was obtained from all participants involved in the study.

Acknowledgments: We thank all study participants for their cooperation. Dr Karani S Vimalaswaran acknowledges support from the British Nutrition Foundation, and the Public Authority for Applied Education and Training of Kuwait for the scholarship given to Ms. Buthaina AlAthari. Dr Buyuktuncer acknowledges the Scientific and Technological Research Council of Turkey (TUBITAK) and Council of Higher Education of Turkey for the scholarship given to Kubra Isgin-Atici.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Sizar, O.; Khare, S.; Goyal, A.; Bansal, P.; Givler, A. Vitamin D Deficiency. StatPearls. Treasure Island (FL): StatPearls Publishing; 2020. Available online: <https://pubmed.ncbi.nlm.nih.gov/30335299/> (Accessed on 3 March 2021).
2. Cashman, K.D.; Dowling, K.G.; Škrabáková, Z.; Gonzalez-Gross, M.; Valtueña, J.; De Henauw, S.; Moreno, L.; Damsgaard, C.T.; Michaelsen, K.F.; Mølgaard, C., et al. Vitamin D deficiency in Europe: pandemic? *Am. J. Clin. Nutr.* **2016**, *103*, 1033-1044.
3. Aji, A.S.; Erwinda, E.; Rasyid, R.; Yusrawati, Y.; Malik, S.G.; Alathari, B.; Lovegrove, J.A.; Lipoeto, N.I.; Vimalaswaran, K.S. A genetic approach to study the relationship between maternal Vitamin D status and newborn anthropometry measurements: the Vitamin D pregnant mother (VDPM) cohort study. *J. Diabetes Metab. Disord.* **2020**, *19*, 91-103.
4. AlFaris, N.A.; AlKehayez, N.M.; AlMushawah, F.I.; AlNaeem, A.N.; AlAmri, N.D.; AlMudawah, E.S. Vitamin D Deficiency and Associated Risk Factors in Women from Riyadh, Saudi Arabia. *Sci. Rep.* **2019**, *9*, 20371.

-
5. Kim, S.H.; Oh, J.E.; Song, D.W.; Cho, C.Y.; Hong, S.H.; Cho, Y.J.; Yoo, B.W.; Shin, K.S.; Joe, H.; Shin, H.S., et al. The factors associated with Vitamin D deficiency in community dwelling elderly in Korea. *Nutr. Res. Pract.* **2018**, *12*, 387-395. 320-321
 6. Chakhtoura, M.; Rahme, M.; Chamoun, N.; El-Hajj Fuleihan, G. Vitamin D in the Middle East and North Africa. *Bone Rep.* **2018**, *8*, 135-146. 322-323
 7. Lips, P.; Cashman, K.D.; Lamberg-Allardt, C.; Bischoff-Ferrari, H.A.; Obermayer-Pietsch, B.; Bianchi, M.L.; Stepan, J.; El-Hajj Fuleihan, G.; Bouillon, R. Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society. *Eur. J. Endocrinol.* **2019**, *180*, 23-54. 324-326
 8. Alpdemir, M.; Alpdemir, M.F. Vitamin D deficiency status in Turkey: A meta-analysis. *Int J Med Biochem* **2019**, *2*, 118-131. 327
 9. Göktaş, O.; Ersoy, C.; Ercan, I.; Can, F.E. Vitamin D status in the adult population of Bursa-Turkey. *Eur. J. Gen. Pract.* **2020**, *26*, 156-162. 328-329
 10. Buyukuslu, N.; Esin, K.; Hizli, H.; Sunal, N.; Yigit, P.; Garipagaoglu, M. Clothing preference affects vitamin D status of young women. *Nutr. Res.* **2014**, *34*, 688-693. 330-331
 11. Yakar, B.; Kaya, M.O. Vitamin D deficiency during pregnancy in Turkey and the effect of the sunlight: a systematic review and meta-analysis. *Turk. J. Biochem.* **2021**, *46*, 129-35. 332-333
 12. Alathari, B.E.; Sabta, A.A.; Kalpana, C.A.; Vimalaswaran, K.S. Vitamin D pathway-related gene polymorphisms and their association with metabolic diseases: A literature review. *J. Diabetes Metab. Disorders.* **2020**, *19*, 1701-1729. 334-335
