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Association of ultra-processed food-related metabolites with selected biochemical markers in the UK Biobank

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Abstract

Background Ultra-processed food (UPF) intake is positively associated with multiple adverse health outcomes. However, the underlying biological mechanisms remain unclear. Serum metabolites may elucidate these mechanisms. We investigated serum metabolites correlated with UPF and un/minimally processed food (UNPF) intake and evaluated their association with selected biochemical markers.

Methods Cross-sectional study within the UK biobank, including a total of 72,817 participants with 24-hour recall dietary data and 134 nuclear magnetic resonance metabolites. UPF and UNPF intakes were evaluated using the NOVA classification, and related metabolites were identified using elastic net penalized regression. A UPF metabolomic signature was computed as a weighted sum of UPF-related metabolites, using elastic net coefficients as weights. Associations between UPF and UNPF-related metabolites, and serum C-reactive protein (CRP), insulin-like growth factor-1(IGF-1), sex hormone-binding globulin (SHBG), and testosterone were examined using multiple quantile regression.

Results Elastic net model identified 17 and 15 metabolites uniquely related to UPF and UNPF intake, respectively. Acetoacetate, acetone, high-density lipoprotein (HDL) diameter, docosahexaenoic acid, linoleic acid, ω-3 fatty acids (FA), total lipids in large HDL cholesterol, and valine levels were decreased, but free cholesterol in extremely small very low-density lipoproteins (LDL), glutamine, glycine, glycoprotein acetyls, lactate, saturated FA, sphingomyelins, triglycerides in large LDL, and triglycerides in medium HDL levels were increased with high UPF intake. Opposite relationships were observed for UNPF intake. Heterogeneous associations were observed between UPF-related metabolites and CRP, IGF-1, SHBG, and testosterone levels. A UPF metabolomic signature was positively associated with CRP (regression coefficient per standard deviation, 1.45, 95% confidence interval, 1.385, 1.515) and negatively associated with IGF-1 (-3.16, -4.493, -1.827) and SHBG (-13.878, -15.291, -12.465).

Conclusion A UPF metabolomic profile, including VLDL free cholesterol, saturated FA, triglycerides, glutamine, glycine, and glycoprotein acetyl was associated with inflammatory, insulin signalling, and reproductive biomarkers. This metabolomic profile should be explored as a potential mediators of UPF-disease associations, and as an objective marker of UPF intake.

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Keywords Ultra-processed food, Metabolites, C-reactive protein, Sex hormone-binding globulin, Insulin-like growth factor-1, UK Biobank

Introduction

Recently, the influence of industrial food processing on modern dietary patterns has gained tremendous recognition from public health authorities [1] beyond the traditional nutrient-based understanding of food [1–3]. Ultra-processing techniques are employed to formulate UPF. These are products with the highest level of food processing, formulated by recombining natural food extracts with industrial-grade sweeteners, emulsifiers, colors, and flavors [3].

These foods are extremely tasty, appealing, palatable, and shelf-stable products such as carbonated and sugared drinks, chocolate and energy bars, biscuits, confectionery, instant noodles, powdered or "fortified" meals, and reconstituted meat and substitutes, among others [3]. Therefore, UPF are becoming increasingly popular in modern consumer diets [4].

Ultra-processed foods are energy-dense, low in fiber and micronutrients, are prone to overconsumption, and tend to displace healthy dietary items from the diet [5]. Meta-analyses of epidemiological evidence suggest that the consumption of UPF may be linked to increased risks of obesity, cardiometabolic outcomes, mental, respiratory, and gastrointestinal health, cancer, and mortality [6]. Several studies have reported associations between UPF intake and intermediate disease markers, mostly focusing on inflammatory biomarkers and CVD-related proteins [7–10].

However, the biological mechanisms underlying these associations remain controversial. Available hypothesized mechanisms include the suboptimal nutrient profile of UPF, alteration of insulin signaling by UPF additives, promotion of gut microbiome dysbiosis, overeating, and increased exposure to neoformed compounds, such as furans, industrial trans-FA, and chemicals in packaging materials, including phthalates, bisphenols, mineral oils, and microplastics [11]. Most theorized mechanisms are extrapolations of the potential effects of nutrient and non-nutrient contents in the UPF and have been criticized for their lack of clarity, specificity, and consistency [12].

Metabolites may elucidate biological mechanisms that underly the relationship between UPF intake and health outcomes [13]. However, investigations into metabolomic correlates of UPF intake are sparse [14–16]. Only two studies have explored the utility of UPF-related biomarkers in predicting clinical endpoints, namely, obesity [16] and chronic kidney disease [14], and only one study examined the correlation between metabolites and varying degrees of food processing [15].

Biochemical markers including C-reactive protein (CRP), insulin-like growth factor-1 (IGF-1), sex hormone-binding globulin (SHBG), and testosterone represent pathways related to systemic inflammation, insulin bioavailability and signaling, hormonal function, and cancer development [17–19]. Experimental studies suggested that these pathways may explain adverse health effects associated with UPF consumption [11]. To provide preliminary mechanistic links in a human population, we identified serum metabolites related to the degree of food processing and examined the association of UPF intake-related metabolites with inflammatory, insulin signaling, and hormonal function biomarkers in UK biobank participants.

Materials and methods

Study design and participants

Participants were sourced from the UK Biobank, a large prospective cohort study conducted at 22 geographically and socioeconomically diverse recruitment sites in the UK. This open resource was established to investigate the determinants of disease in middle-aged and older adult participants. At least half a million participants aged 40–69 years were recruited at baseline between 2006 and 2010. The details of this study have been described previously [20].

In this analysis, 210,948 of 502,357 participants completed at least one dietary assessment questionnaire at baseline, first, second, third, or fourth repeat assessments between 2009–2010, 2011, and 2012, respectively. Participants who were only involved in the first, second, and third cycles were excluded because they lacked corresponding metabolomic data assessed in the same period ($n = 60{,}421$). Out of 150,527 remaining participants, 73,373 were excluded because they lacked metabolite measurements at baseline (2006–2010) and repeat assessments in 2012, leaving 77,149 participants with baseline or follow-up diet and metabolomic data. Participants with extreme metabolite values, defined as outside four interquartile ranges from the median, were further excluded, resulting in a final analytical sample of 72,817 participants (Fig. 1).

The UK Biobank Cohort Study was approved by the Northwest Multi-Centre Research Ethics Committee (21/NW/0157). All the participants provided written informed consent before participating in the study. The current study was approved by the Institutional Review Board of Kangwon National University (KWNU-IRB-2023-03-003), and data access was approved under Research ID 102,492.

