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Association between a low–carbohydrate diet and macronutrient intake with the gut microbiome, and their interaction with dyslipidemia among Korean adults

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Abstract

Background The prevalence of dyslipidemia has increased in recent years; however, it remains a modifiable condition through diet and gut microbiome modulation. Yet, evidence from population-based studies remains limited. This study aimed to investigate the relationships among a low-carbohydrate diet (LCD), macronutrient intake, and the gut microbiome, and to evaluate their interaction effects on dyslipidemia in a Korean population.

Methods Data were drawn from two population-based studies: the Korean Microbiome Study (KMS) and the Korea National Health and Nutrition Examination Survey (KNHANES). We included 2,178 participants aged 20–80 years from the KMS (2017–2019) and 12,938 participants from the KNHANES (2017–2019). The LCD score and percentage of energy intake from macronutrients were calculated using either a food frequency questionnaire or a 24-hour dietary recall. Dyslipidemia was assessed based on fasting blood tests. Gut microbiota was profiled by sequencing the V3-V4 region of the 16S rRNA gene in the KMS. Multivariate logistic regression models including interaction terms were used to evaluate the joint effects of diet and the gut microbiome on dyslipidemia.

Results A higher LCD score was associated with lower odds of atherogenic dyslipidemia and low high–density lipoprotein (HDL) cholesterolemia in both studies. Although both studies showed a positive trend for fat intake and a negative trend for carbohydrate intake in relation to hypercholesterolemia, the level of significance differed slightly. We identified 38 microbial genera associated with LCD score and macronutrient intake. Notably, fat intake showed beneficial associations with triglyceride and HDL cholesterol levels in individuals carrying *Bifidobacterium* (p for interaction = 0.0017) and *Lachnospiraceae UCG–004* (p for interaction = 0.0482), respectively. In contrast, low carbohydrate intake was associated with increased odds of hypercholesterolemia in individuals harboring *Lachnoclostridium* (odds ratio: 3.79; 95% confidence interval: 2.01–7.17; p for interaction < 0.0001). No significant associations were observed in individuals lacking these genera. Similar interaction effects were observed at the amplicon sequence variant level for *Bifidobacterium* and *Lachnospiraceae UCG–004*.

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Conclusions These findings provide population-based evidence for the interactive role of fat and carbohydrate intake with gut microbiota in influencing dyslipidemia among Koreans.

Keywords Low–carbohydrate diet, Fat intake, Carbohydrate intake, Hypertriglyceridemia, Low HDL cholesterolemia, Hypercholesterolemia, Gut Microbiome

Introduction

Dyslipidemia is a prevalent cardiometabolic disorder characterized by elevated lipid levels, including cholesterol and triglyceride (TG) levels, which carries the highest attributable risk of cardiovascular disease (CVD) mortality [1, 2]. According to the World Health Organization's estimates in 2008, hypercholesterolemia has a global prevalence of 39% for adults worldwide and is responsible for around 2.6 million deaths annually, representing about 4.5% of worldwide mortality [3]. Furthermore, the number of global deaths attributed to elevated levels of low–density lipoprotein cholesterol (LDL–C) was 3.7 million in 2021 [4]. In Korea, the prevalence of hypercholesterolemia has increased from 14.9% in 2013 to 26.1% in 2023. The trend of hypertriglyceridemia prevalence has shown a slight decline over the past decade; however, it is still as high as 13.2% [5]. Nevertheless, dyslipidemia is modifiable by environmental factors such as eating a healthy diet [6].

Appropriate intake of macronutrients, including carbohydrates, proteins, and fats, has long been considered an important dietary factor in chronic disease management since they play a fundamental role not only in the production of energy but also in metabolic processes. As Koreans have high–carbohydrate diets and a higher carbohydrate intake than non–Asian populations [7, 8], appropriate carbohydrate intake for prevention of chronic disease has drawn increasing attention in Korea. Numerous studies have demonstrated the association between a high carbohydrate intake and increased risk of cardiovascular disorders among Koreans [9–11]. Hence, a low–carbohydrate diet (LCD) may be an alternative; however, the increased intake of animal foods and saturated fat caused by an LCD may lead to increased cholesterol levels [12–14]. Moreover, the quality of carbohydrates may be a more crucial dietary factor for CVD [15]. Therefore, it is essential to take into account the overall effects of macronutrient composition and their quality on cardiometabolic health.