 13. Ebadi, M.; Montano-Loza, A.J. Perspective: improving vitamin D status in the management of COVID-19. *Eur. J. Clin. Nutr.* **2020**, *74*, 856-859. 336-337
 14. Zhang, S.; Miller, D.D.; Li, W. Non-Musculoskeletal Benefits of Vitamin D beyond the Musculoskeletal System. *Int. J. Mol. Sci.* **2021**, *22*. 338-339
 15. AlQuaiz, A.M.; Alrasheed, A.A.; Kazi, A.; Batais, M.A.; Alhabeeb, K.M.; Jamal, A.; Fouda, M.A. Is 25-Hydroxyvitamin D Associated with Glycosylated Hemoglobin in Patients with Type 2 Diabetes Mellitus in Saudi Arabia? A Population Based Study. *Int. J. Environ. Res. Public Health.* **2021**, *18*, 2805. 340-342
 16. Anderson, J.L.; May, H.T.; Horne, B.D.; Bair, T.L.; Hall, N.L.; Carlquist, J.F.; Lappé, D.L.; Muhlestein, J.B. Relation of Vitamin D Deficiency to Cardiovascular Risk Factors, Disease Status, and Incident Events in a General Healthcare Population. *Am. J. Cardiol.* **2010**, *106*, 963-968. 343-345
 17. Brock, K.; Huang, W.Y.; Fraser, D.R.; Ke, L.; Tseng, M.; Stolzenberg-Solomon, R.; Peters, U.; Ahn, J.; Purdue, M.; Mason, R.S., et al. Low vitamin D status is associated with physical inactivity, obesity and low vitamin D intake in a large US sample of healthy middle-aged men and women. *J. Steroid Biochem. Mol. Biol.* **2010**, *121*, 462-466. 346-348
 18. Manna, P.; Achari, A.E.; Jain, S.K. Vitamin D supplementation inhibits oxidative stress and upregulate SIRT1/AMPK/GLUT4 cascade in high glucose-treated 3T3L1 adipocytes and in adipose tissue of high fat diet-fed diabetic mice. *Arch. Biochem. Biophys.* **2017**, *615*, 22-34. 349-351
 19. Larrick, B.M.; Kim, K.H.; Donkin, S.S.; Teegarden, D. 1,25-Dihydroxyvitamin D regulates lipid metabolism and glucose utilization in differentiated 3T3-L1 adipocytes. *Nutr. Res.* **2018**, *58*, 72-83. 352-353
 20. Zemel, M.B. Nutritional and endocrine modulation of intracellular calcium: implications in obesity, insulin resistance and hypertension. *Mol. Cell Biochem.* **1998**, *188*, 129-136. 354-355
 21. Maestro, B.; Molerio, S.; Bajo, S.; Dávila, N.; Calle, C. Transcriptional activation of the human insulin receptor gene by 1,25-dihydroxyvitamin D(3). *Cell Biochem. Funct.* **2002**, *20*, 227-232. 356-357
 22. Vimalaswaran, K.S.; Berry, D.J.; Lu, C.; Tikkanen, E.; Pilz, S.; Hiraki, L.T.; Cooper, J.D.; Dastani, Z.; Li, R.; Houston, D.K. Causal relationship between obesity and vitamin D status: bi-directional Mendelian randomization analysis of multiple cohorts. *PLoS Med.* **2013**, *10*, e1001383. 358-360
 23. Saneei, P.; Salehi-Abargouei, A.; Esmailzadeh, A. Serum 25-hydroxy vitamin D levels in relation to body mass index: a systematic review and meta-analysis. *Obes. Rev.* **2013**, *14*, 393-404. 361-362
 24. Al-Dabhani, K.; Tsilidis, K.K.; Murphy, N.; Ward, H.A.; Elliott, P.; Riboli, E.; Gunter, M.; Tzoulaki, I. Prevalence of vitamin D deficiency and association with metabolic syndrome in a Qatari population. *Nutr. Diabetes.* **2017**, *7*, e263. 363-364
 25. Alathari, B.E.; Bodhini, D.; Jayashri, R.; Lakshmipriya, N.; Shanthi Rani, C.S.; Sudha, V.; Lovegrove, J.A.; Anjana, R.M.; Mohan, V.; Radha, V., et al. A Nutrigenetic Approach to Investigate the Relationship between Metabolic Traits and Vitamin D Status in an Asian Indian Population. *Nutrients.* **2020**, *12*. 365-367