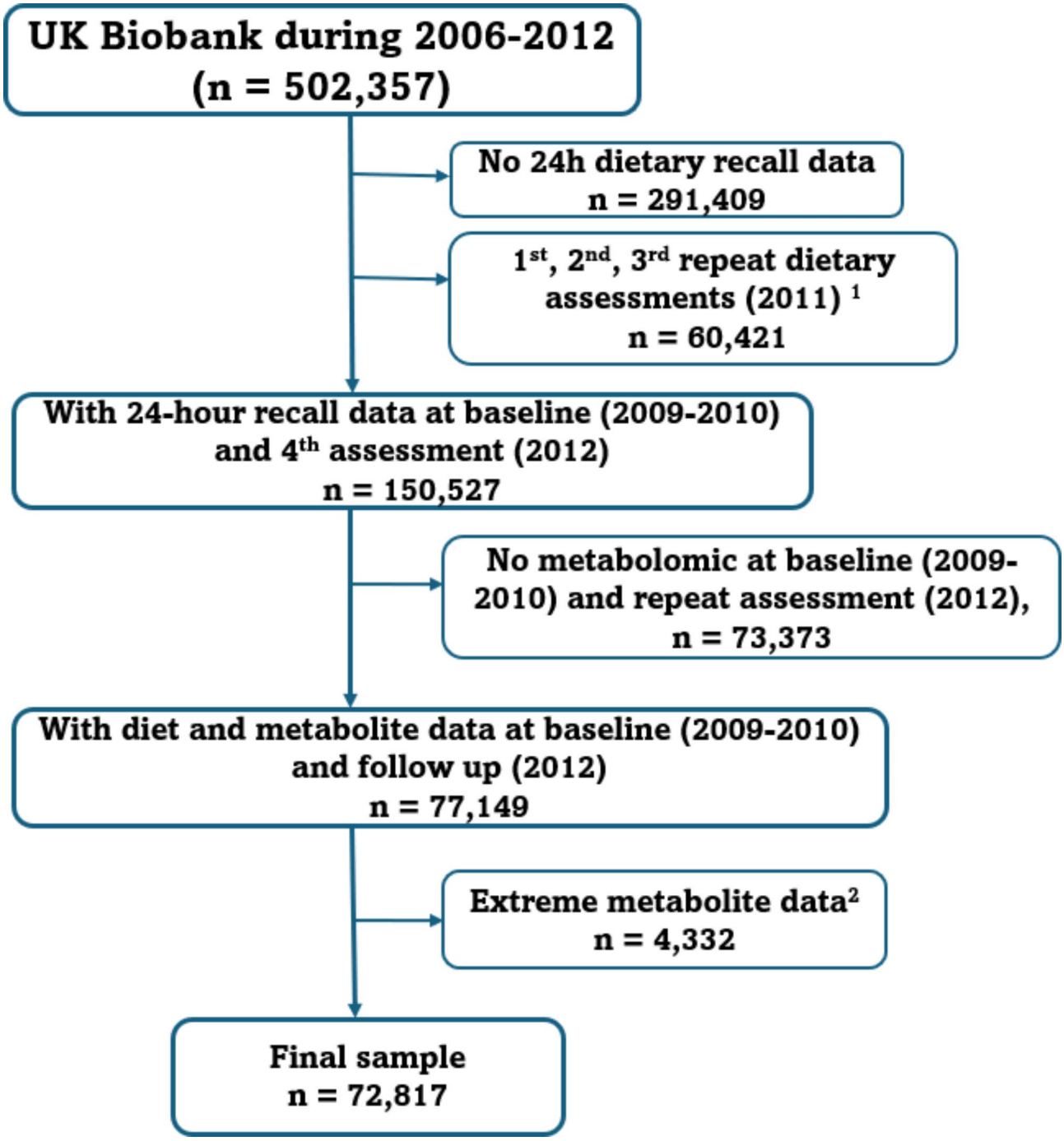

Fig. 1 Selection of study participants. [1] Excluded because metabolites were not measured in 2011, [2] Metabolite values beyond 4 interquartile ranges from the median value

Evaluation of dietary intake and classification of food processing

The Oxford Web-based 24-hour Dietary Questionnaire (WebQ) was used to assess the intake of 238 food and beverage items. Baseline assessments were conducted at the recruitment sites between April 2009 and September 2010 via a participant-administered touch screen questionnaire administered by participants, and repeat assessments were conducted over four cycles. During repeat assessments, participants were sent email invitations to complete online questionnaires between February and April 2011 (cycle 1), June to September 2011 (cycle 2), October to December 2011 (cycle 3), and April to June 2012 (cycle 4) [21]. Participants selected the foods consumed in the previous 24 h and were prompted to select the portion sizes consumed. Energy and nutrient

intake were estimated by linking portion sizes to the UK Nutrient database [22]. The performance of the online WebQ has been shown to be comparable to that of the interviewer administered WebQ [23], and both questionnaires have been validated using biomarkers [24].

Using the NOVA system, we categorized each food item on the WebQ based on the degree of processing [5]. The NOVA system classifies foods as unprocessed or minimally processed (UNPF), culinary ingredients, processed foods, or UPF. The consumed weight of each food item was calculated by multiplying the reported portion sizes by the standard weights published by Perez-Cornago et al. [22]. These weights were summed to determine total UPF and UNPF consumption (g/d). The intake of each NOVA group was expressed as a proportion of the total dietary intake (% of food weight) to account for non-nutrient components. The classification of food items by the NOVA system is shown in Supplemental Table 1.

Assessment of biochemical markers

Trained UK Biobank phlebotomists collected about 45 mL of blood into sample collection tubes (ethylenediaminetetraacetic acid, plasma or serum separator tubes) during recruitment (2006–2010). Participants were not required to fast since the UK biobank intended to collect samples that are applicable to various conditions [25]. Collected blood samples were transported to the UK Biobank central processing and archiving facility in Stockport at 4 °C. Samples were automatically aliquoted to create subsamples which were stored at -80 °C or in liquid Nitrogen at separate archive sites. For processing, small aliquots of 1.4 mL were automatically created and assayed in chronological order of collection within two days. Circulating IGF-1 was quantified using immunoassays with immune analysers (DiaSorin Liaison XL [Diasorin S.p.A]. Sex hormones and CRP were quantified by chemiluminescent assays using Beckman Coulter DXI 800 (Beckman Coulter UK, Ltd) and immunoturbimetric methods using Beckman Coulter AU 5800 (Beckman Coulter UK, Ltd) respectively [26].

Metabolomic profiling

A large-scale, targeted serum nuclear magnetic resonance spectroscopy-based metabolomics platform developed by Nightingale Health Plc. was used to quantify circulating metabolites. This platform enables the simultaneous and granular quantification of lipoprotein subclasses, circulating fatty acids (FA), amino acids, triglycerides, creatinine, glycolysis-related metabolites, and ketone bodies [27]. The detailed assessment methods have been described elsewhere [27, 28] and are briefly illustrated in the Supplementary Methods. Of the 249 assayed metabolites, we focused on 134 metabolites, excluding ratios (81) and sums (34).

