Food neophobia associates with poorer dietary quality, metabolic risk factors, and increased disease outcome risk in population-based cohorts in a metabolomics study

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ABSTRACT

Background: Food neophobia is considered a behavioral trait closely linked to adverse eating patterns and reduced dietary quality, which have been associated with increased risk of obesity and noncommunicable diseases.

Objectives: In a cross-sectional and prospective study, we examined how food neophobia is associated with dietary quality, health-related biomarkers, and disease outcome incidence in Finnish and Estonian adult populations.

Methods: The study was conducted based on subsamples of the Finnish DIetary, Lifestyle, and Genetic determinants of Obesity and Metabolic syndrome (DILGOM) cohort ($n = 2982$; age range: 25–74 y) and the Estonian Biobank cohort ($n = 1109$; age range: 18–83 y). The level of food neophobia was assessed using the Food Neophobia Scale, dietary quality was evaluated using the Baltic Sea Diet Score (BSDS), and biomarker profiles were determined using an NMR metabolomics platform. Disease outcome information was gathered from national health registries. Follow-up data on the NMR-based metabolomic profiles and disease outcomes were available in both populations.

Results: Food neophobia associated significantly (adjusted $P < 0.05$) with health-related biomarkers [e.g., ω-3 (n–3) fatty acids, citrate, α_1-acid glycoprotein, HDL, and MUFA] in the Finnish DILGOM cohort. The significant negative association between the severity of food neophobia and ω-3 fatty acids was replicated in all cross-sectional analyses in the Finnish DILGOM and Estonian Biobank cohorts. Furthermore, food neophobia was associated with reduced dietary quality (BSDS: β: -0.03 ± 0.006; $P = 8.04 \times 10^{-5}$), increased fasting serum insulin (β: 0.004 ± 0.0013; $P = 5.83 \times 10^{-3}$), and increased risk of type 2 diabetes during the ~8-y follow-up (HR: 1.018 ± 0.007; $P = 0.01$) in the DILGOM cohort.

Conclusions: In the Finnish and Estonian adult populations, food neophobia was associated with adverse alteration of health-related biomarkers and risk factors that have been associated with an increased risk of noncommunicable diseases. We also found that food neophobia associations with ω-3 fatty acids and associated metabolites are mediated through dietary quality independent of body weight. *Am J Clin Nutr* 2019;110:233–245.

Keywords: food neophobia, Baltic Sea Diet Score, dietary quality, dietary behavior, Estonian Biobank cohort, metabolome, type 2 diabetes, cardiovascular disease

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Supplemental Tables 1–16, Supplemental Methods, and Supplemental Figure 1 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: BSDS, Baltic Sea Diet Score; CHD, coronary heart disease; hs-CRP, high-sensitivity C-reactive protein; CVD, cardiovascular disease; DILGOM, DIetary, Lifestyle, and Genetic determinants of Obesity and Metabolic syndrome study; FNS, Food Neophobia Scale; HbA1c, glycated hemoglobin; PC, principal component; THL, National Institute for Health and Welfare; T2D, type 2 diabetes.

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Introduction

Food neophobia is a behavioral trait in which a person desists from tasting and experiencing unfamiliar or novel foods. Previous studies have shown that food neophobia is a highly heritable trait, with heritability estimates up to 78% (1). To this end, a 7-degree Food Neophobia Scale (FNS) questionnaire has been developed for the reliable measurement of food neophobia (2). Food neophobia is associated with several factors, including age, gender, personality features, living area, education level, and socioeconomic status (3–7). Furthermore, a high prevalence of food neophobia has been detected in children in particular and in people with low socioeconomic status living in rural areas (8, 9). To some extent, food neophobia in children can be considered a normal and developmentally appropriate response characterized as "omnivore's dilemma," in which the sampling of new food items may provide a source of nutrition or toxicity, thus potentially resulting in neophobic behavior.

Food neophobia is also associated with the development of other eating disorders and a reduced intake of fish and vegetables, leading to reduced overall dietary quality (4, 9). Previously, reduced dietary quality has been associated with an increased risk of obesity and subsequent chronic diseases [e.g., cardiovascular disease (CVD), coronary heart disease (CHD), and type 2 diabetes (T2D)] and inflammation (10–13). However, evidence of the role played by individual food items in inflammation, CVD, and T2D is still quite scarce and contradictory (14–18). Food items such as fruit, vegetables, whole grains, fish, and low-fat milk products are considered beneficial with regard to reducing obesity-induced inflammation, CVD, and T2D, whereas processed red meat and alcohol are considered risk factors (14, 19–21). Contrary to individual food items, whole-diet approaches based on dietary scores have achieved greater success in assessing associations between dietary quality and health-related risk factors (17, 22–24). In particular, scores based on Dietary Approaches to Stop Hypertension, the Alternate Healthy Eating index, and the Mediterranean diet have been well acknowledged in predicting health outcomes (22, 25, 26).

Food neophobia and its association with dietary quality and health both at the molecular level and at the disease outcome level are still underresearched in adult populations (6, 9). The aim of our study was to assess how food neophobia is associated with dietary quality and health-related biomarkers by examining the Baltic Sea Diet Score (BSDS) and NMR metabolomic profiles of the Finnish adult population. Furthermore, we investigated whether there is an association between food neophobia and health-related adverse outcomes for CVD, CHD, and T2D. The Estonian Biobank cohort was utilized to replicate findings from the NMR-based metabolomics and disease outcomes. Better understanding and recognition of behavioral eating disorders and dietary quality could provide valid noninvasive tools for the assessment and prediction of future risk for metabolic comorbidities.

Methods

Study design

A cross-sectional design was adopted for the study in order to investigate the association between food neophobia and dietary quality, NMR-based metabolomic profiles, and metabolic risk markers in Finnish and Estonian population-based cohorts (**Figure 1**). Because follow-up NMR-based metabolomic samples were available from subsamples of both cohorts, the food neophobia association with the metabolomic profile was also examined in a prospective manner (Figure 1). To determine whether food neophobia association with the metabolomic profile is mediated through dietary quality, we also investigated the association between dietary quality and the metabolomic profile. The food neophobia association with disease incidence was also studied in a prospective manner because we had follow-up information on CVD, CHD, and T2D disease incidence, which was available in national health and death registries for both cohorts. NMR-based metabolomic profiles were primary outcome variables of the study, and dietary quality, metabolic risk markers, and disease outcome incidence were secondary variables.

Study populations and data collection

The research was conducted based on the DIetary, Lifestyle, and Genetic determinants of Obesity and Metabolic syndrome (DILGOM) 2007 study and the follow-up DILGOM 2014 study (27). The DILGOM 2007 study was a sub-cohort of the National FINRISK 2007 study, a national health examination study including questionnaires, measurements, and blood sample collection. Both of the DILGOM studies were carried out by the National Institute for Health and Welfare (THL) in Finland (28). FINRISK studies were conducted every 5 y to monitor risk factors for major noncommunicable diseases in a random sample across 5 regions in Finland (29). The DILGOM study aimed to observe more closely how diet, psychosocial factors, lifestyle, environment, and genetics are linked to obesity and metabolic syndrome. The baseline DILGOM 2007 study sample ($n = 5024$) consisted of men and women aged 25–74 y. A total of 4581 participants were invited to participate in the DILGOM 2014 follow-up study, after excluding those who had since died, those who had moved abroad, and those whose contact information was no longer available ($n = 443$). All of the invited participants received the study questionnaire by mail [participation: $n = 3735$ (82%)], which also included the FNS questions. The participants from 2 original study areas (Helsinki and Turku) were also invited for clinical examination and sampling [$n = 1312$ (74%)]. For study purposes, individuals from the DILGOM 2007 who had completed the FNS questionnaire and for whom there were data on NMR-based metabolomic profile and anthropometric measurements ($n = 2982$) were included in the analytical sample (Figure 1, **Table 1**). Follow-up clinical measurements and sample information were available for a subsample of the selected individuals ($n = 1118$) (Figure 1). The study protocol for the DILGOM cohort was approved by the Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District. The participants gave written informed consent in accordance with the Declaration of Helsinki.