 26. Jiang, X.; Kiel, D.P.; Kraft, P. The genetics of vitamin D. *Bone* **2019**, *126*, 59-77. 368
 27. Wang, J.; Hu, F.; Feng, T.; Zhao, J.; Yin, L.; Li, L.; Wang, Y.; Wang, Q.; Hu, D. Meta-analysis of associations between TCF7L2 polymorphisms and risk of type 2 diabetes mellitus in the Chinese population. *BMC Med. Genet.* **2013**, *14*, 8. 369-370
 28. Adeyemo, A.A.; Tekola-Ayele, F.; Doumatey, A.P.; Bentley, A.R.; Chen, G.; Huang, H.; Zhou, J.; Shriner, D.; Fasanmade, O.; Okafor, G., et al. Evaluation of Genome Wide Association Study Associated Type 2 Diabetes Susceptibility Loci in Sub Saharan Africans. *Front. Genet.* **2015**, *6*, 335. 371-373
 29. El Hajj Chehadah, S.; Osman, W.; Nazar, S.; Jerman, L.; Alghafri, A.; Sajwani, A.; Alawlaqi, M.; AlObeidli, M.; Jelinek, H.F.; AlAnouti, F., et al. Implication of genetic variants in overweight and obesity susceptibility among the young Arab population of the United Arab Emirates. *Gene.* **2020**, *739*, 144509. 374-376
 30. Ouhaibi-Djellouli, H.; Mediene-Benchekor, S.; Lardjam-Hetraf, S.A.; Hamani-Medjaoui, I.; Meroufel, D.N.; Boulenouar, H.; Hermant, X.; Saidi-Mehtar, N.; Amouyel, P.; Houti, L., et al. The TCF7L2 rs7903146 polymorphism, dietary intakes and type 2 diabetes risk in an Algerian population. *BMC Genet.* **2014**, *15*, 134-134. 377-379

-
31. Loos, R.J.; Lindgren, C.M.; Li, S.; Wheeler, E.; Zhao, J.H.; Prokopenko, I.; Inouye, M.; Freathy, R.M.; Attwood, A.P.; Beckmann, J.S., et al. Common variants near MC4R are associated with fat mass, weight and risk of obesity. *Nat. Genet.* **2008**, *40*, 768-775. 380
 32. Gao, L.; Wang, L.; Yang, H.; Pan, H.; Gong, F.; Zhu, H. MC4R Single Nucleotide Polymorphisms Were Associated with Metabolically Healthy and Unhealthy Obesity in Chinese Northern Han Populations. *Int. J. Endocrinol.* **2019**, 2019, 4328909-4328909. 382
 33. O'Beirne, S.L.; Salit, J.; Rodriguez-Flores, J.L.; Staudt, M.R.; Abi Khalil, C.; Fakhro, K.A.; Robay, A.; Ramstetter, M.D.; Al-Azwani, I.K.; Malek, J.A., et al. Type 2 Diabetes Risk Allele Loci in the Qatari Population. *PLoS One.* **2016**, *11*, e0156834. 384
 34. Kalantari, S.; Sharafshah, A.; Keshavarz, P.; Davoudi, A.; Habibipour, R. Single and multi-locus association study of TCF7L2 gene variants with susceptibility to type 2 diabetes mellitus in an Iranian population. *Gene.* **2019**, *696*, 88-94. 386
 35. Alathari, B.E.; Aji, A.S.; Ariyasra, U.; Sari, S.R.; Tasrif, N.; Yani, F.F.; Sudji, I.R.; Lovegrove, J.A.; Lipoeto, N.I.; Vimalaswaran, K.S. Interaction between Vitamin D-Related Genetic Risk Score and Carbohydrate Intake on Body Fat Composition: A Study in Southeast Asian Minangkabau Women. *Nutrients.* **2021**, *13*. 388
 36. Alsulami, S.; Nyakotey, D.A.; Dudek, K.; Bawah, A.M.; Lovegrove, J.A.; Annan, R.A.; Ellahi, B.; Vimalaswaran, K.S. Interaction between Metabolic Genetic Risk Score and Dietary Fatty Acid Intake on Central Obesity in a Ghanaian Population. *Nutrients.* **2020**, *12*. 391