Assessment of covariate information

Sociodemographic characteristics, lifestyle, and family history of disease were assessed at baseline using a self-administered touchscreen questionnaire. Pre-existing medical conditions and intake of medications were assessed using a verbal interview by a UK biobank nurse [20]. Physical activity was assessed using a validated short version of the International Physical Activity Questionnaire and expressed as MET-minutes/week [29]. Physical measurements were performed by trained staff at the UK Biobank. After removing shoes and heavy clothing, weight was measured to the nearest 0.1 kg using a body composition analyzer (Tanita BC-418MA), and height was measured using a height scale (Seca 202). Body mass index (BMI) was calculated as the ratio of weight (kg) to height (m^2) [29].

Categorical covariates were defined as follows: sex (men, women), ethnicity (White, African/Caribbean, Asian/Chinese, Mixed/others), index of multiple deprivation (quintiles), employment (whether actively employed or not), highest educational level attained (none, vocational training, ordinary [O'] level/middle school, advanced [A'] level/high school, and college and above), and annual income (0–18000, 18000–30,999, 31,000–51,999, 52,000–100,000, and 100,000 £).

Lifestyle factors were defined as follows: alcohol consumption, smoking (never, current, or past), and sleep duration (hours/day). Pre-existing diabetes, cancer, and cardiovascular disease (CVD) were defined as yes/no based on self-reported diagnostic reports verified by UK biobank nurses, and documented use of medication for the reported conditions.

Statistical analysis

Continuous variables were summarised as mean (standard deviation [SD]) or median (interquartile range [IQR]), and categorical variables were described using frequencies (percentages), both overall and by tertiles of UPF and UNPF intake. Missing data were imputed using multiple imputations with chained equations. Metabolite, UPF, and UNPF data were log-transformed and SD-scaled. We used Pearson's correlation to examine the correlations among metabolites and between metabolites, UPF, and UNPF intakes.

To identify metabolites related to UPF and UNPF intake while handling multicollinearity between metabolites, elastic net-penalized linear regression models were fit to separately predict the intake of UPF and UNPF from 134 metabolites [30]. We trained elastic net models on all available data using 10-fold cross-validation repeated 20 times to obtain the best regularization parameters. The

computed regularization parameters were applied to penalize the regression coefficients and select the important metabolite features that correlated with the intake of each NOVA food group. Metabolites were penalized; however, age, sex, total energy intake, ethnicity, index of multiple deprivation, education level, income, physical activity, sleep duration, BMI, pre-existing diabetes, CVD, cancer, and medication intake were unpenalized. We chose these covariates following previous studies [10, 14, 31].

To evaluate the collective effect of UPF-related metabolites on selected biochemical markers, we computed a UPF metabolite score (metabolomic signature) as the sum of the products of the coefficients obtained from the elastic net regression and the raw metabolite values [31].

UPF-metabolomic signature = $\sum_{1}^{n} (selected\ metabolite\ x\ \beta\ )$;

where β is the regression coefficient from the elastic net model, and n is the maximum number of metabolites selected by the model.

To assess the utility of the identified metabolites, we divided participants into high versus low UPF intake groups and determined whether the selected metabolites could effectively distinguish between high and low UPF consumers, independent of total energy intake. Initially, a baseline model incorporating covariates and total energy intake was built. Then, a second model that included UPF-related metabolites was developed. The adequacy index (AI) was calculated as the ratio of the log-likelihood for the baseline model to that of the model with metabolites. The additional predictive value provided by metabolites was quantified as (1-AI) × 100 [32].

We then used multivariate-adjusted quantile regression models to examine the association of UPF and UNPF with biochemical disease markers, adjusting for the covariates described above. We also tested the association between UPF intake-related metabolites and biochemical markers using multivariate-adjusted quantile regression models. To evaluate the collective effects of UPF-related metabolites on disease biomarkers, the median values of the biochemical markers, per 1-SD of the UPF metabolomic signature, were determined using multivariate quantile regression.

Data analysis was conducted using the R software version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as $P < 0.05$.

Table 1 General characteristics of study participants

Characteristic	*n* = 72,817
Demographic	
Age, years, mean (SD)	56.0 (8.0)
Sex, women, %	39,814 (55.0)
Highest education level, College and above, %	34,514 (47.0)
Annual income, £, %	
< 18,000	12,662 (17.0)
Actively employed, %	43,822 (60.0)
Index of multiple deprivation, median (IQR)	-2.35 (-3.74, -0.01)
Ethnicity, White, %	70,276 (97.0)
Lifestyle	
Alcohol intake, g/d, median (IQR)	0.0 (0.0, 26.0)
Current drinker	68,137 (93.6)
Current smoker	5,397 (7.4)
MET-min/week, median (IQR)	1,770 (836, 3,393)
Moderate exercise, %	60,034 (82.0)
Sleep duration, h/d, median (IQR)	7.00 (7.00, 8.00)
Sleep hours, 6–8, %	
BMI, kg/m^2, mean (SD)	26.9 (4.6)
Total energy intake, Kcal/d, mean (SD)	2,073 (683)
UPF, Median (IQR)	24.0 (16.0, 35.0)
UNPF, Median (IQR)	58.0 (45.0, 68.0)
Plausible energy reporting, %	70,269 (96.5)
Medical	
CVD, %	1,544 (2.1)
Cancer, %	6,341 (8.7)
Diabetes, %	2,566 (3.5)
Use of medication, %	61,972 (85.0)

IQR, interquartile range, SD, standard deviation, CVD, cardiovascular disease, UPF, ultra-processed foods, UNPF, unprocessed/minimally processed foods

Results

Characteristics of study participants

Table 1 presents the participants' general characteristics. The mean (SD) age of participants was 56 (8.0) years, the mean (SD) BMI was 26.9, and the majority were women, white by ethnicity, had completed college, earned £31,000–51,999, and were actively employed. In terms of lifestyle factors, a significant proportion of participants were current drinkers, never smoked, engaged in moderate physical activity, and slept for 6–8 h a day. The mean (SD) total energy intake was 2,073 (683) kcal/day, and the median (IQR) proportions of UPF, UNPF, and PF in the total diet were 24 (16–35), 58 (45–68), and 4 (1–10) %, respectively. Among the participants, 2.1, 8.7, and 8.5% reported a medical diagnosis of CVD, cancer, and diabetes, respectively, and more than three-quarters reported using medication.