The Estonian Biobank cohort was utilized as a replication study sample for food neophobia associations with NMR-based metabolomic profiles and disease outcomes. The main objective of the Estonian Biobank study was to investigate the environmental, genetic, and behavioral background of common diseases and traits in the Estonian population (30). The cohort

was a volunteer-based sample of the Estonian adult population (n = 52,000) recruited from throughout Estonia in 2002–2010. The existing data were collected by means of health examinations and questionnaires regarding lifestyle, diet, and clinical diagnoses. The data used for the study were collected during initial recruitment (2002–2010) and during the follow-up examination (2011–2013), from which individuals with relevant information (first examination, n = 1109; second examination, n = 953) were included in the study (Figure 1, Table 1). DNA, white blood cells, and blood plasma were extracted from the obtained blood samples. For a subset of the Estonian Biobank cohort, NMR-based metabolomic profiling was conducted at both the first and the second examination (Figure 1). The Estonian Biobank study was approved by the Ethics Review Committee on Human Research of the University of Tartu and the Estonian Genome Center, University of Tartu scientific committee. Written informed consent was obtained from participants in accordance with the Declaration of Helsinki.

Measurement of food neophobia

We used a validated 7-degree FNS for the reliable measurement of food neophobia (**Supplemental Table 1**) (2). The questionnaire included 10 statements (e.g., "I am constantly sampling new and different foods") that respondents rated on a scale from 1 (strongly agree) to 7 (strongly disagree). The severity of food neophobia was calculated as the total score for all questions. The FNS ranged from 10 to 70, where higher scores indicate a greater level of food neophobia. Some of the questions were reverse scored compared with the original phrasing, which was taken into account when calculating the total scores. No official distinctive thresholds or cutoff values have been determined to specify food neophobia. However, the total FNS scores can be artificially divided into 3 groups based on the existing literature: food neophilics (10–24), median group (25–39), and food neophobics (40–70). These were used in our study for categorization, if needed (8). Although it has been demonstrated that excluding 2 or 4 items from the FNS can improve the method when used in some countries, including Finland (31), we decided to use the original 10-point FNS scale to ensure comparability between the investigated Finnish and Estonian cohorts. No previous data exist on the efficacy of the reduced FNS in the Estonian population. For both populations, FNS was measured only once, during the second study visits for *1*) DILGOM 2014 and *2*) the Estonian Biobank cohort 2010–2012. Food neophobia is considered a relatively stable trait during adulthood (4), which is why we justified the use of singular measured FNS scores for the baseline, follow-up, and longitudinal analyses in our analytical sample consisting of adults. The majority of the existing literature demonstrates that the level of food neophobia varies during childhood and adolescence, not adulthood (4). However, note that some studies

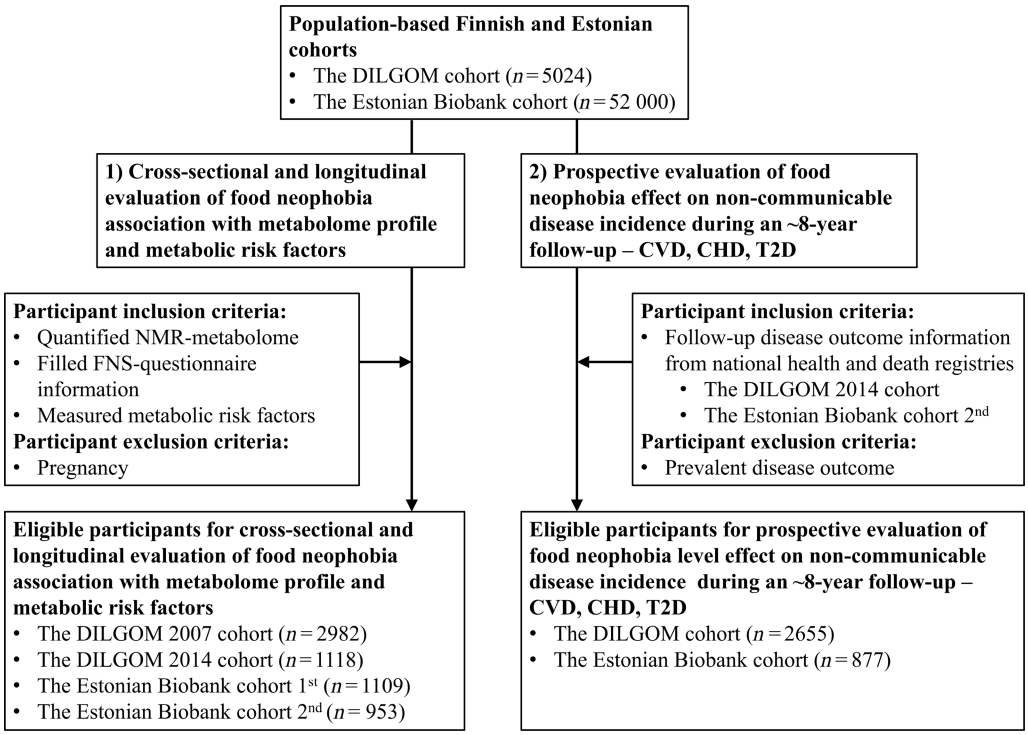

FIGURE 1 Flowchart of the study design and participant selection. The study consisted of *1*) cross-sectional and longitudinal analysis of food neophobia association with health-related biomarkers measured with an NMR-based metabolomics platform and *2*) longitudinal analysis of the association of food neophobia with chronic disease (e.g., CHD, CVD, and T2D) incidence in the Finnish DILGOM (n = 2982) and Estonian Biobank cohorts (n = 1109). Food neophobia association with dietary quality and metabolic risk markers was also studied cross-sectionally in the Finnish DILGOM cohort. Inclusion and exclusion criteria for sample size determination are shown. CHD, coronary heart disease; CVD, cardiovascular disease; DILGOM, DIetary, Lifestyle, and Genetic determinants of Obesity and Metabolic syndrome study; FNS, Food Neophobia Scale; T2D, type 2 diabetes.

TABLE 1 Study population baseline characteristics categorized by the level of food neophobia[1]

	DILGOM 2007 cohort				Estonian Biobank cohort, first examination			
	Food neophilics	Median group	Food neophobics	Total	Food neophilics	Median group	Food neophobics	Total
Sample size, *n* (%)	891 (29.9)	1217 (40.8)	874 (29.3)	2982 (100)	258 (23.3)	591 (53.3)	260 (23.4)	1109 (100)
Gender								
Men, *n* (%)	406 (45.6)	549 (45.1)	418 (47.8)	1373 (46)	127 (49.2)	289 (48.9)	124 (47.7)	540 (48.7)
Women, *n* (%)	485 (54.4)	668 (54.9)	456 (52.2)	1609 (54)	131 (50.8)	302 (51.1)	136 (52.3)	569 (51.3)
Age, y	48 ± 12.3	53.1 ± 12.5	57.1 ± 11.7	52.7 ± 12.7	41.4 ± 14.5	50.3 ± 15.2	55.4 ± 14.6	49.4 ± 15.6
BMI, kg/m^2	26.1 ± 4.4	26.6 ± 4.7	26.8 ± 4.6	26.5 ± 4.6	26.3 ± 4.7	27 ± 4.9	28.2 ± 5.3	27.1 ± 5
Education level								
Low, *n* (%)	162 (18.3)	316 (26.1)	324 (37.2)	802 (27.0)	19 (7.4)	63 (10.7)	55 (21.1)	137 (12.4)
Median, *n* (%)	271 (30.7)	446 (36.8)	313 (35.9)	1030 (34.7)	122 (47.5)	349 (59.0)	151 (58.1)	622 (56.1)
High *n* (%)	451 (51.0)	450 (37.1)	234 (26.9)	1135 (38.3)	116 (45.1)	179 (30.3)	54 (20.8)	349 (31.5)
Living region								
Urban, *n* (%)	442 (49.6)	510 (41.9)	305 (34.9)	1257 (42.2)	155 (60.1)	321 (54.3)	118 (45.4)	594 (53.6)
Rural, *n* (%)	449 (50.4)	707 (58.1)	569 (65.1)	1725 (57.8)	103 (39.9)	270 (45.7)	142 (54.6)	515 (46.4)
FNS	18.2 ± 4.0	31.9 ± 4.3	47.6 ± 6.9	32.4 ± 12.4	19.1 ± 3.9	32.1 ± 4.3	45.5 ± 5.2	32.2 ± 10.1