Two decades ago, Halton et al. [16] suggested the LCD score to evaluate the effects of relative levels of carbohydrate, protein, and fat intake on diseases. An LCD refers to a diet with a low intake of carbohydrates and a high intake of proteins and fats, and the LCD score is a comprehensive approach explaining diet and disease association [16]. A number of studies have explored the association between the LCD score and cardiovascular risk factors or diseases [17–21]; however, these associations are still inconclusive. Other risk factors that may influence the association between macronutrient intake and CVDs may help address this discrepancy.

Another environmental factor which plays an important role in the development of CVDs and is linked with dietary habits is the gut microbiome. The composition and functionality of the gut microbiome induced by diet is a key regulator in the pathogenesis of CVDs. For instance, intake of energy and monounsaturated fatty acids was negatively associated with an abundance of *Bacteroides* and *Bifidobacterium*, respectively, in monozygotic twins [22]. An animal–based diet including beef, pork, bacon, and cheeses increases the abundance of *Alistipes*, *Bilophila*, and *Bacteroides* which are bile–tolerant microorganisms [23]. These diet–induced microbial changes affect many bile acid reactions in host metabolism and even lead to CVD [24]. Additionally, the gut microbiota affect the acquisition and storage of fat via the processing of polysaccharides [25].

The effects of an LCD on the gut microbiome and cardiometabolic risk factors were also investigated in several previous clinical studies. In a 12 week–intervention study, weight loss was greater among participants with a higher abundance of *Bacteroides* at baseline in the LCD group [26]. In another 12–week intervention, healthy LCDs including whole grain, plant protein, and unsaturated fats decreased body fat mass, Firmicutes/Bacteroidetes ratio, and abundance of *Ruminococcus callidus*, and upregulated the lipid biosynthesis pathway [27]. Although many experimental studies have demonstrated the relationship between macronutrient intake, the gut microbiome, and cardiovascular risk factors, there is limited evidence on the influence of the gut microbiome on the association between macronutrient intake and dyslipidemia in population–based observational studies.

Therefore, we aimed to investigate the association between macronutrient intake and the gut microbiome and their interaction with dyslipidemia in a Korean population using LCD scores and two population–based studies in Korea.

Methods

Study design and participants

Data from two population–based cross–sectional studies, the Korean Microbiome Study (KMS) and Korea National Health and Nutrition Examination Survey (KNHANES), were used in this study. First, we examined the association between LCD scores and dyslipidemia in

the KMS and KNHANES to confirm how the association differed in the two studies. Then we identified the LCD score–associated gut microbiome and examined the association between the LCD score, macronutrient intake, and gut microbiome with dyslipidemia in the KMS. Finally, we aimed to predict the potential effect of the gut microbiome on dyslipidemia in the KNHANES based on the results from the KMS. The overall study design is described in Fig. 1.

The KMS is an on–going study conducted by the Korea Food Research Institute (Wanju, Republic of Korea) since 2017, which aims to investigate the association between the gut microbiome and disease and related risk factors, including diet and lifestyle, among the Korean population. Detailed information about the study and its major results have been previously reported [28]. Study participants were recruited between 2017 and 2019 from individuals undergoing health checkups at Chung–Ang University Hospital in Seoul and Chungbuk Hospital in Chungcheongbuk-do, representing two distinct urban regions in Republic of Korea. The exclusion criteria included: participants aged less than 20 years or more than 80 years ($n = 32$); those who had implausible energy intake (< 450 kcal/day or > 4,000 kcal/day) ($n = 34$); those who had missing data on potential confounding variables ($n = 4$). Individuals who were administered antibiotics within 3 months before study commencement, those who were pregnant or lactating, those with a history of major gastrointestinal surgery or disorders, and those who had been diagnosed with, or were undergoing treatment for severe diseases including cancer or CVDs were excluded for study recruitment. Finally, 2,178 participants (men: 521; women: 1,657) were included in the final analysis. This study was approved by the Institutional Review Board (IRB) of Chung–Ang University Hospital (Seoul, Republic of Korea) (approval number: 1750–002–281) and Chungbuk National University Hospital (Cheongju, Republic of Korea) (approval number: 2019–04–014). All participants provided written informed consent.