The correlation matrix of the metabolites is displayed in Supplementary Fig. 1. Distinct correlated metabolic groups were observed, and notable correlations between the metabolites and the degree of food processing are detailed in Supplementary Fig. 2.

Participants' characteristics according to UPF and UNPF intake

The characteristics of participants according to UPF intake are shown in Supplementary Table 2 A-C. The highest consumption of UPF was more prevalent among men, less educated, lowest income earners, Black

participants, never drinkers and current smokers. In addition, highest UPF consumers exhibited lower physical activity levels, higher BMI, more total energy intake, and a higher prevalence of CVD, diabetes, and use of medication, but lower prevalence of cancer compared to lowest consumers. Reverse trends in participants' characteristics were observed according to UNPF intake.

Metabolites related to UPF and UNPF intake

The elastic net-selected metabolites related to UPF and UNPF intake are shown in Fig. 2 and Supplemental Table 3. Ketone bodies (acetoacetate, acetone), high density lipoprotein (HDL) diameter, polyunsaturated fatty acids (PUFA) [docosahexaenoic acid, linoleic acid, w-3 FA], total lipids in large HDL, and valine were negatively correlated with UPF intake, whereas free cholesterol in extremely small very low density lipoprotein (VLDL), amino acids (glutamine, glycine), glycoprotein acetyls, lactate, saturated FA, and lipids (sphingomyelins, triglycerides in large low density lipoprotein (LDL) and medium HDL) were positively correlated with UPF intake. Opposite relationships were observed between UNPF and these metabolites, except for acetoacetate, albumin, and sphingomyelin. Serum metabolites correlated with UPF intake were largely reproduced when we restricted the sample to participants who only participated in baseline diet and metabolomic assessments (Supplementary Table 4).

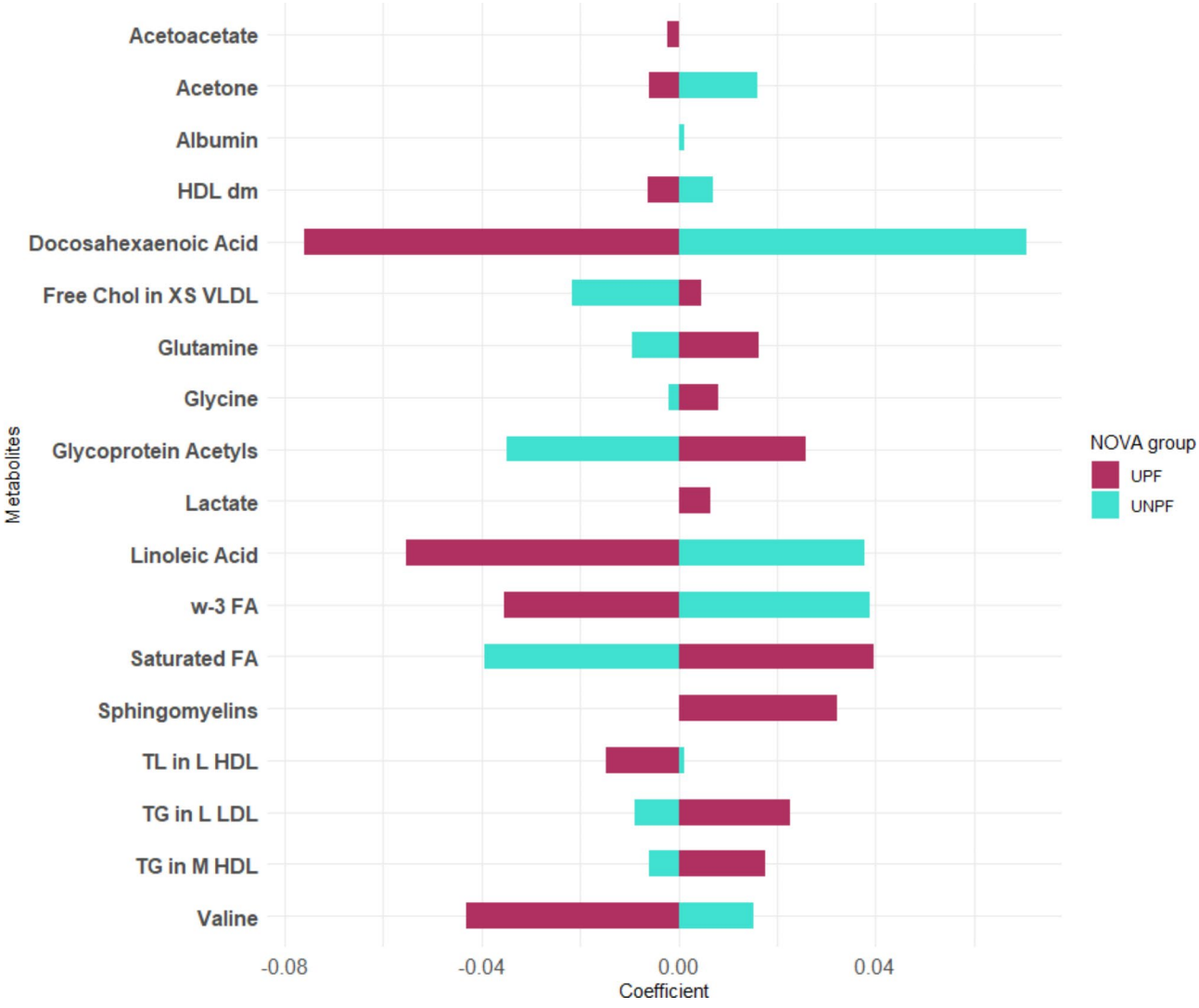

Fig. 2 Metabolites correlated with UPF and UNPF intake. Coefficients were computed using elastic net regularization, with UPF or UNPF as dependent variables and metabolites as predictors (penalized), while allowing age, sex, total energy intake, ethnicity, index of multiple deprivation, education level, income, physical activity, sleep duration, BMI, pre-existing diabetes, CVD, cancer and intake of medication. Dm, diameter; FA, fatty acid; L, large; M, medium; TL, total lipids; XS extremely small