[1]Excluding FNS, which was gathered during the second study visits. Values are means ± SDs for age, BMI, and FNS. Sample size, gender, education level, and living region are depicted as frequency (cumulative percentage). For the Finnish DILGOM 2007 cohort, regions were defined as follows: urban (Helsinki, Vantaa, Turku, and Loimaa) and rural (North Karelia, Northern Savo, and Oulu). Education level was defined in the Estonian Biobank cohort as follows: low, below secondary education; median, secondary education; and high, higher education. For the Finnish DILGOM cohort, education levels were defined by dividing individuals into thirds based on number of years of education. DILGOM, DIetary, Lifestyle, and Genetic determinants of Obesity and Metabolic syndrome study; FNS, Food Neophobia Scale.

have detected increased levels of food neophobia in the elderly population aged 66–80 y (3).

Determination of dietary quality in the DILGOM cohort

Dietary information was available in the DILGOM studies from a validated 131-item FFQ, designed to assess habitual diet during the preceding 12 mo, calculated by using the national food composition database (Fineli) and in-house software (Finessi) (32). An FFQ-based BSDS was applied for dietary quality assessment because locally tailored diets are needed to effectively measure the associations between a healthy diet and health outcomes in other populations, such as Scandinavians. Dietary scores such as the BSDS have the advantage of taking into account the complex interactions and cumulative effects of multiple foods and nutrients within the diet compared with the information from individual food items (32). The BSDS has been proven to predict overall dietary quality in the Finnish population and is a valid tool for assessing diet–disease relations (32). Previously, the BSDS has been examined in relation to lower abdominal obesity and lower weight gain (27), cardiometabolic risk factors, obesity-related markers of inflammation, and diabetes (11–13, 33).

In total, 9 components are included in the BSDS (**Table 2**). BSDS components are scored on a scale from 0 to 3, apart from alcohol, which is scaled from 0 to 1. Overall dietary quality can be assessed by calculating the total sum score of the BSDS categories, which ranges between 0 and 25. It is noteworthy that for some categories, the scoring method is negative, which has to be accounted for. Higher scores for the BSDS are indicative of higher dietary quality. FFQ-based dietary information for BSDS calculation was gathered during the DILGOM 2007 and the DILGOM 2014 follow-up. In addition, specific FFQ-based dietary component information (e.g., energy intake, protein intake, carbohydrate intake, and fat intake) from both data collections was utilized to further assess food neophobia association with dietary quality factors. No comparable dietary information was available from the Estonian Biobank cohort.

Metabolomic data preparation and management

A high-throughput NMR metabolomics platform was used for the quantification of blood lipids and metabolic measures in both study populations (34, 35). The full process and methods of sample preparation and quantification utilized in this study are described in detail elsewhere (34, 35). Briefly, the samples were measured using a Bruker AVANCE III HD NMR 500-MHz spectrometer equipped with a cryogenically cooled TCI CryoProbe Prodigy (34, 35). For the protocol, the used measurement temperature was set to 36.95 degrees Celsius. A wide distribution of different lipoprotein subclasses (e.g., VLDL, LDL, and HDL), fatty acids, and apolipoproteins and a broad selection of small molecules, such as glycolysis precursors, amino acids, and inflammation biomarkers, were included in the metabolites quantified and analyzed (**Supplemental Table 2**). The selection included 14 lipoprotein subclasses that were analyzed as part of the full metabolite profile. Furthermore, the quantified lipoproteins were divided into subclasses according to particle size. In total, samples from DILGOM 2007 ($n = 2982$) and DILGOM 2014 ($n = 1118$) participants and 228 different metabolites were extracted and quantified. In addition, samples from Estonian Biobank cohort participants at baseline ($n = 1109$) and during follow-up ($n = 953$), provided by the Estonian Genome Center, and 225 metabolites were available for replication. The Estonian Biobank cohort samples were gathered during the first study visit between 2002–2010 and during the follow-up of 2010–2012.

TABLE 2 BSDS components and scoring in the Finnish DILGOM cohort[1]

Score component	Content	Scoring	Points range
Fruits and berries	Apples, pears, and berries	Positive[2]	0–3
Vegetables	Tomatoes, cucumber, leafy vegetables, roots, cabbage, and peas	Positive	0–3
Low-fat milk	Low-fat and fat-free milk	Positive	0–3
Cereals	Rye, oats, and barley	Positive	0–3
Fish	Salmon and freshwater fish	Positive	0–3
Meat products	Beef, pork, processed meat products, and sausages	Negative[3]	0–3
Total fat[4]	Total fat intake	Negative	0–3
Fat ratio	The ratio of PUFA to saturated fat and *trans* fatty acids	Positive	0–3
Alcohol[5]	Ethanol intake	Negative	0–1

[1]BSDS, Baltic Sea Diet Score; DILGOM, DIetary, Lifestyle, and Genetic determinants of Obesity and Metabolic syndrome study.
[2]Highest consumption third received the highest points.
[3]Lowest consumption quartile received the highest points.
[4]Total fat intake as percentage of energy intake.
[5]Moderate ethanol intake ≤ 20 g for men and ≤ 10 g for women received 1 point; otherwise, 0 points were given. Total BSDS ranges from 0 to 25, where higher scores are indicative of healthier overall diet (37).

Assessment of metabolic risk factors and disease outcomes

Numerous quantified and determined measures were available to assess cardiovascular and glucose metabolism comorbidities. Concentrations of high-sensitivity C-reactive protein (hs-CRP), glycated hemoglobin (HbA1c), glucose, and insulin were determined from fasting (> 8h) venous blood samples in the central laboratory of THL. In addition, anthropometric measures, BMI (in kg/m^2), and waist circumference, used for metabolic risk status assessment, were determined. Waist circumference was measured midway between the lower rib margin and iliac crest, with rounding to the nearest 0.5 cm. Metabolic risk factors, biomarkers, and anthropometric measures were obtained from the Finnish DILGOM 2007 and follow-up DILGOM 2014 studies. Only BMI was available from the metabolic risk factor information from the Estonian Biobank cohort initial recruitment (2002–2010).

Disease outcomes (prevalences and incidences) and specific diagnostic criteria for CVD, CHD, and T2D were collected from national health registries to assess possible risks associated with food neophobia in relation to disease outcomes in both populations (**Supplemental Methods**) (32). The primary endpoints for disease outcomes in this study were newly diagnosed CVD, CHD, and T2D during follow-up. Disease outcomes were collected from *1*) the Finnish hospital discharge register for nonfatal outcomes and the causes of death register for fatal outcomes and *2*) the Estonian health and death registries. In both populations, disease outcomes were linked and followed for each participant using a personal identification number given to every permanent resident. The International Classification of Diseases (http://www.who.int/classifications/icd/en/) was used to identify disease outcomes (Supplemental Methods). The Finnish and Estonian cohorts were followed until December 31, 2015, so that the average follow-up time was 8 y for disease outcomes in both populations.

Statistical analysis

NMR metabolomic data skewness, normality, and outliers were assessed with dot plots and histograms to ensure data quality and reducibility of the results. Outliers were removed based on an SD > 4 from the mean metabolite concentration. A scaled logarithmic transformation was applied to normalize metabolite variable distributions in all of the metabolomic analyses. In addition, pregnant individuals were excluded from all metabolomic analyses (Figure 1).