The KNHANES is a national survey which has been annually conducted since 1998 by the Korea Disease Control and Prevention Agency (KDCA) (Cheongju, Republic of Korea) to identify the health status of Korean people aged more than 1 years old. The sampling frame of KNHANES was based on the most recent 'Population and Housing Census' data published by Statistics Korea (KOSTAT) to ensure the selection of a representative sample of the Korean population. More detailed information regarding the study has been previously described [29]. A total of 24,229 individuals participated in the survey from 2017 to 2019. The exclusion criteria included: participants aged less than 20 years or more than 80 years (n = 4,805), those who are pregnant or lactating (n = 141), those who had been diagnosed with or were undergoing treatment for severe disease including cancer or CVDs (n = 1,834), those who did not participate in the nutrition

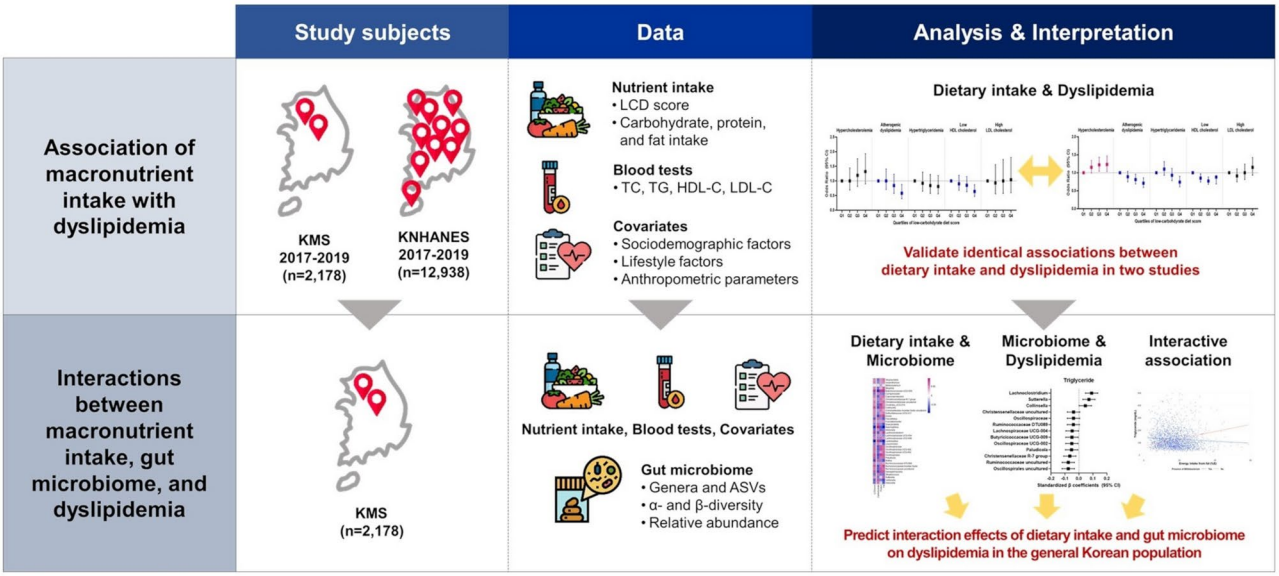

Fig. 1 Study design investigating the association between macronutrient intake, gut microbiome, and dyslipidemia in Korean adults. The association of macronutrient intake and dyslipidemia was evaluated in a population–based study, the KMS and the association was verified in a national survey data, the KNHANES. Adults aged 20 to 80 years were included and LCD scores were used for assessment of macronutrient intake. Stool samples were collected exclusively in the KMS and gut microbiome profiling was conducted. We then identified the LCD score–related gut microbiome and investigated the interactive association of LCD score, macronutrient intake and gut microbiome on dyslipidemia which may applicable to the general Korean population. HDL–C, high density lipoprotein cholesterol; KMS, Korean Microbiome Study; KNHANES, Korea National Health and Nutrition Examination Survey; LCD, low–carbohydrate diet; LDL–C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride

survey or had implausible energy intake (< 500 kcal/day or > 5,000 kcal/day) (n = 2,486), and those who had missing data on related clinical parameters or potential confounding variables (n = 2,025). Finally, 12,938 participants (men: 5,466; women: 7,472) were included in the final analysis. Stool samples were not collected in the KNHANES. All participants submitted written informed consent and the protocols for data collection were approved by the IRB of the KDCA (approval numbers: 2018–01–03–P–A, 2018–01–03–C–A, and 2018–01–03–2 C–A). The flowchart of participant selection is shown in Figure S1.

Dietary assessment and calculation of LCD score

Dietary intakes were assessed using a semi–quantitative food frequency questionnaire (FFQ) [30] in the KMS and a 1–day 24–h dietary recall method in the KNHANES [29]. The FFQ was validated by comparing the energy and nutrient intakes between the 3-day diet records from four seasons and two FFQs, one at the beginning and the other at the end of the study among the Korean population. In brief, the median correlation coefficients for all nutrients were 0.39, indicating a moderate level [30]. Participants of the KMS completed their previous year's average consumption of 106 food items in the FFQ with nine choices of frequencies (never to three times per day). Participants of the KNHANES provided information on their consumption of types, amount, and recipes of food and dishes over the last 24 h. The nutrient intakes of the participants from the KMS and KNHANES were assessed based on each nutrient database.