 37. Cai, J.; Zhang, Y.; Nuli, R.; Zhang, Y.; Abudusemaiti, M.; Kadeer, A.; Tian, X.; Xiao, H. Interaction between dietary patterns and TCF7L2 polymorphisms on type 2 diabetes mellitus among Uyghur adults in Xinjiang Province, China. *Diabetes. Metab. Syndr. Obes.* **2019**, *12*, 239-255. 394
 38. Speliotes, E.K.; Willer, C.J.; Berndt, S.I.; Monda, K.L.; Thorleifsson, G.; Jackson, A.U.; Allen, H.L.; Lindgren, C.M.; Luan, J.a.; Mägi, R., et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat. Genet.* **2010**, *42*, 937-948. 397
 39. Ding, W.; Xu, L.; Zhang, L.; Han, Z.; Jiang, Q.; Wang, Z.; Jin, S. Meta-analysis of association between TCF7L2 polymorphism rs7903146 and type 2 diabetes mellitus. *BMC Med. Genet.* **2018**, *19*, 38. 400
 40. Isgin-Atici, K.; Alsulami, S.; Turan-Demirci, B.; Surendran, S.; Sendur, S.N.; Lay, I.; Karabulut, E.; Ellahi, B.; Lovegrove, J.A.; Ali-kasifoglu, M., et al. FTO gene-lifestyle interactions on serum adiponectin concentrations and central obesity in a Turkish population. *Int. J. Food Sci. Nutr.* **2021**, *72*, 375-385. 402
 41. Vimalaswaran, K.S. A nutrigenetics approach to study the impact of genetic and lifestyle factors on cardiometabolic traits in various ethnic groups: findings from the GeNuIne Collaboration. *Proc. Nutr. Soc.* **2020**, *79*, 194-204. 405
 42. Vimalaswaran, K.S. Gene-nutrient interactions on metabolic diseases: Findings from the GeNuIne Collaboration. *Nutr. Bull.* **2017**, *42*, 80-86. 407
 43. World Health Organization. Body Mass Index. 2008. Available online: <https://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi> (accessed on 31 August 2021). 409
 44. World Health Organization. Waist circumference and waist-hip ratio. 2011. Report of a WHO expert consultation, Geneva, 8-11 December 2008. Available online: <https://apps.who.int/iris/handle/10665/44583>. (accessed on 31 August 2021). 411
 45. Peltz, G.; Aguirre, M.T.; Sanderson, M.; Fadden, M.K. The role of fat mass index in determining obesity. *Am. J. Hum. Biol.* **2010**, *22*, 639-647. 413
 46. Ross, A.C.; Manson, J.E.; Abrams, S.A.; Aloia, J.F.; Brannon, P.M.; Clinton, S.K.; Durazo-Arvizu, R.A.; Gallagher, J.C.; Gallo, R.L.; Jones, G., et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J. Clin. Endocrinol. Metab.* **2011**, *96*, 53-58, doi:10.1210/jc.2010-2704. 415
 47. Bonora, E.; Formentini, G.; Calcaterra, F.; Lombardi, S.; Marini, F.; Zenari, L.; Saggiani, F.; Poli, M.; Perbellini, S.; Raffaelli, A. HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. *Diabetes Care.* **2002**, *25*, 1135-1141. 418
 48. Frese, E.M.; Fick, A.; Sadowsky, H.S. Blood pressure measurement guidelines for physical therapists. *Cardiopulm. Phys. Ther. J.* **2011**, *22*, 5-12. 421
 49. Rakicioglu N, Tek Acar N, Ayaz A, Pekcan G. *Photograph Catalog of Food and Dishes: Portion Sizes and Amounts*, 2nd. ed.; Ata Ofset Pub: Ankara, Turkey; 2009. 423
 50. Saglam, M.; Arikan, H.; Savci, S.; Inal-Ince, D.; Bosnak-Guclu, M.; Karabulut, E.; Tokgozoglu, L. International physical activity questionnaire: reliability and validity of the Turkish version. *Percept. Mot. Skills.* **2010**, *111*, 278-284. 425
 51. IPAQ scoring protocol. Available online: <https://sites.google.com/site/theipaq/scoring-protocol> (accessed on 10 May 2021). 427