Linear regression was used to assess relations between the level of food neophobia and metabolome biomarker concentrations in a cross-sectional study design in both baseline and follow-up data sets of DILGOM and Estonian Biobank cohorts. In addition, longitudinal analyses of these cohorts were performed to evaluate changes occurring in metabolite concentration in relation to the level of food neophobia. Smoking status, BMI, age, gender, education level, diabetes status, fasting time, and living region were taken into account as possible confounding factors in the cross-sectional metabolomic analyses. In the longitudinal metabolomic analyses, we accounted for metabolite baseline concentration, age at baseline, BMI change during follow-up, smoking status, gender, and education level at the baseline. Similar analyses were conducted on the replication material gathered from the Estonian Biobank cohort.

Linear regression was also used to assess the association between dietary quality (BSDS) and NMR platform metabolites to detect whether dietary quality mediates the association of food neophobia on metabolic measures in the DILGOM cohort. Mediation analysis was further complemented by *1*) assessing the association between FNS and BSDS and *2*) applying the BSDS as a covariate in the aforementioned food neophobia metabolomic analyses. Metabolomic analyses were adjusted in a similar manner as mentioned previously for the cross-sectional metabolomic analyses assessing the association of food neophobia. Analysis of BSDS association with food neophobia was adjusted for education level, age, gender, BMI, and living region.

The association of food neophobia with metabolic risk factors (hs-CRP, HbA1c, fasting serum insulin and glucose, BMI, and waist circumference) was also assessed with linear regression; analyses were adjusted for smoking status, BMI, age, gender, education level, and living region. Scaled logarithmic transformation was applied for risk biomarkers but not for the

anthropometric measures. Moreover, BMI was excluded as a covariate from the anthropometric measure analyses due to high intercorrelation with waist circumference. Individuals with prevalent CVD, CHD, or T2D disease outcomes were excluded from the data before analysis as possible confounding factors.

We used the Cox proportional hazards regression model to investigate whether the severity of food neophobia was associated with the future incidence of diseases during the follow-up time of ~8 y in the Finnish and Estonian populations. CHD, CVD, and T2D prevalences and incidences were coded in a binomial manner in the data set used for statistical analysis. The analyses were adjusted for baseline age, baseline BMI, baseline education level, and smoking status. Proportional hazard assumption tests were conducted to ensure model validity. Individuals with prevalent CVD, CHD, or T2D outcomes were excluded from the disease outcome analyses (Figure 1).

In all the analyses, individuals with missing data were excluded, and only individuals with complete information on the necessary variables were included. Many of the same subclass metabolites highly correlate with each other, as was detected by principal component (PC) analysis, which showed a total of 24 PCs explaining > 95% of the variation seen in the data set. The multiple-testing corrected significance level in the highly correlated data was set accordingly ($P < 0.05/24$ PCs; i.e., $P < 0.0021$) in all analyses regarding NMR metabolomics. R statistical software was used for all the statistical analyses (version 3.3.3 or higher).

Results

The association of food neophobia with NMR-based metabolomic profiles in the Finnish DILGOM population-based cohort

Overall, individuals with higher levels of food neophobia exhibited adverse metabolomic profiles compared with food neophilics (**Figure 2**). In the cross-sectional analysis of DILGOM 2007, we observed an inverse association between the level of food neophobia and several metabolite concentrations and their ratios, such as *1*) the ratio of ω-3 fatty acids to total fatty acids (β: -0.006 ± 0.002; adjusted $P = 3.47 \times 10^{-3}$), *2*) cholesterol esters in very large HDL cholesterol particles (β: -0.005 ± 0.001; adjusted $P = 0.01$), *3*) total cholesterol in very large HDL cholesterol particles (β: -0.005 ± 0.001; adjusted $P = 0.02$), and *4*) the concentration of very large HDL particles (β: -0.004 ± 0.001; adjusted $P = 0.05$). In contrast, a positive association was found for *1*) the ratio of MUFA to total fatty acids (β: 0.005 ± 0.002; adjusted $P = 0.05$), *2*) α_1-acid glycoprotein (β: 0.006 ± 0.001; adjusted $P = 2.50 \times 10^{-3}$), and *3*) citrate (β: 0.008 ± 0.002; adjusted $P = 5.44 \times 10^{-6}$) (**Figure 3**, **Supplemental Table 3**).

These findings were further supported by the cross-sectional analyses of the DILGOM 2014 cohort, in which food neophobia associated similarly with the ratio of ω-3 fatty acids to total fatty acids (β: -0.009 ± 0.003; adjusted $P = 0.04$) and α_1-acid glycoprotein (β: 0.008 ± 0.003; adjusted $P = 0.06$) (**Supplemental Table 4**). In the DILGOM 2014 cohort, the most significant association was found for the ratio of 22:6 DHA to total fatty acids (β: -0.01 ± 0.003; adjusted $P = 0.02$)—a metabolite belonging to the group of ω-3 fatty acids. Overall, in both DILGOM 2007 and DILGOM 2014, a higher level of food neophobia was associated with negative cardiometabolic outcomes on lipid metabolites (e.g., decreases in ω-3 fatty acids and very large HDL fractions and an increase in MUFAs) and inflammation-related biomarkers (e.g., an increase in α_1-acid glycoprotein), whereas lower levels of food neophobia predicted the opposite—more favorable concentrations of health-related biomarkers (Figure 2, Supplemental Tables 3 and 4).

Finally, we used the data from both studies to conduct a longitudinal analysis to explore whether the level of food neophobia associated with serum metabolome profile modulation during the 8-y follow-up (**Supplemental Table 5**). The findings from cross-sectional analyses on ω-3 fatty acids were further corroborated because food neophobia associated most significantly with changes in metabolites associated with ω-3 fatty acids, such as the ratio of 22:6 DHA to total fatty acids (β: -0.003 ± 0.0009; adjusted $P = 0.02$) (Supplemental Table 5).

Replication: The association of food neophobia with NMR-based metabolomic profiles in the Estonian Biobank cohort

Cross-sectional analysis of the Estonian Biobank cohort first examination samples replicated the inverse association between the severity of food neophobia and ω-3 associated metabolites (**Supplemental Table 6**). Significant findings were detected for *1*) the ratio of ω-3 fatty acids to total fatty acids (β: -0.013 ± 0.003; adjusted $P = 1.10 \times 10^{-3}$), *2*) the level of ω-3 fatty acids (β: -0.011 ± 0.003; adjusted $P = 3.28 \times 10^{-3}$), *3*) the ratio of 22:6 DHA to total fatty acids (β: -0.014 ± 0.003; adjusted $P = 4.05 \times 10^{-4}$), and *4*) the level of 22:6 DHA (β: -0.012 ± 0.003; $P = 0.01$; adjusted $P = 8.98 \times 10^{-4}$) (Supplemental Table 6). These findings were confirmed by the cross-sectional analysis on the second time point samples, where *1*) the ratio of ω-3 fatty acids to total fatty acids (β: -0.011 ± 0.003; adjusted $P = 9.59 \times 10^{-3}$), *2*) the level of ω-3 fatty acids (β: -0.01 ± 0.003; adjusted $P = 0.05$), and *3*) the ratio of 22:6 DHA to total fatty acids (β: -0.011 ± 0.003; adjusted $P = 0.04$) were also significantly associated with the level of food neophobia (**Supplemental Table 7**). No significant association was found in the longitudinal analysis of the Estonian Biobank cohort, although cholesterol esters in very large HDL cholesterol and total cholesterol in very large HDL cholesterol reached nominal ($P < 0.05$) significance (**Supplemental Table 8**). Overall, similar to observations in the Finnish population, levels of food neophobia were associated with a similar modulation of the metabolomic profile in the Estonian Biobank cohort, especially regarding ω-3 fatty acids (**Figure 4**, **Supplemental Table 9**).