For assessment of LCD score, carbohydrate, protein, and fat intakes were calculated by applying standard conversion factors as follows: carbohydrate and protein (% Energy) = (4 [kcal] x carbohydrate or protein [g] / total energy) x 100, and fat (% Energy) = 9 [kcal] x fat (g) / total energy) x 100. Participants were divided into 11 strata based on the percentages of energy from each nutrient. For carbohydrates, the lowest to highest strata were scored from 10 to 0 points. Conversely, the lowest to highest strata were scored from 0 to 10 points for proteins and fats. The scores of the three macronutrients were summed for LCD score calculation (range: 0 to 30). The higher the score, the lower the proportion of energy intake from carbohydrates and the higher proportion of energy intake from proteins and fats. Detailed information of the macronutrient intake used for determining the LCD score is described in Table S1. A healthy LCD (HLCD) score was also calculated to assess the quality of carbohydrates using consumption of less healthy carbohydrates from refined grains such as white rice, noodles, bread, cereal, snacks, potatoes, sugar, sweets, desserts, and sugar–sweetened beverages. The sum of the ranks of protein and fat intake, and a reversed rank of less healthy carbohydrate intake, was used to calculate the HLCD score.

We further assessed the interactive effect of the gut microbiome on dyslipidemia according to the acceptable macronutrient distribution range (AMDR) of the Dietary Reference Intakes for Koreans 2020: carbohydrates 55–65%, fat 15–30% [31].

Assessment of dyslipidemia

Dyslipidemia was determined based on the guidelines for Korean [32] in the KMS and KNHANES. Dyslipidemia is classified into four types: hypercholesterolemia, defined as a total cholesterol (TC) level of 240 mg/dL or more or the use of lipid–lowering medication; hypertriglyceridemia, defined as a TG level of 200 mg/dL or more; low high–density lipoprotein (HDL) cholesterolemia, defined as an HDL cholesterol (HDL–C) level of less than 40 mg/dL for men and less than 50 mg/dL for women; and a high–LDL cholesterolemia, defined as an LDL–C level of 160 mg/dL or more. Additionally, atherogenic dyslipidemia, which is defined as elevated TG (≥ 150 mg/dL) and low HDL–C (< 40 mg/dL for men and < 50 mg/dL for women) levels, was also assessed [33].

Blood samples were drawn at examination sites from individuals with an overnight fast before the examination. In the KMS, serum levels of TC, TG, and HDL–C were assessed using an ADVIA 1650 chemistry analyzer (Siemens, Tarrytown, NY, USA) or cobas c 702 module (Roche Diagnostics System, Basel, Switzerland). In the KNHANES, TC, TG, and HDL–C levels were measured using a Hitachi Automatic Analyzer 7600–210 (Hitachi, Tokyo, Japan) in 2017 and 2018, and a Labospect 008AS (Hitachi, Tokyo, Japan) in 2019. The LDL–C level in both studies was estimated using the Friedewald equation: LDL–C = TC – (TG/5 + HDL–C) [34].

Gut microbiome profiling

Stool samples were self–sampled using OMNIgene–GUT tubes (DNA Genotek, Ottawa, Canada). DNA extraction and 16S rRNA sequencing were performed following a method that has been previously described [35]. In brief, DNA was extracted from each stool sample using a QIAamp DNA Stool Mini Kit (Qiagen, Hilden, Germany), along with an additional bead–beating procedure. The library for the V3–V4 hypervariable regions of the 16S rRNA gene was constructed using extracted DNA according to the 16S Metagenomic Sequencing Library Preparation protocol (part no. 15044223 Rev. B; Illumina, San Diego, CA, USA). DNA libraries were sequenced on a MiSeq instrument (Illumina, San Diego, CA, USA). The DADA2 pipeline [36] of the QIIME2 (2023.02 version) package [37] was employed for sequence quality control and feature table construction. Taxonomic assignment was performed using the QIIME2 classify–sklearn

algorithm by a pre–trained naïve Bayes classifier on the V3–V4 fragments of the 16S SILVA database (version 138) [38]. The names of the amplicon sequence variants (ASVs) were determined with their assigned genus name and rank of average abundance among ASVs significantly associated with dietary intake and dyslipidemia.