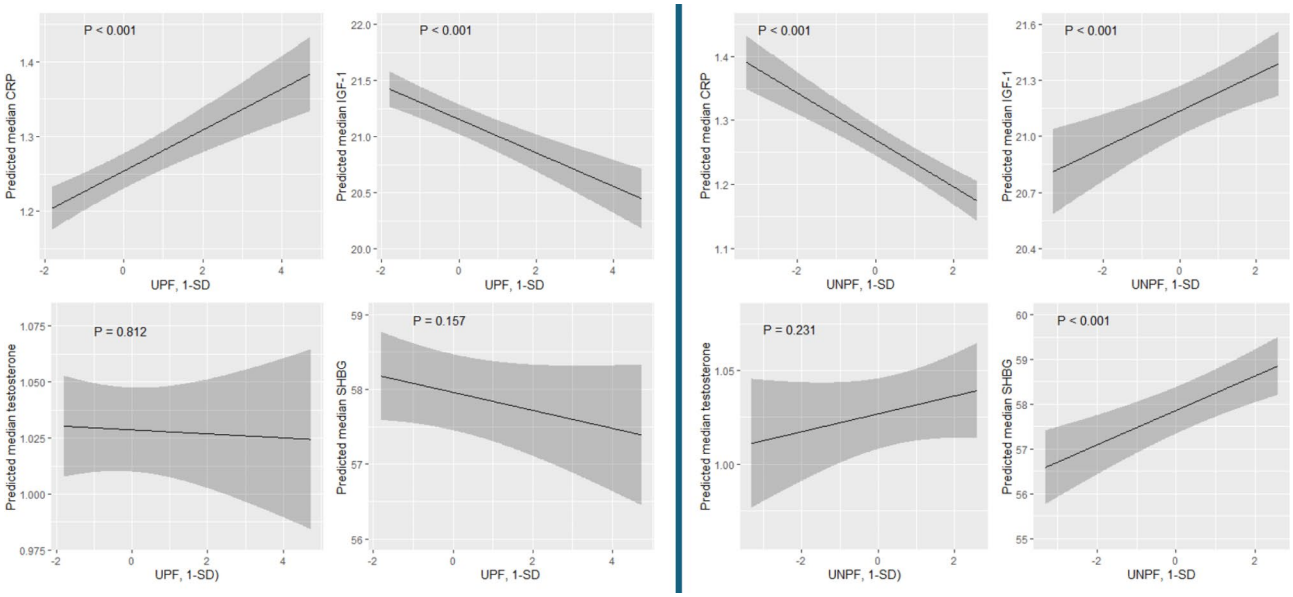

Fig. 3 Predicted median values of selected disease biochemical markers per 1-SD increase in UPF/UNPF intake. Predicted values were computed via quantile regression adjusted for age, sex, total energy intake, ethnicity, index of multiple deprivation, education level, income, physical activity, sleep duration, BMI, pre-existing diabetes, CVD, cancer, and intake of medication. IGF-1, insulin-like growth factor-1; UPF, ultra-processed food; CRP, c-reactive protein; SHBG, sex-hormone binding globulin; SD, standard deviation

Table 2 Association of UPF and UPF-metabolomic signature with selected disease biochemical markers

	UPF intake		Metabolomic signature	
	β (per 1-SD)	95% CI	β (per 1-SD)	95% CI
CRP	0.060	0.047, 0.073	1.4557	1.385, 1.515
IGF-1	-0.0464	-0.060, -0.033	-3.1669	-4.493, -1.827
SHBG	-0.0041	-0.018, 0.009	-13.8784	-15.291, -12.465
Testosterone	0.0028	-0.011, 0.016	-0.0566	-0.1252, 0.0120

Regression coefficients were adjusted for age, sex, total energy intake, ethnicity, index of multiple deprivation, education level, income, physical activity, sleep duration, BMI, pre-existing diabetes, CVD, cancer, and intake of medication. CRP, c-reactive protein; IGF-1, insulin-like growth factor-1; SHBG, sex-hormone binding globulin

Association of UPF and UNPF intake with CRP, IGF-1, SHBG, and testosterone

Ultra-processed food intake was positively associated with CRP but negatively associated with IGF-1 levels. In contrast, UNPF intake was negatively associated with CRP and positively associated with IGF-1 and SHBG levels (Fig. 3; Table 2).

Association between UPF -related metabolites with CRP, IGF-1, SHBG, and testosterone

The median values of biochemical markers per 1-SD increase in UPF-related metabolites are depicted in Fig. 4 and Supplementary Table 5.

Amino acids

Elevated CRP negatively correlated with glutamine, glycine, and valine. In addition, valine negatively correlated with IGF-1 and SHBG but positively correlated with testosterone levels. On the other hand, glutamine and glycine were both inversely associated with testosterone levels, while glutamine was positively associated with SHBG levels.

Cholesterol

Elevated levels of CRP and IGF-1 correlated with large, but SHBG correlated with small HDL particles. However, free cholesterol in extremely small VLDL was elevated in participants with high levels of biochemical markers, with exception of IGF-1 which showed lower levels.

Fatty acids

Low levels of biochemical markers were reported in individuals with high saturated fatty acid levels. A similar trend was observed for w-3 FA, with exception of testosterone which was positively associated with high w-3 FA levels. On the other hand, linoleic and docosahexaenoic acid levels were positively correlated with IGF-1, SHBG, and testosterone levels. In terms of CRP, higher levels