Food neophobia associates with poorer dietary quality in the DILGOM cohort

Food neophobia associates with reduced dietary quality, as we found an inverse significant ($P < 0.05$) association between FNS and BSDS in the DILGOM 2007 (**Table 3**) and DILGOM 2014 studies (**Supplemental Table 10**). This was confirmed by observed significant ($P < 0.05$) differences in several nutrient intakes between different levels of food neophobia in

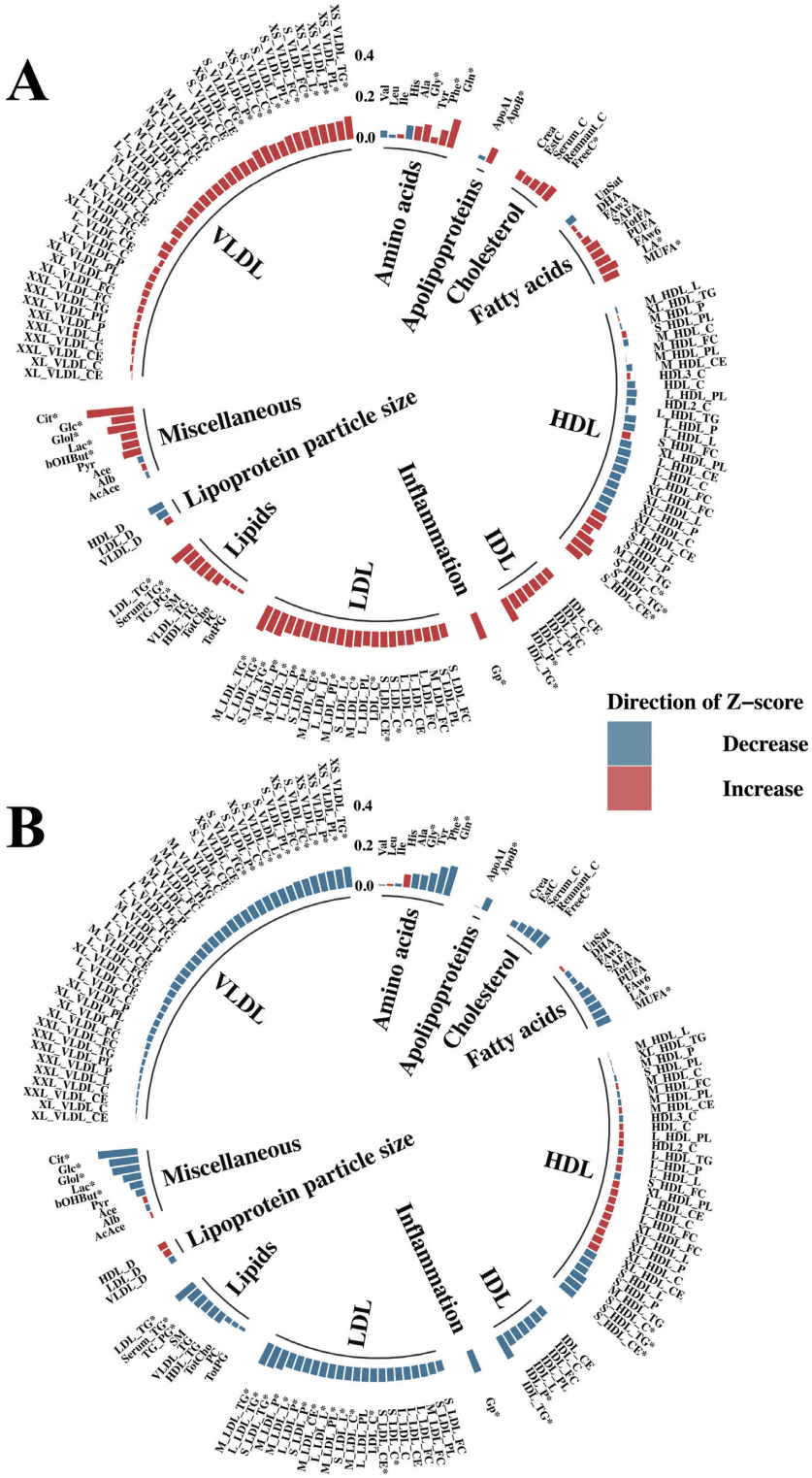

FIGURE 2 Overall differences in the metabolomic profile between different groups of food neophobia in the Finnish DILGOM cohort. Overall levels of NMR-based metabolomics of the Finnish DILGOM 2007 cohort ($n = 2982$) were set as reference values to which food neophobics (FNS 40–70) in panel A and food neophilics (FNS 10–24) in panel B were compared. The median group (FNS 25–39) compared to the reference level is depicted in **Supplemental Figure 1**. For plotting, 150 health-related biomarkers were selected to demonstrate the overall differences in metabolomic profile between different levels of food neophobia. Depicted polar plots are derived from metabolite raw values, where outliers based on 4 SD from the mean have been excluded. Plotted metabolite values are represented as an SD change from the set reference z score. The red color indicates an increase and the blue a decrease compared with the reference z score. The height of the bars depicts the z score level, and the scale is plotted on the figure apex vertically. Metabolites are ordered according to subclass and z score values. Overall, more adverse trends in the metabolomic profile are detected in a linear fashion going from food neophilics to food neophobics. *Significant difference between food neophobia groups, $P < 0.05$. Significant differences were calculated from an unadjusted linear regression model. DILGOM, DIetary, Lifestyle, and Genetic determinants of Obesity and Metabolic syndrome study; FNS, Food Neophobia Scale.

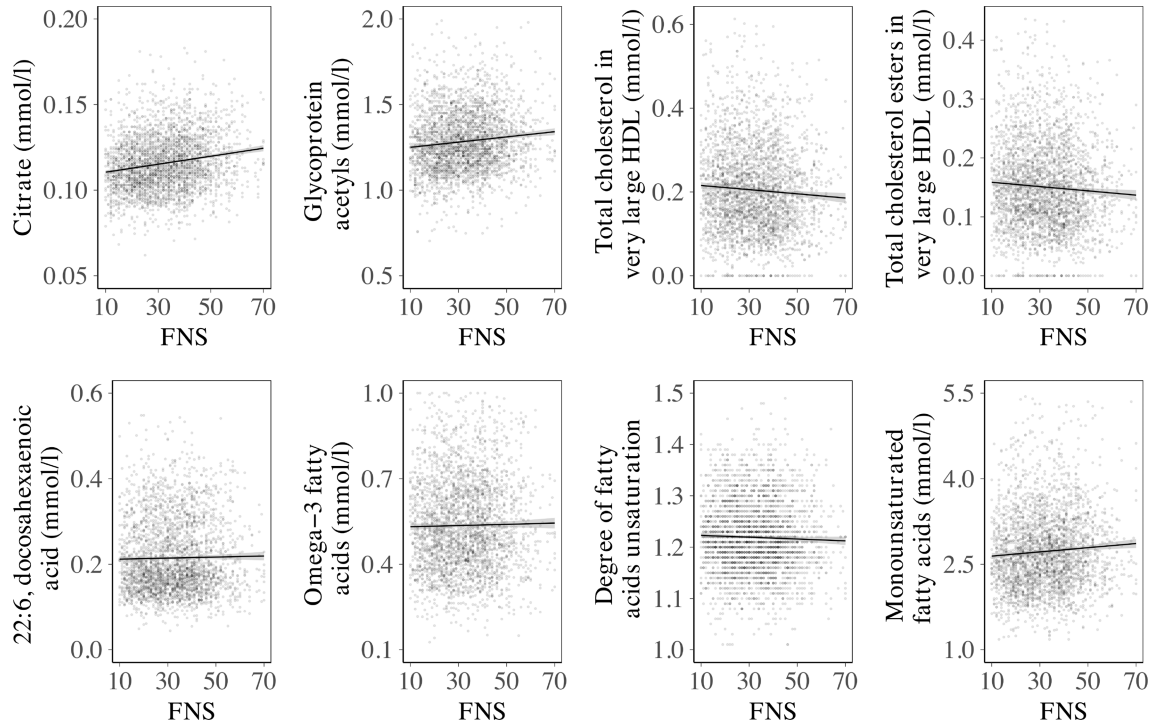

FIGURE 3 Food neophobia association with metabolite concentrations in the Finnish DILGOM 2007 cohort. The figure depicts alteration of metabolites at different levels of food neophobia in the Finnish DILGOM 2007 cohort ($n = 2982$). For plotting, we selected metabolites that most significantly (adjusted $P < 0.05$) associated with the level of food neophobia at baseline of both the DILGOM cohort and the Estonian Biobank cohort. The FNS score is represented on the x axis ranging from 10 to 70, where higher scores indicate a higher level of food neophobia. Metabolite concentration is depicted on the y axis. The gray hue around the plotted lines represents SE variation from the curve. DILGOM, DIetary, Lifestyle, and Genetic determinants of Obesity and Metabolic syndrome study; FNS, Food Neophobia Scale.