Covariates

All the participants of the KMS and KNHANES completed the questionnaire reporting their sociodemographic information, lifestyle, and medical history. The participants also underwent anthropometric examination. Sociodemographic variables included age, sex, education level, and household income. Education level was divided into two groups: lower and higher than college. Household income was divided into two groups: less than and more than or equal to 3,000,000 Korean Won (KRW)/month (approximately 2,050 United States dollars [USD]/month) for the KMS, and approximately less than 2,500,000–3,000,000 KRW/month (first and second quartile) and more than or equal to 2,500,000–3,000,000 KRW/month (third and fourth quartile) for the KNHANES. Drinking status was classified as non– or past–drinker and current drinker. For the KNHANES, non– or past–drinker was someone who had not drunk alcohol over the last year and a drinker was someone who had drunk alcohol more than once a month over the last year. Smoking status was classified as non– or past–smoker and current smoker. Physical activity was classified into two groups based on the time spent doing vigorous physical activity: inactive and active (> once a week for 10–15 min). For the KMS, two different examination sites (Seoul and Cheongju) were considered. Body mass index (BMI) was calculated by dividing the measured body weight (kg) by the square of the measured height (m) (kg/m^2). Use of lipid-lowering medications was categorized into two groups: non-users and users.

Statistical analysis

General statistics

The general characteristics of study participants were analyzed using the chi–squared test for categorical variables and a generalized linear model in the KMS and regression model in the KNHANES for continuous variables. A multivariate logistic regression model was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for dyslipidemia. Confounding variables included age, sex, BMI, education level, household income, drinking status, smoking status, physical activity, total energy intake, and examination site (only for the KMS) for the multivariate analysis. Use of lipid-lowering medications was additionally included in the sensitivity analysis. Missing values for dietary intake, gut microbiome, outcome, and confounding variables were excluded during the participant selection stage. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and the PROC SURVEY command in SAS for the KNHANES, applying sample weights, strata, and clusters, which incorporates a complex sampling design for a national survey.

Gut microbiome statistical analysis

We calculated intra– and inter–individual diversity using alpha diversity quantified by Shannon's diversity, Pielou's evenness, and observed features (ASVs) and Faith's phylogenetic diversity (PD) and beta diversity quantified by Bray–Curtis distance, respectively, after rarefying to 10,000 reads/sample. Associations of alpha diversity with LCD score and macronutrient intake were assessed using a generalized linear model with adjustment for confounding variables. The effects of LCD score and macronutrient intake on the microbial community structure were estimated using the Adonis method of QIIME2 (2023.02 version), with adjustment for confounding variables. We defined the presence of an individual genus and ASV as more than 20% of participants with an average relative abundance of more than 0.00001. The relative abundances of taxa were used after arcsine square root transformation. The false discovery rate (FDR) was calculated using the Benjamini–Hochberg procedure for multiple testing, and an FDR of less than 0.2 was considered significant. A generalized linear model was used for the analysis of the association between dietary intake and the microbiome, and between the microbiome and lipid parameters, with adjustment for confounding variables. A multivariate logistic regression model was used for the analysis of the association between the microbiome and dyslipidemia. For interaction analysis, an interaction term of a dietary variable with a variable referring to the presence or absence of an individual genus or ASV was added to a multivariate generalized linear model and multivariate logistic regression model. Graphical representations were performed in R version 4.2.2 [39] and GraphPad Prism software 10 (GraphPad Software Inc., San Diego, CA, USA).

Results

General participant characteristics

The general characteristics of the participants of the two studies according to LCD score quartile groups are described in Table 1. The median LCD score of the quartile groups was 3, 12, 19, and 27 in the KMS, and 4.8, 12.2, 18.0, and 24.3 in the KNHANES, respectively. The KMS had a higher proportion of women than men. Participants of the KMS and KHANES with higher LCD scores tended to be younger, current drinkers, physically active, had higher education levels, and higher household incomes. The proportion of participants in the