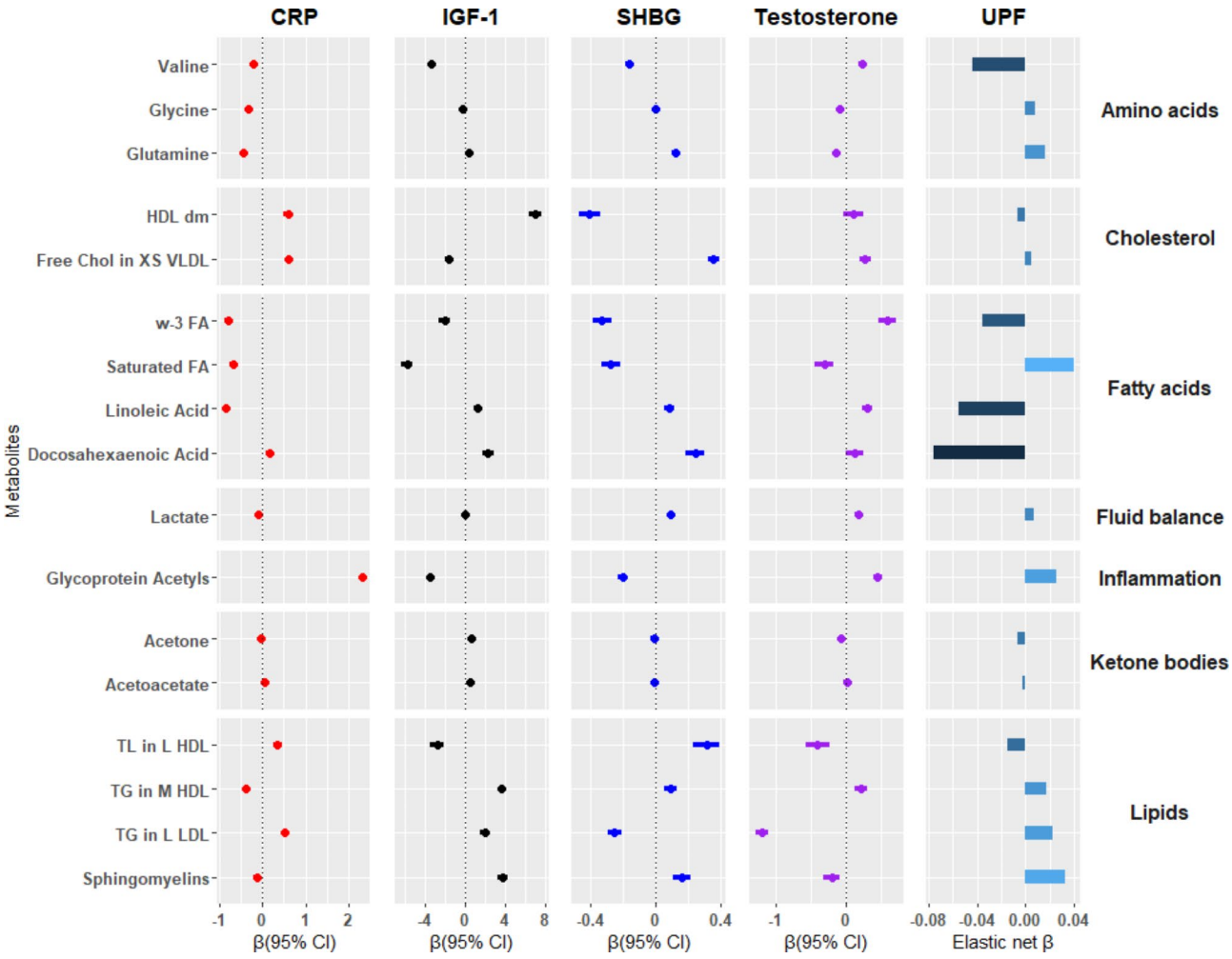

Fig. 4 Regression coefficients and 95% CI for the association of UPF-related metabolites and biochemical markers. Adjustments were made for age, sex, total energy intake, ethnicity, index of multiple deprivation, education level, income, physical activity, sleep duration, body mass index, pre-existing diabetes, cardiovascular disease, cancer, and medication intake. Abbreviations: Dm, diameter; FA, fatty acid; L, large; M, medium; TL, total lipids; XS, extremely small

were reported with high docosahexaenoic acid and low linoleic acid levels.

Fluid balance and inflammation

We found a positive correlation between lactate and SHBG and testosterone. Glycoprotein acetyl was positively correlated with CRP and testosterone, but inversely correlated with IGF-1 and SHBG.

Ketone bodies

Acetoacetate was positively associated with high levels of CRP and SHBG, while acetone was positively associated with SHBG and inversely associated with CRP and IGF-1 levels.

Other lipids

Triglycerides in large LDL positively correlated while CRP and IGF-1 but inversely correlated with SHBG and testosterone. However, TG in medium HDL inversely correlated with CRP and positively correlated with other markers. Furthermore, Total lipids in large HDL were positively associated with high levels of CRP and SHBG but lower levels of IGF-1 and testosterone. Sphingomyelins positively correlated with IGF-1 and SHBG, but inversely correlated with CRP and testosterone.

Association of the UPF-metabolomic signature with CRP, IGF-1, SHBG, and testosterone

The metabolomic signature of UPF strongly predicted CRP, IGF-1, SHBG, and testosterone levels compared with UPF intake alone (Fig. 5; Table 2).

The percentage of predictive information contributed by metabolites to the prediction of UPF intake is shown in Table 3. UPF-related metabolites accounted for 13% of the variation in UPF intake beyond total energy intake.