both of the DILGOM studies (Table 3, Supplemental Table 10). Our significant findings on the ω-3 fatty acids in the metabolomic analyses were further supported by higher intakes of PUFAs in food neophilics (Table 3). Food neophilia was also associated with some healthier aspects of diet, such as higher intake of MUFAs, fiber, and protein. Individuals with food neophilia also consumed lower amounts of saturated fatty acids, carbohydrates, and salt. In contrast, alcohol was least consumed by individuals with a higher level of food neophobia.

Poorer dietary quality mediates food neophobia association with serum metabolome profile

The BSDS was significantly associated with a group of the same metabolites (e.g., ω-3 fatty acids, DHA, PUFA, and MUFA; degree of unsaturation) as the FNS score in the DILGOM 2007 cohort (**Figure 5**, **Supplemental Table 11**) and the DILGOM 2014 cohort (**Supplemental Table 12**) after accounting for detected associations in both the DILGOM and Estonian Biobank cohorts. Furthermore, we found that BSDS was more strongly associated (adjusted $P < 10^{-6}$) with the aforementioned metabolite concentrations compared with the FNS score in the DILGOM 2007 cohort (Supplemental Table 11) and the DILGOM 2014 cohort (Supplemental Table 12). The observed metabolite findings and significant association between BSDS and FNS suggest that the association of food neophobia with metabolite profiles (e.g., ω-3 fatty acids) is partially mediated through differences in dietary quality. We tested this further by accounting for BSDS in the model when testing the FNS association with metabolite concentrations in the DILGOM 2007 cohort (**Supplemental Table 13**) and the DILGOM 2014 cohort (**Supplemental Table 14**). Adding BSDS to the model diminished our significant association of FNS with ω-3 fatty acids and MUFA concentrations (adjusted $P > 0.05$). In contrast, FNS association with α_1-acid glycoprotein, citrate, and HDL cholesterol metabolites persisted as significant, thus implying that dietary quality might have a selective role in mediating food neophobia association with certain serum metabolites (Figure 5).

Association of food neophobia with metabolic risk factors and disease outcomes

Food neophobia was not associated ($P > 0.05$) with waist circumference or BMI in the DILGOM 2007 cohort (**Supplemental Table 15**) or the DILGOM 2014 cohort (**Supplemental Table 16**). Similarly, no significant association was found between FNS and BMI in the Estonian Biobank cohort. However, of the recognized metabolic risk factor biomarkers influencing the risk of CVD, CHD, and T2D, the level of food neophobia associated in the DILGOM 2007 cohort significantly with fasting serum insulin concentration (β: 0.004 ± 0.013; $P = 5.83 \times 10^{-3}$) but not with CRP and serum glucose concentrations (Supplemental Table 15). Similarly, in the DILGOM 2014 cohort, the food neophobia association with serum insulin concentrations

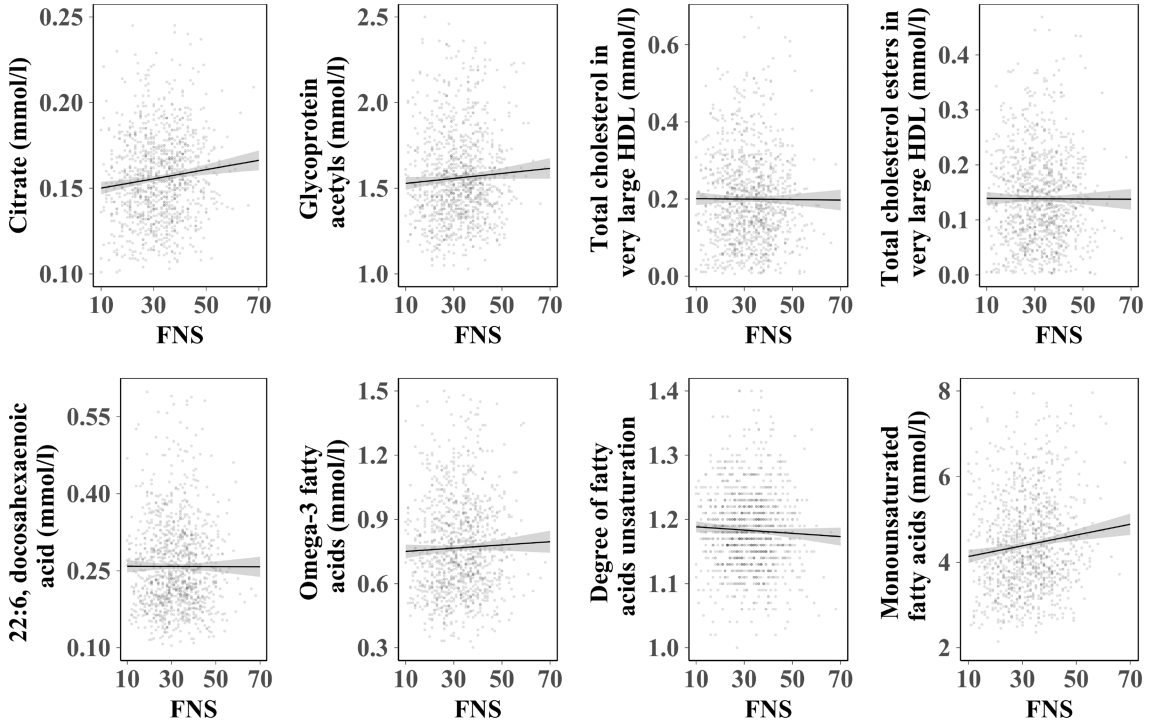

FIGURE 4 Food neophobia association with metabolite concentrations in the Estonian Biobank cohort first examination. The figure depicts alteration of metabolites at different levels of food neophobia in the Estonian Biobank cohort ($n = 1108$). For plotting, we selected metabolites that most significantly (adjusted $P < 0.05$) associated with the level of food neophobia at baseline of both the DILGOM cohort and the Estonian Biobank cohort. The FNS score is represented on the x axis ranging from 10 to 70, where higher scores indicate a higher level of food neophobia. Metabolite concentration is depicted on the y axis. The gray hue around the plotted lines represents SE variation from the curve. DILGOM, DIetary, Lifestyle, and Genetic determinants of Obesity and Metabolic syndrome study; FNS, Food Neophobia Scale.

approached significance (β: 0.004 ± 0.002; $P = 0.08$). No significant associations were found between food neophobia and the other measured metabolic risk factors in the DILGOM 2014 cohort (Supplemental Table 16).