Table 1 General characteristics of two population–based studies in Korea

	KMS (2017–2019) (*n* = 2,178)				KNHANES (2017–2019)[a] (*n* = 12,938)			
	Quartiles of LCD score				Quartiles of LCD score			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
N	569	561	473	575	3382	3117	3451	2988
LCD score								
Median (range)	3 (0–7)	12 (8–15)	19 (16–22)	27 (23–30)	4.8 (0–9)	12.2 (10–15)	18.0 (16–21)	24.3 (22–30)
Sociodemographic factors								
Sex (%)								
Women	76.6	73.8	77.2	76.9	58.0	47.3	46.8	49.3
Age, years (Mean ± SE)	56.5 ± 0.6	54.3 ± 0.6	50.6 ± 0.7	46.1 ± 0.6	56.3 ± 0.4	47.6 ± 0.4	43.6 ± 0.3	40.6 ± 0.3
Education level (%)								
Higher than college graduate	39.0	40.6	51.6	57.0	26.9	43.9	52.3	55.8
Household income[b] (%)								
Higher than middle level	38.1	47.8	59.8	65.4	46.9	62.4	69.0	71.0
Health–related factors								
Drinking status (%)								
Current drinker	30.1	37.6	43.1	51.3	65.1	80.1	83.7	84.6
Smoking status (%)								
Current smoker	9.0	9.1	7.6	9.2	16.8	22.6	21.9	20.1
Physical activity[b] (%)								
Active	35.2	33.5	32.1	40.7	6.0	10.8	14.1	17.7
BMI (kg/m^2) (Mean ± SE)	23.5 ± 0.1	23.6 ± 0.1	23.3 ± 0.1	23.4 ± 0.1	23.9 ± 0.1	23.9 ± 0.1	23.8 ± 0.1	24.0 ± 0.1
Use of lipid-lowering medications (%)	9.5	8.6	9.3	6.8	15.4	10.6	7.7	6.6
Dietary intake (Mean ± SE)								
Energy intake (kcal/day)	1336.7 ± 24.0	1503.8 ± 24.2	1554.2 ± 26.4	1604.3 ± 23.9	1680.2 ± 16.4	1944.9 ± 17.4	2082.2 ± 16.8	2146.1 ± 18.7
% Energy intake from carbohydrate	78.8 ± 0.2	71.3 ± 0.2	65.3 ± 0.2	55.1 ± 0.2	76.3 ± 0.1	64.3 ± 0.2	57.3 ± 0.2	47.2 ± 0.2
% Energy intake from protein	10.6 ± 0.1	12.9 ± 0.1	14.6 ± 0.1	17.6 ± 0.1	11.2 ± 0.0	13.3 ± 0.1	15.1 ± 0.1	18.5 ± 0.1
% Energy intake from fat	8.5 ± 0.2	14.5 ± 0.2	19.3 ± 0.2	26.9 ± 0.2	11.1 ± 0.1	16.9 ± 0.1	22.6 ± 0.1	30.3 ± 0.2

BMI, body mass index; KMS, Korean Microbiome Study; KNHANES, Korea National Health and Nutrition Examination Survey; LCD, low–carbohydrate diet; Q, quartile; SE, standard error

[a] All values assessed for KNHANES were obtained by applying the complex sampling effect and appropriate sampling weights of the national survey

[b] Median level of household income was approximately 2,500,000–3,000,000 KRW per month; physical activity was determined based on the time spent for vigorous physical activity: active (more than once a week for 10–15 min) and inactive

KNHANES using lipid-lowering medications was lower in the group with a higher LCD score than in the group with a lower LCD score, whereas the KMS showed an inconsistent trend. The highest quartile group of LCD score in the KMS and KNHANES had the highest energy intake. The mean intake of percentage of energy intake from carbohydrates in the KMS was higher than that in the KNHANES and that from fats in the KMS was lower than that in the KNHANES.

Association of LCD score with dyslipidemia

The ORs and 95% CIs for dyslipidemia across the quartile groups of LCD score are presented in Fig. 2 and Table S2. Even though significances in several associations are slightly different between the KMS and KNHANES, the trends of associations are similar. In the KMS, the highest quartile group of LCD score had a lower prevalence of atherogenic dyslipidemia (OR: 0.58; 95% CI: 0.39–0.88; p for trend = 0.0089) and low–HDL cholesterolemia (OR: 0.64; 95% CI: 0.47–0.87; p for trend = 0.0053) compared with the lowest quartile group. The prevalence of hypertriglyceridemia was lower in the highest quartile group of LCD score than the lowest quartile group; however, the association was not significant (OR: 0.81; 95% CI: 0.56–1.18; p for trend = 0.2334). Similarly, the highest quartile group of LCD score had a lower prevalence of atherogenic dyslipidemia (OR: 0.71; 95% CI: 0.59–0.86; p for trend = 0.0002), hypertriglyceridemia