 52. Institutes of Medicine (IOM) (2002/2005) Panel on Macronutrients, Panel on the Definition of Dietary Fiber, Subcommittee on Upper Reference Levels of Nutrients, Subcommittee on Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. DRI Dietary reference intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. 2005. Available online: https://www.nal.usda.gov/sites/default/files/fnic_uploads/energy_full_report.pdf (accessed on cited 22 April 2021). 428
 53. World Health Organisation. Diet, nutrition and the prevention of chronic diseases. 2003. Report of a Joint WHO/FAO Expert Consultation. Available online: http://apps.who.int/iris/bitstream/handle/10665/42665/WHO_TRS_916.pdf?sequence=1. (accessed on 10 May 2021) 433
 54. Lu, L.; Bennett, D.A.; Millwood, I.Y.; Parish, S.; McCarthy, M.I.; Mahajan, A.; Lin, X.; Bragg, F.; Guo, Y.; Holmes, M.V., et al. Association of vitamin D with risk of type 2 diabetes: A Mendelian randomisation study in European and Chinese adults. *PLoS Med* **2018**, *15*, e1002566. 436

-
55. Buijsse, B.; Boeing, H.; Hirche, F.; Weikert, C.; Schulze, M.B.; Gottschald, M.; Kühn, T.; Katzke, V.A.; Teucher, B.; Dierkes, J., et al. Plasma 25-hydroxyvitamin D and its genetic determinants in relation to incident type 2 diabetes: a prospective case-cohort study. *Eur. J. Epidemiol.* **2013**, *28*, 743-752. 439-441
56. Wang, G.; Li, Y.; Li, L.; Yu, F.; Cui, L.; Ba, Y.; Li, W.; Wang, C. Association of the vitamin D binding protein polymorphisms with the risk of type 2 diabetes mellitus: a meta-analysis. *BMJ Open.* **2014**, *4*, e005617. 442-443
57. Vimalaswaran, K.S.; Power, C.; Hyppönen, E. Interaction between vitamin D receptor gene polymorphisms and 25-hydroxyvitamin D concentrations on metabolic and cardiovascular disease outcomes. *Diabetes Metab.* **2014**, *40*, 386-389. 444-445
58. Shen, F.; Wang, Y.; Sun, H.; Zhang, D.; Yu, F.; Yu, S.; Han, H.; Wang, J.; Ba, Y.; Wang, C., et al. Vitamin D receptor gene polymorphisms are associated with triceps skin fold thickness and body fat percentage but not with body mass index or waist circumference in Han Chinese. *Lipids Health Dis.* **2019**, *18*, 97. 446-448
59. Khan, R.J.; Riestra, P.; Gebreab, S.Y.; Wilson, J.G.; Gaye, A.; Xu, R.; Davis, S.K. Vitamin D Receptor Gene Polymorphisms Are Associated with Abdominal Visceral Adipose Tissue Volume and Serum Adipokine Concentrations but Not with Body Mass Index or Waist Circumference in African Americans: The Jackson Heart Study. *J. Nutr.* **2016**, *146*, 1476-1482. 449-451
60. Chen, C.; Chen, Y.; Weng, P.; Xia, F.; Li, Q.; Zhai, H.; Wang, N.; Lu, Y. Association of 25-hydroxyvitamin D with cardiometabolic risk factors and metabolic syndrome: a mendelian randomization study. *Nutr. J.* **2019**, *18*, 61. 452-453
61. Mackawy, A.M.H.; Badawi, M.E.H. Association of vitamin D and vitamin D receptor gene polymorphisms with chronic inflammation, insulin resistance and metabolic syndrome components in type 2 diabetic Egyptian patients. *Meta Gene.* **2014**, *2*, 540-556. 454-455
62. Karonova, T.; Grineva, E.; Belyaeva, O.; Bystrova, A.; Jude, E.B.; Andreeva, A.; Kostareva, A.; Pludowski, P. Relationship Between Vitamin D Status and Vitamin D Receptor Gene Polymorphisms With Markers of Metabolic Syndrome Among Adults. *Front. Endocrinol. (Lausanne)*. **2018**, *9*, 448. 456-458