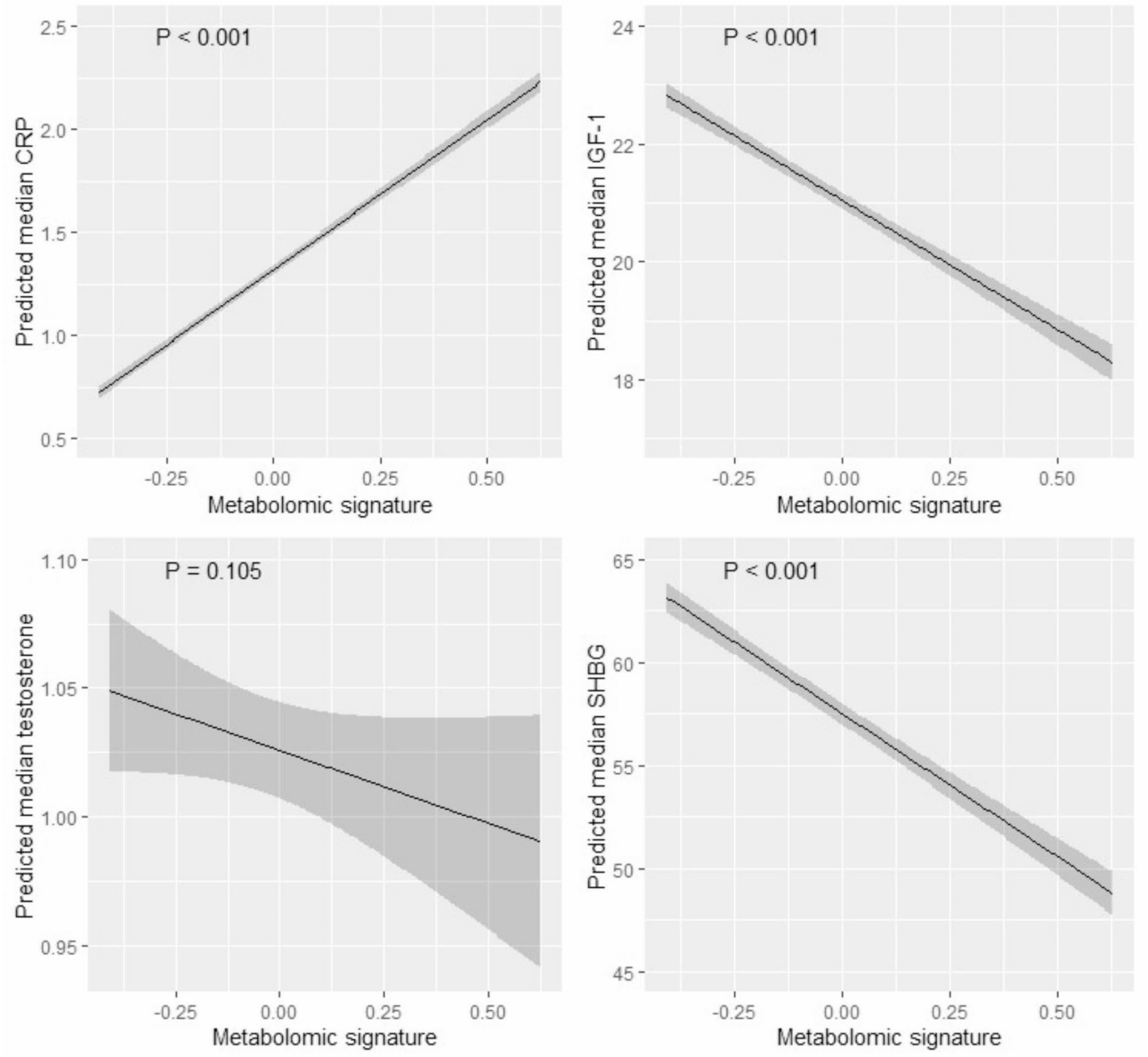

Fig. 5 Predicted median values of selected disease biochemical markers. Values are calculated per 1-SD increase in UPF-metabolomic signature, adjusted for age, sex, total energy intake, ethnicity, index of multiple deprivation, education level, income, physical activity, sleep duration, BMI, pre-existing diabetes, CVD, cancer and intake of medication. CRP, c-reactive protein; IGF-1, insulin-like growth factor-1; SHBG, sex-hormone binding globulin

Table 3 Prediction of UPF intake by metabolomic signature vs. energy intake

	Base model	Plus metabolites	% New information
LR χ^2	6079.63	6876.89	13%
C-statistic	0.662	0.673	
Brier	0.230	0.227	
Adequacy	0.870		

LR X^2, Log-likelihood ratio chi-square

Discussion

Summary of findings

Ketone bodies, PUFA, HDL diameter, total lipids in large HDL, and valine decreased with high UPF intake, while free cholesterol in extremely small VLDL, glutamine, glycine, glycoprotein acetyls, lactate, saturated FA, sphingomyelins, and triglycerides ($n = 2$) increased. These metabolites enhanced the prediction of UPF intake beyond total energy intake. UPF-related metabolites correlated with CRP, IGF-1, SHBG, and testosterone, with the UPF metabolomic signature more strongly associated

with CRP and inversely with IGF-1 and SHBG than UPF intake alone.

Interpretation

Fatty acid metabolites correlated with UPF intake

Few studies incorporated the degree of food processing during identification of diet-related metabolites, with some reporting findings that are generally consistent with ours [16]. Unsaturated FA (Docosahexaenoic acid, w-3, linoleic acid) were inversely correlated with high UPF intake [14, 33]. Dietary sources of unsaturated fatty acids include fatty fish, seafood, nuts, and seeds [34, 35], which do not typically constitute UPF. In contrast, saturated FA were associated with high UPF intake, consistent with a high saturated FA composition of UPF [36–38].

Cholesterol and other lipids correlated with UPF intake

We found altered lipoprotein profiles with increased UPF consumption, which is supported by previous reports that UPF intake is associated with elevated triglycerides [39, 40] and LDL cholesterol [41], low HDL cholesterol [39–41], and incident dyslipidemia [42]. With respect to lipoprotein subclasses, an UPF diet was inversely associated with HDL particle size [43]. Simple sugars, refined starches, and added sugars in UPF have been shown to increase small, dense LDL levels [67] and triglyceride concentrations [44, 45] via enhanced lipogenesis [46]. Moreover, phthalates in UPF packaging materials are associated with dyslipidemia [47]. The increase in circulating sphingomyelins with high UPF intake is likely linked to dietary sources of these metabolites such as processed milk, cream, butter, and cheese [48]. Additionally, high saturated FA in UPF can activate genes involved in synthesis of ceramides, which are precursors to sphingomyelin biosynthesis [49].

Ketone bodies and amino acids correlated with UPF intake

Ketone bodies (acetoacetate, acetone) were negatively correlated with UPF consumption. Low circulating ketone bodies result from ample digestible carbohydrates (e.g., sugars, starches) and high systemic insulin levels linked to high-UPF diets [38, 50]. On the other hand, amino acids (high glutamic acid and low valine levels) were related to high UPF intake [15]. Glutamine is derived from glutamate [51] in monosodium glutamate rich UPF [52]. Low valine levels with UPF consumption suggest a deficiency of this essential amino acid in UPF diets.

Inflammatory metabolites correlated with UPF intake

High levels of the proinflammatory glycoprotein acetyl [53] with high UPF intake agrees with low levels of this marker among individuals with high intake of high-quality diets [35, 54]. Moreover, a positive association of proinflammatory cytokines and high UPF intake has been previously reported [10]. Emulsifiers in UPF (carboxymethylcellulose and polysorbate-80), may induce inflammation via microbiota dysregulation [54–57], and typical UPF packaging materials contain bisphenol A [58], an endocrine-disrupting chemical associated with inflammation and oxidative stress [59].

Association of UPF and UPF-related metabolites with CRP, IGF-1, SHBG, and testosterone

High intake of UPF was positively correlated with CRP and inversely correlated with IGF-1. In line with our findings, high UPF was positively correlated with several biomarkers of inflammation [10]. Moreover, a randomized controlled trial (RCT) showed that high UPF intake caused high levels of CRP, excessive energy, carbohydrate and fat intake, and excessive energy intake which are indicative of inflammation [60]. Increased free fatty acids due to high UPF intake was also reported in a RCT [60]. High circulating free fatty acids and other lipids associated with UPF intake may suppress growth hormone-induced synthesis of IGF-1 [61]. On the other hand, UPF-related metabolites were associated with biochemical markers of inflammation, growth, and reproductive function, suggesting that UPF may moderate specific upstream metabolites, resulting in regulation of downstream pathways involving inflammation, insulin-signaling, steroids, and hormonal regulation.

Association of ketone bodies and amino acids with biochemical markers

Acetoacetate was positively associated with high levels of CRP and IGF-1, while acetone was positively associated with IGF-1 and inversely associated with CRP and testosterone levels. Ketone bodies moderate short-term oxidative and inflammatory reactions [62], but also mitigate inflammation by dampening NFkB and inflammasome activity [50]. Glycine and glutamine contribute to reduction of inflammation [63, 64]. However, branched-chain amino acids such as valine are linked to cardiometabolic diseases, indicating proinflammatory effects [65, 66].

Lipid metabolites associated with biochemical markers

Polyunsaturated FA were generally inversely correlated with the inflammatory marker CRP [53], and positively associated with IGF-1, and reproductive biomarkers. Polyunsaturated FA are associated with lower levels of inflammation via regulation of cytokine production [67–69]. However, elevated CRP alongside high docosahexaenoic acid levels was unexpected, considering its anti-inflammatory effects. This observation might be explained by DHA supplementation in individuals with inflammatory diseases.