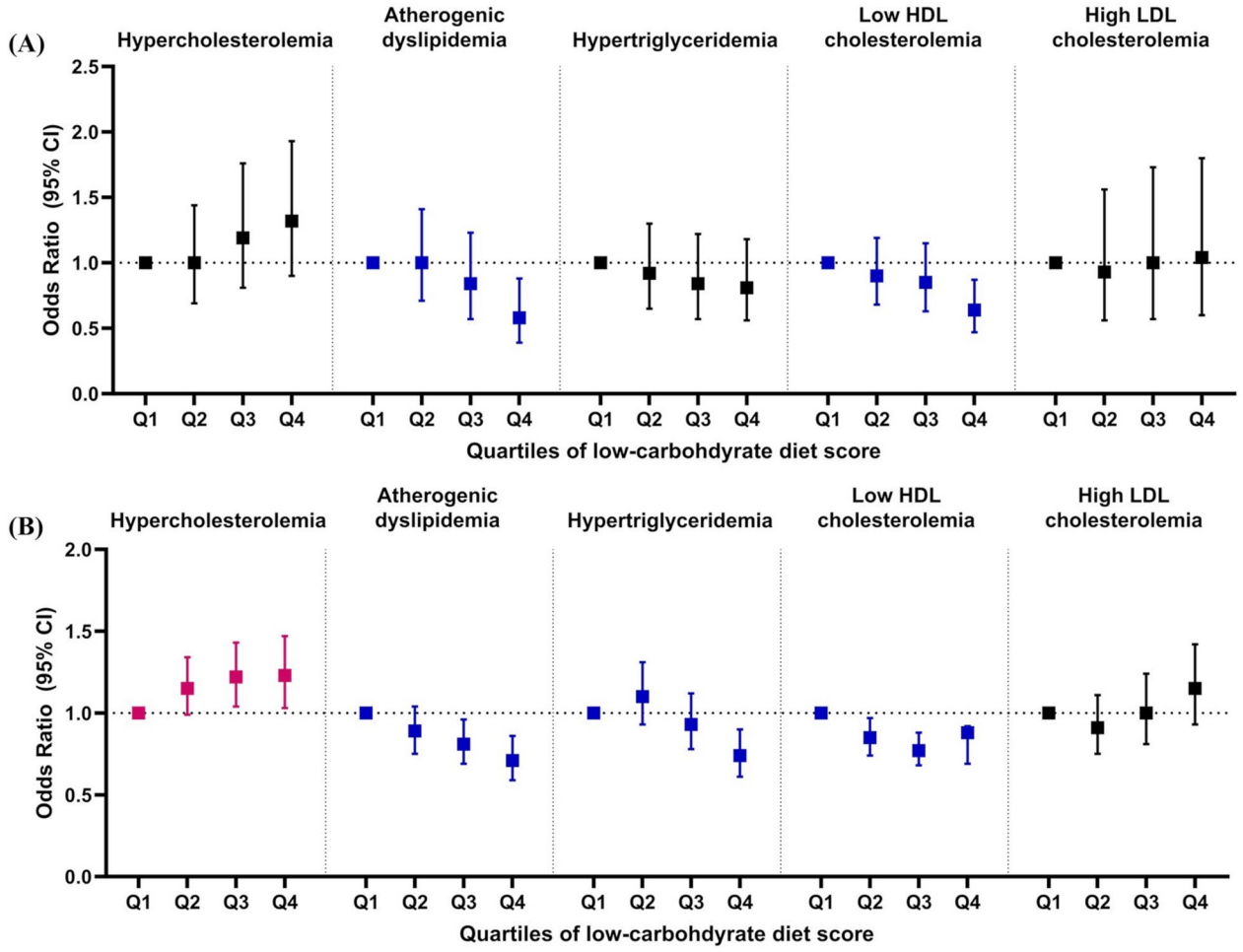

Fig. 2 Association of LCD score and dyslipidemia in (**A**) KMS and (**B**) KNHANES. ORs, 95% CIs, and p values for the trends were obtained from the multivariate logistic regression after adjusting for age, sex, BMI, education level, household income, drinking status, smoking status, physical activity, total energy intake, and examination site (only for the KMS). Navy: negatively associated, p for trend < 0.05; Magenta: positively associated, p for trend < 0.05; CI, confidence interval; HDL, high density lipoprotein; KMS, Korean Microbiome Study; KNHANES, Korea National Health and Nutrition Examination Survey; LCD, low–carbohydrate diet; LDL, low density lipoprotein; OR, odds ratio

(OR: 0.74; 95% CI: 0.61–0.90; p for trend = 0.0006), and low–HDL cholesterolemia (OR: 0.80; 95% CI: 0.69–0.92; p for trend = 0.0007) compared with the lowest quartile group in the KNHANES. The hypercholesterolemia was positively associated with LCD score in the KNHANES (OR: 1.23; 95% CI: 1.03–1.47; p for trend = 0.0135). However, the association of hypercholesterolemia with LCD score was not significantly associated in the KMS (OR: 1.32; 95% CI: 0.90–1.93; p for trend = 0.1212). The association of high–LDL cholesterolemia with LCD score was not significant in the KMS (OR: 1.04; 95% CI: 0.60–1.80; p for trend = 0.8682) and KNHANES (OR: 1.15; 95% CI: 0.93–1.42; p for trend = 0.1490). In the sensitivity analysis (Table S3), additional adjustment for lipid-lowering medication use did not alter the significance levels, except for hypercholesterolemia in the KNHANES (OR: 1.20; 95% CI: 0.96–1.49; p for trend = 0.0679).