In addition, Cox regression analysis revealed that higher levels of food neophobia predicted a higher incidence of newly diagnosed T2D in the DILGOM cohort in the fully adjusted model (HR: 1.018 ± 0.007; $P = 0.01$), thus supporting our finding

TABLE 3 Descriptive statistics of nutrition in the different groups of food neophobia in the DILGOM 2007 cohort

	Descriptive statistics			Linear regression statistics		
Diet component	Food neophilics	Median group	Food neophobics	n[1]	Estimate (SE)	P value
BSDS[2,3]	12.95 ± 4	13.21 ± 4.18	13.12 ± 4.24	869/1184/843	−0.025 (0.006)	8.04×10^{-5}
Energy, kJ	10,435.06 ± 3376	10,331.02 ± 3611	10,661.31 ± 3897	869/1184/843	5.74 (5.61)	3.06×10^{-1}
Carbohydrates,[3] *E%*	48.04 ± 5.91	49.08 ± 5.97	50.33 ± 6.29	869/1184/843	0.067 (0.009)	2.41×10^{-12}
Protein,[3] *E%*	17.92 ± 2.44	17.8 ± 2.45	17.31 ± 2.61	869/1184/843	−0.028 (0.004)	1.06×10^{-11}
Fat, *E%*	31.31 ± 4.76	30.91 ± 4.89	30.76 ± 5.05	869/1184/843	−0.004 (0.008)	5.82×10^{-1}
Fat, saturated,[3] *E%*	11.4 ± 2.23	11.31 ± 2.39	11.65 ± 2.62	869/1184/843	0.016 (0.004)	2.40×10^{-5}
Fat, monounsaturated,[3] *E%*	11.2 ± 2.17	11 ± 2.19	10.83 ± 2.23	869/1184/843	−0.007 (0.004)	4.60×10^{-2}
Fat, polyunsaturated,[3] *E%*	5.59 ± 1.17	5.52 ± 1.18	5.31 ± 1.12	869/1184/843	−0.009 (0.002)	3.27×10^{-6}
Fiber, g/MJ	2.95 ± 0.9	3.08 ± 0.96	3.11 ± 0.95	869/1184/843	−0.002 (0.001)	1.63×10^{-1}
Alcohol,[3] *E%*	2.73 ± 3.07	2.2 ± 3.1	1.6 ± 2.88	869/1184/843	−0.035 (0.005)	1.45×10^{-13}
NaCl,[3] g/MJ	0.92 ± 0.14	0.93 ± 0.14	0.92 ± 0.15	869/1184/843	−0.001 (0.0002)	5.95×10^{-8}

[1]Frequency (food neophilics/median group/food neophobics).
[2]Baltic Sea Diet Score.
[3]Significant association ($P < 0.05$) with food neophobia and diet components. Descriptive statistics are presented as mean (SD) unless otherwise noted. Descriptive statistics are unadjusted for other factors. For BSDS and energy intake, regression model was adjusted for education level, age, gender, BMI, and living region. For other measures, BMI was excluded from the regression model to avoid overcorrection. Linear regression model was used for all variables. None of the nutrient variables were transformed for association estimation. The DILGOM 2014 follow-up dietary information is depicted in Supplemental Table 10, where food neophobia associated significantly ($P < 0.05$) with all the same diet components. *E%*, energy percentage; kJ, kilojoule; g/MJ, grams per megajoule.

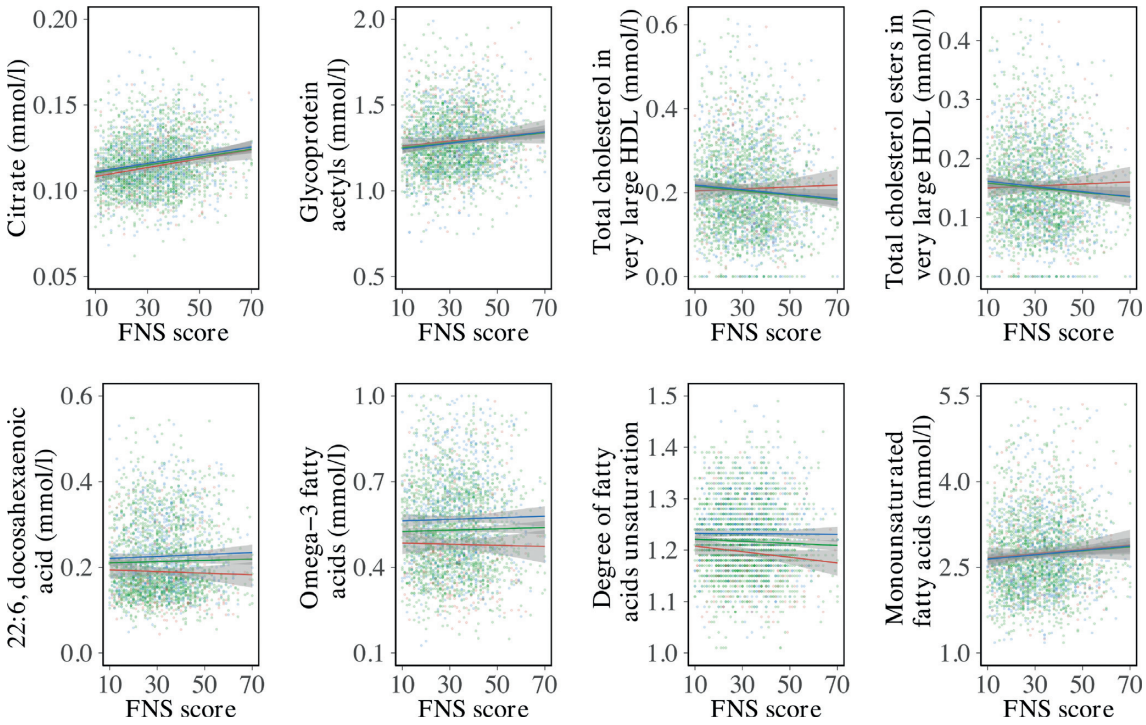

FIGURE 5 Food neophobia and dietary quality association with significant metabolite concentrations. The figure depicts the most significant metabolite alteration in relation to the FNS and dietary quality as measured by the BSDS in the DILGOM 2007 cohort ($n = 2935$). For plotting, we selected metabolites that most significantly (adjusted $P < 0.05$) associated with the level of food neophobia at baseline of both the DILGOM cohort and the Estonian Biobank cohort. Separate curves present metabolite-level alteration in different BSDS categories. The BSDS categories used were *1*) low dietary quality (0–8), *2*) median dietary quality (9–16), and *3*) high dietary quality (17–24). Colors for the representative BSDS categories are as follows: red, low dietary quality; green, median dietary quality; and blue, high dietary quality. The gray hue around the plotted lines represents SE variation from the curve. The figure particularly indicates that dietary quality mediates food neophobia effects on ω-3 fatty acids and associated metabolites (e.g., DHA, degree of fatty acid unsaturation), whereas food neophobia (and other related factors) mediates more directly differences in citrate, glycoprotein acetyls (mainly α_1-acid glycoprotein), very large HDLs, and MUFAs. BSDS, Baltic Sea Diet Score; DILGOM, DIetary, Lifestyle, and Genetic determinants of Obesity and Metabolic syndrome study; FNS, Food Neophobia Scale.

on the association between food neophobia and fasting serum insulin concentrations (**Table 4**). In contrast, the level of food neophobia did not associate with the incidence of CVD and CHD in the DILGOM cohort. In the Estonian Biobank cohort, higher levels of food neophobia predicted a higher incidence of CHD (HR: 1.027 ± 0.011; $P = 0.012$), whereas no association with CVD and T2D was detected (Table 4).

Discussion

This study is the first to comprehensively assess the association of food neophobia with health-related biomarkers at the level of the NMR-based metabolome. Food neophobia was significantly associated with several health-related biomarkers, most strongly with ω-3 fatty acids in both the Finnish DILGOM and Estonian Biobank cohorts. In addition, food neophobia was associated with poorer overall dietary quality in Finnish individuals when measured by a score that illustrates healthy Nordic diet and individual nutrient intake categories. Furthermore, a high level of food neophobia was associated with an adverse alteration of fasting serum insulin and an increased incidence of T2D in the Finnish DILGOM cohort, whereas an increased incidence of CHD was detected in the Estonian Biobank cohort.