63. World Health Organisation. National household health survey – prevalence of noncommunicable disease risk factors in Turkey 2017–2018. Available online: <https://www.euro.who.int/en/countries/turkey/publications/national-household-health-survey-prevalence-of-noncommunicable-disease-risk-factors-in-turkey-2017-2018> (Accessed on 21 April 2021). 459-461
64. Freire, R.D.; Cardoso, M.A.; Gimeno, S.G.A.; Ferreira, S.R.G. Dietary Fat Is Associated With Metabolic Syndrome in Japanese Brazilians. *Diabetes Care.* **2005**, *28*, 1779-1785. 462-463
65. Narasimhan, S.; Nagarajan, L.; Vaidya, R.; Gunasekaran, G.; Rajagopal, G.; Parthasarathy, V.; Unnikrishnan, R.; Anjana, R.M.; Mohan, V.; Sudha, V. Dietary fat intake and its association with risk of selected components of the metabolic syndrome among rural South Indians. *Indian J. Endocrinol. Metab.* **2016**, *20*, 47-54. 464-466
66. Turkey Dietary Guidelines, Ministry of Health of Turkey Publication.No: 1046. Ankara: Ministry of Turkey Health Publication 2016. Available online: <https://dosyasb.saglik.gov.tr/Eklenti/10922,17ocaktuberingilizcepdf.pdf?0>. (Accessed on 2 April 2021). 467-468
67. Ross AC, Taylor CL, Yaktine AL, Del Valle HB, eds. *Dietary Reference Intakes for Calcium and Vitamin D*. National Academies Press: Washington (DC), US. 2011. Available online: <https://www.ncbi.nlm.nih.gov/books/NBK56070/> (Accessed on 22 May 2021). 469-470
68. Park, C.Y.; Shin, Y.; Kim, J.-H.; Zhu, S.; Jung, Y.S.; Han, S.N. Effects of high fat diet-induced obesity on vitamin D metabolism and tissue distribution in vitamin D deficient or supplemented mice. *Nutr. Metab. (Lond)*. **2020**, *17*, 44. 471-472
69. Szymczak-Pajor, I.; Śliwińska, A. Analysis of Association between Vitamin D Deficiency and Insulin Resistance. *Nutrients*. **2019**, *11*, 794. 473-474
70. dos Santos, L.R.; Lima, A.G.A.; Braz, A.F.; de Sousa Melo, S.R.; Morais, J.B.S.; Severo, J.S.; de Oliveira, A.R.S.; Cruz, K.J.C.; do Nascimento Marreiro, D. Role of vitamin D in insulin resistance in obese individuals. *Nutrire*. **2017**, *42*, 17. 475-476
71. Mitri, J.; Muraru, M.D.; Pittas, A.G. Vitamin D and type 2 diabetes: a systematic review. *Eur. J. Clin. Nutr.* **2011**, *65*, 1005-1015. 477
72. Mirhosseini, N.; Vatanparast, H.; Mazidi, M.; Kimball, S.M. The Effect of Improved Serum 25-Hydroxyvitamin D Status on Glycemic Control in Diabetic Patients: A Meta-Analysis. *J Clin Endocrinol Metab* **2017**, *102*, 3097-3110. 478-479
73. Pourshahidi, L.K. Vitamin D and obesity: current perspectives and future directions. *Proc. Nutr. Soc.* **2014**, *74*, 115-124. 480
74. Rafiq, S.; Jeppesen, P.B. Body Mass Index, Vitamin D, and Type 2 Diabetes: A Systematic Review and Meta-Analysis. *Nutrients*. **2018**, *10*, 1182. 481-482
75. de Oliveira, L.F.; de Azevedo, L.G.; da Mota Santana, J.; de Sales, L.P.C.; Pereira-Santos, M. Obesity and overweight decreases the effect of vitamin D supplementation in adults: systematic review and meta-analysis of randomized controlled trials. *Rev Endocr Metab Disord* **2020**, *21*, 67-76. 483-485