Associations of PUFAs with IGF-1 may be linked to their genetic regulation of IGF-1 biosynthesis [18]. Positive associations of fatty acids with reproductive biomarkers may be due to activation of biosynthesis of the fatty acids by sex hormones [70], and may reflect a favourable lipid profile associated with SHBG as previously reported [71]. The association of low saturated FA with high CRP may be explained by decreased consumption of these FA in chronic disease states, given the popular connection between saturated fats and CVD risk.

Lipoprotein components (cholesterol in extremely small VLDL and triglycerides in large LDL) positively correlated while CRP. Altered lipid profiles typically accompany inflammation [72]. In terms of IGF-1, lipoprotein components (HDL diameter, TG in medium HDL and large LDL, and sphingomyelins) positively correlated with IGF-1. In contrast, cholesterol in extremely small VLDL, and total lipids in large HDL were associated with low IGF-1 levels. Lipids influence IGF-1 via moderation of hepatic synthesis [73].

Insulin-like growth factor-1 is synthesized in the liver, adipose tissue, and skeletal muscles through growth hormone (GH) stimulation, promoting somatic growth, cell proliferation, and protein synthesis [74]. Our results suggest that UPF-related metabolites are involved in the regulation of GH activity. Increased levels of circulating lipid species and acetoacetate with an increase in IGF-1 may reflect GH-induced lipolysis, lipid oxidation, and regulation of lipoprotein metabolism [61].

With respect to SHBG, our results are consistent with a previous cross-sectional study that showed strong positive associations of SHBG with various lipid metabolites, especially those beneficial to cardiometabolic health [71]. SHBG is a sex hormone-specific binding glycoprotein responsible for transporting sex steroids and consequently regulating circulating free testosterone and estrogen. Low SHBG has been linked to insulin resistance and type 2 diabetes [71], and cardiovascular outcomes through moderation of lipid metabolites [75]. Considering the opposite association of the same lipid metabolites with circulating testosterone, our findings suggest that sex hormone availability may be a link through which UPF intake may be associated with cardiometabolic disease risk.

Association glycoprotein acetyl with biochemical markers

Glycoprotein acetyl positively correlated with CRP and testosterone, but inversely with IGF-1 and SHBG levels. Glycoprotein acetyl is a biomarker of inflammation [53]. Moreover, the association between several inflammatory biomarkers and IGF-1 has been previously reported [19]. IGF-1 has been shown to moderate macrophage function and inflammatory activity [76]. On the other hand, SHBG has been shown to exhibit anti-inflammatory properties [71].

To our knowledge, we are the first to broadly examine the metabolomic profile of UPF intake in relation to biomarkers of inflammation, insulin signaling, and reproductive function. Our results suggest that high UPF consumption may alter specific metabolic pathways, such as a reduction in PUFA, anti-inflammatory amino acids, and beneficial lipoprotein composition; and an increase in inflammatory proteins and triglycerides. The alteration of systemic metabolites may be linked to low-grade inflammation, dysregulation of insulin signaling, and sex hormone bioavailability, suggesting potential biological mechanisms by which UPF consumption promote adverse health outcomes. These findings emphasize detrimental effects of UPF consumption on metabolic health and suggest that limiting UPF consumption and promoting UNPF intake may improve metabolic health in the general population.

Strengths and limitations

In this large cross-sectional analysis, we explored the metabolome across different levels of food processing. Utilizing a comprehensive metabolomics database, we explored metabolomic profiles at different levels of food processing, revealing no overlap between metabolites related to UPF and UNPF, suggesting specificity of identified metabolites, and potential utility of identified metabolites as biomarkers of UPF consumption. Metabolites potentially circumvented biases and dietary measurement errors inherent in self-reported diet, and misclassification bias associated with the NOVA system [77]. Elastic net regression improved model predictability, effectively handled multicollinearity, and facilitated joint modeling of metabolites without correction for multiple tesing [78]. Investigating associations with downstream biochemical biomarkers of cardiometabolic diseases provided insights into mechanisms underlying the links between UPF consumption and disease. We emphasized the role of metabolites in enhancing the diet-disease relationship beyond questionnaire-reported intake.

However, this study had limitations. The major limitation was the use of metabolites measured by a targeted metabolomics approach, suggesting that some UPF-related metabolites could not be identified, making comparisons with previous studies challenging. The NMR platform used in the UK biobank primarily captured large molecular, and high-concentration metabolites [79–81], which limited the variety of identified UPF-related metabolites. Furthermore, dynamic relationships between UPF consumption and metabolites could not be evaluated in a cross-sectional study, but previous studies support the stability of diet-metabolite relationships over time. Unmeasured confounding factors deserve mention

since they are characteristic of nutritional epidemiological studies. Furthermore, we could not evaluate diverse sex hormones, such as estradiol, which were measured in a limited number of women. Finally, the cross-sectional design of our study precluded causal conclusions.

Conclusions

Using the UK Biobank, we showed that metabolites spanning multiple pathways were specifically correlated with UPF intake, indicating their potential use as objective markers of UPF intake. These metabolites were related to selected biomarkers of systemic inflammation, cell proliferation, insulin signaling, and sex hormone regulation, suggesting that UPF may be linked to disease pathophysiology by moderating inflammation, insulin signaling, cell proliferation, and the regulation of sex hormone bioavailability and function.

Abbreviations

UPF	Ultra-processed foods
UNPF	Unprocessed/minimally processed foods
CRP	C-reactive protein
IGF-1	Insulin-like growth factor
SHBG	Sex hormone binding globulin
SE	Standard error
CVD	Cardiovascular disease
WebQ	Web-based questionnaire
MET	Metabolic equivalent of task
BMI	Body mass index
SD	Standard error
IQR	Interquartile range
HDL	High density lipoprotein
VLDL	Very low-density lipoprotein
LDL	Low density lipoprotein
TG	Triglycerides
TNF	Tumour necrosis factor
IL	Interleukin
GH	Growth hormone

Supplementary Information

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Supplementary Material 1

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Author contributions

AK designed the study, acquired data, conducted statistical analyses, interpreted the results, and wrote the original manuscript. BC, JL and CK contributed to the interpretation of results and manuscript editing. SA-L participated in the study design, data curation, and was responsible for administering the project. SA-L and C.K acquired funding. All authors read and approved the final manuscript.

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Data availability

Data may be obtained from a third party and are not publicly available. The analysed data are publicly available after submitting an application via the UK biobank application portal at https://www.ukbiobank.ac.uk/.

Declarations

Ethics approval and consent to participate

The UK Biobank Cohort Study was approved by the Northwest Multi-Centre Research Ethics Committee (21/NW/0157). All the participants provided written informed consent before participating in the study. The current study was approved by the Institutional Review Board of Kangwon National University (KWNUIRB-2023-03-003), and data access was approved under Research ID 102492.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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