Several studies have shown that higher levels of food neophobia associate strongly with reduced dietary quality in both children (4, 36–38) and adults (1, 9, 39), thus suggesting that the level of food neophobia relates significantly to eating behavior and dietary quality throughout the whole life span. Our results support these findings because we detected poorer dietary quality in individuals with higher food neophobia when measured by BSDS and specific dietary intake components. Furthermore, dietary quality is known to contribute to circulating concentrations of health-related biomarkers, where dietary effects are mediated mainly through the composition of daily food metabolome and changes in body weight/composition (40–42). Previously, it has been hypothesized that higher food neophobia along with adverse dietary behavior and quality result in increased adiposity and body weight. However, to date, contradictory findings have been reported on a food neophobia association with adiposity and body weight. These disparities in findings are most likely due to differences in the study population age (9, 43). We did not detect an association between adiposity measures and the level of food neophobia in either the Finnish DILGOM or the Estonian Biobank cohort, which suggests that our findings on the metabolome might reflect the actual composition of the diet. However, various factors, including physical activity, gender, and genetics, also contribute to the alteration of the metabolomic

TABLE 4 Statistics and results of Cox proportional hazards model on disease outcomes, T2D, CHD, CVD, in the Finnish DILGOM and Estonian Biobank cohort[1]

Category		Descriptive statistics of disease outcomes				Cox proportional hazards model results				
Disease	Cohort	n[2]	Prevalence	Incidence	Follow-up time, y	n	Coefficient	HR (SE)	z score	P value
T2D	DILGOM cohort	2982	207	140	8	2655	0.018	1.018 (0.007)	2.52	0.01
	Estonian Biobank	1109	58	64	7.53	877	0.002	1.002 (0.016)	0.111	0.91
CHD	DILGOM cohort	2982	74	115	8.28	2655	−0.006	0.994 (0.009)	−0.7	0.48
	Estonian Biobank	1109	191	114	7.21	877	0.027	1.027 (0.011)	2.504	0.01
CVD	DILGOM cohort	2982	111	155	8	2655	0.001	0.99 (0.007)	−0.018	0.86
	Estonian Biobank	1109	18	25	7.71	877	0.034	1.034 (0.03)	1.135	0.26

[1]For Cox proportional hazards regression analysis, individuals with past disease outcomes and missing data were excluded. Follow-up time is presented as years for the whole study sample. Analysis was adjusted for baseline age, living region, gender, BMI, and smoking status in the DILGOM cohort. In the Estonian Biobank cohort, baseline age, baseline BMI, smoking status, and lipid treatment were accounted for in the analysis. Proportion hazard assumption was met in all the models. The *region* variable in the Finnish DILGOM cohort and *smoking status* in the Estonian Biobank cohort were set as strata in the analysis on T2D. CHD, coronary heart disease; CVD, cardiovascular disease; DILGOM, DIetary, Lifestyle, and Genetic determinants of Obesity and Metabolic syndrome study; T2D, type 2 diabetes.

[2]Frequency.

profile, making it difficult to distinguish single factors having independent effects.

Interestingly, we observed a consistent association between food neophobia and NMR-based metabolite ω-3 fatty acids—a suggested objective biomarker for PUFA intake (44). Supporting this hypothesis, we also detected a significant alteration in PUFA intake in different levels of food neophobia, where food neophobics had lower intakes. Moreover, the food neophobia association with dietary quality has been reported to associate with fish intake in particular—a major source of dietary PUFA (6, 45). Overall, previous studies together with our findings demonstrate potent evidence for an existing pathway between food neophobia, dietary quality relating to fish and PUFA intake, and circulating concentrations of serum ω-3 fatty acids. In addition, even after adjustment for dietary quality, food neophobia was significantly associated with higher concentrations of α_1-acid glycoprotein and citrate—biomarkers linked to inflammation, increased mortality, and adverse disease outcomes (46). These findings imply that dietary quality might have only a selective role in mediating food neophobia association with the serum metabolome profile (i.e., ω-3 fatty acids).

A growing body of large-scale metabolic profiling studies have unveiled a number of biomarkers that are associated with health outcomes. Circulating concentrations of ω-3 fatty acids (e.g., EPA, DHA, and α-linolenic acid) and HDL have been inversely associated with a risk of CVD and all-cause mortality, whereas MUFA, α_1-acid glycoprotein, and citrate concentrations have been associated positively with increased risk of chronic diseases (35). Consequently, our findings on the association between food neophobia and ω-3 fatty acids (decreased), HDL (decreased), α_1-acid glycoprotein (increased), MUFA (increased), and citrate (increased) concentrations suggest increased risk of CVD/CHD and T2D in individuals with high levels of food neophobia. These findings are supported by the significant association between food neophobia and fasting serum insulin levels together with the T2D incidence in healthy moderate-risk individuals in the DILGOM cohort (47, 48). Furthermore, it is well characterized that T2D is also a major risk factor for CVD/CHD (49). To this end, an association between food neophobia and the incidence of CHD was detected in the Estonian Biobank cohort, reinforcing our deduction of a plausibly increased risk of disease susceptibility, although the detected effect sizes in both cohorts were small. Larger longitudinal cohorts with a longer follow-up are needed to further confirm the role of food neophobia and its association with chronic disease risk. Moreover, better understanding of eating-related behavioral traits and dietary quality association with the serum metabolite profile is needed to more accurately predict health outcomes. Our study generates new hypotheses suggesting that the serum metabolome profile, especially lipids (e.g., ω-3 fatty acids, MUFA, and HDL), α_1-acid glycoprotein, and citrate, could potentially be used as a more objective and precise predictor in the assessment of dietary quality, dietary/lifestyle behavior, and subsequent health outcomes if validated by future studies.

We consider our study to have several possible limitations, including partially self-reported anthropometric measures in DILGOM 2014 (27) and consideration of whether the study populations constitute a representative sample of the general adult population. In addition, the NMR-based metabolome in the Finnish DILGOM cohort was determined in serum but was determined in plasma in the Estonian Biobank cohort, causing a minor effect with regard to comparability. The fact that FNS was gathered from the study participants in both populations during the second study visit is also a possible limitation. However, we believe this had only minor effects on our results, considering *1*) the stability of food neophobia as a trait during adulthood, *2*) the consistency of our results, and *3*) the moderate length of our study follow-up. We also recognize the use of a translated FNS in both Finnish and Estonian populations as a possible limitation because it is well acknowledged that nonequivalencies in vocabulary, experiences, and concepts in dietary behavior in different cultures may introduce bias. On the other hand, the strengths of the study include *1*) large study sample sizes; *2*) follow-up of the study samples regarding the NMR-based metabolome, dietary information, and disease outcomes; *3*) validity of the study cohorts; and *4*) successful partial replication of metabolome results in a different study population with a different nationality and cultural background.

In conclusion, in the Finnish and Estonian adult populations, a higher level of food neophobia was associated with lower dietary quality, adverse concentrations of health-related biomarkers, and a higher incidence of chronic diseases. The association of food neophobia with a blood serum metabolomic profile seems to be mostly mediated through dietary quality independent of body weight and adiposity. We suggest that by identifying individuals with higher food neophobia (e.g., in adolescence) and associated detrimental dietary behavior and reduced dietary quality, it is possible to prevent and reduce future risk of metabolic diseases. Further studies are needed to verify and extend our findings and to determine the nature of causality between food neophobia, dietary quality, serum metabolite profile, and future disease risk in other countries and in relation to other cultural backgrounds.

The authors' responsibilities were as follows—KK and MP: designed the research plan; NK, LM, JS, KB, and SM: responsible for data collection and conducting research on the Finnish DILGOM cohort; KF, TE, and NT: responsible for data collection and conducting research on the Estonian Biobank cohort; HVS, NT, KF, AJ, and KK: performed statistical analysis; HVS, KK, and MP: had primary responsibility for the final content; and all authors: contributed to writing the manuscript and read and approved the final manuscript. The authors report no conflicts of interest.

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