76. Park, J.M.; Park, C.Y.; Han, S.N. High fat diet-Induced obesity alters vitamin D metabolizing enzyme expression in mice. *Biofactors*. **2015**, *41*, 175-182. 486-487
77. Cannell, J.J.; Grant, W.B.; Holick, M.F. Vitamin D and inflammation. *Dermatoendocrinol.* **2015**, *6*, e983401-e983401. 488
78. Park, J.E.; Pichiah, P.B.T.; Cha, Y.-S. Vitamin D and Metabolic Diseases: Growing Roles of Vitamin D. *J. Obes. Metab. Syndr.* **2018**, *27*, 223-232. 489-490
79. Mellenthin, L.; Wallaschofski, H.; Grotevendt, A.; Völzke, H.; Nauck, M.; Hannemann, A. Association between serum vitamin D concentrations and inflammatory markers in the general adult population. *Metabolism*. **2014**, *63*, 1056-1062. 491-492
80. Florez, H.; Martinez, R.; Chacra, W.; Strickman-Stein, N.; Levis, S. Outdoor exercise reduces the risk of hypovitaminosis D in the obese. *J. Steroid Biochem. Mol. Biol.* **2007**, *103*, 679-681. 493-494
81. Cheng, S.; Massaro, J.M.; Fox, C.S.; Larson, M.G.; Keyes, M.J.; McCabe, E.L.; Robins, S.J.; O'Donnell, C.J.; Hoffmann, U.; Jacques, P.F., et al. Adiposity, cardiometabolic risk, and vitamin D status: the Framingham Heart Study. *Diabetes*. **2010**, *59*, 242-248. 495-496
82. Gangloff, A.; Bergeron, J.; Lemieux, I.; Després, J.P. Changes in circulating vitamin D levels with loss of adipose tissue. *Curr. Opin. Clin. Nutr. Metab. Care*. **2016**, *19*, 464-470. 497-498

-
83. Larsen, S.C.; Ängquist, L.; Moldovan, M.; Huikari, V.; Sebert, S.; Cavadino, A.; Ahluwalia, T.S.; Skaaby, T.; Linneberg, A.; Husemoen, L.L., et al. Serum 25-Hydroxyvitamin D Status and Longitudinal Changes in Weight and Waist Circumference: Influence of Genetic Predisposition to Adiposity. *PLoS One*. **2016**, *11*, e0153611. 499
500
501
 84. LeBlanc, E.S.; Rizzo, J.H.; Pedula, K.L.; Ensrud, K.E.; Cauley, J.; Hochberg, M.; Hillier, T.A. Associations between 25-hydroxyvitamin D and weight gain in elderly women. *J Womens Health (Larchmt)* **2012**, *21*, 1066-1073. 502
503
 85. Young, K.A.; Engelman, C.D.; Langefeld, C.D.; Hairston, K.G.; Haffner, S.M.; Bryer-Ash, M.; Norris, J.M. Association of plasma vitamin D levels with adiposity in Hispanic and African Americans. *J. Clin. Endocrinol. Metab.* **2009**, *94*, 3306-3313. 504
505
 86. Heitz, A.; Mai, X.M.; Chen, Y.; Sun, Y.Q. Serum 25-hydroxyvitamin D level in relation to weight change and the risk of weight gain in adults of normal weight at baseline: the Norwegian HUNT cohort study. *BMJ Open*. **2020**, *10*, e039192. 506
507
 87. Berry, D.J.; Vimalaswaran, K.S.; Whittaker, J.C.; Hingorani, A.D.; Hyppönen, E. Evaluation of genetic markers as instruments for Mendelian randomization studies on vitamin D. *PLoS One*. **2012**, *7*, e37465. 508
509
 88. Hüls, A.; Krämer, U.; Carlsten, C.; Schikowski, T.; Ickstadt, K.; Schwender, H. Comparison of weighting approaches for genetic risk scores in gene-environment interaction studies. *BMC Genet.* **2017**, *18*, 115. 510
511
 89. Babb de Villiers, C.; Kroese, M.; Moorthie, S. Understanding polygenic models, their development and the potential application of polygenic scores in healthcare. *J. Med. Genet.* **2020**, *57*, 725-732. 512
513
 90. Lewis, C.M.; Vassos, E. Polygenic risk scores: from research tools to clinical instruments. *Genome Med.* **2020**, *12*, 44. 514
515
516