Furthermore, the association between the HLCD score and dyslipidemia was also evaluated. The general characteristics of the participants of the two studies according to the quartile groups of HLCD score are presented in Table S4. In the KMS, the HLCD score showed a positive tendency with hypercholesterolemia. However, the significant association with atherogenic dyslipidemia was not observed. In contrast, the HLCD score was associated with all parameters of dyslipidemia in the KNHANES (Table S5). Given that the associations between the LCD score and dyslipidemia were consistently observed in KMS and KNHANES, while the associations between HLCD and dyslipidemia were not, we focused subsequent analyses on LCD score.

Association between gut microbial diversity and LCD score and dyslipidemia factors

In the KMS, a higher LCD score was associated with higher alpha diversity measured by Faith's PD (β = 0.2961; p = 0.0359; FDR = 0.1436) (Table 2). Similarly, the percentage of energy intake from protein was positively associated with observed ASVs (β = 5.2976; p = 0.0022; FDR = 0.0044) and Faith's PD (β = 0.4266; p = 0.0016; FDR = 0.0044). In contrast, the percentage of energy intake from carbohydrates was negatively associated with Faith's PD (β=−0.3263; p = 0.0213; FDR = 0.0852). The percentage of energy intake from fat was not associated with the alpha diversity index. The percentage of energy intake from protein showed the strongest positive associations between alpha diversity and macronutrient intake.

We also assessed associations of LCD score and macronutrient intake with inter–individual variation in overall microbiota composition using Bray–Curtis distance (Fig. 3A and Table S6). The strongest association was observed between beta diversity and percentage of energy intake from fats (Adonis R^2 = 0.0018; p = 0.001; FDR = 0.0013) followed by energy from carbohydrates, LCD score, and percentage of energy intake from proteins.

Association between relative abundance of gut microbial genera and LCD score

We identified 38 microbial genera associated with LCD score using a generalized linear model in the KMS (Fig. 3B and C). The top five genera significantly positively associated with higher LCD scores were *Butyricicoccaceae UCG-009*, *Lachnoclostridium*, *Collinsella*, *Senegalimassilia*, and uncultured genus of Oscillospirales. The relative abundance of these genera were negatively associated with the percentage of energy intake from carbohydrates, and positively associated with that from proteins and fats. In contrast, the top five genera significantly negatively associated with higher LCD scores were *Lactobacillus*, *Haemophilus*, *Rothia*, *Veillonella*, and *Faecalitalea*. The relative abundance of these genera were positively associated with the percentage of energy intake from carbohydrate, and negatively associated with that from proteins and fats (Fig. 3B and Table S7).

Additionally, the highest quartile group of LCD score had a significantly high relative abundance of *Plaudicola*, Oscillospirales uncultured, *Senegalimassilia*, *Defluviitaleaceae UCG–011*, and uncultured genus of Coriobacteriales, whereas it had a significantly low relative abundance of *Faecalitalea*, *Lactobacillus*, *Haemophilus*, *Veillonella*, and *Bifidobacterium* compared with the lowest quartile group (Fig. 3C and Table S8).

Association between LCD score–associated genera and dyslipidemia

Associations between LCD score–associated genus and lipid parameters were estimated (Fig. 3D and Table S9). For example, the higher the abundance of *Lachnoclostridium*, the higher the TC level (β = 0.0588; p = 0.0057). We also assessed the ORs and 95% CIs for dyslipidemia factors according to the presence or absence of LCD score–associated genus in the KMS (Fig. 3E and Table

Table 2 Association of LCD score and macronutrient intake with gut microbiome α–diversity based on KMS

		Standardized Coefficient (SE)	*p*–value	FDR
LCD score	Shannon's diversity	0.0029 (0.0163)	0.8602	0.8602
	Pielou's evenness	−0.0012 (0.0013)	0.3559	0.4745
	Observed ASVs	3.2215 (1.8080)	0.0749	0.1498
	Faith's PD	0.2961 (0.1410)	0.0359	0.1436
Carbohydrate intake (%E)	Shannon's diversity	−0.0079 (0.0164)	0.6316	0.6316
	Pielou's evenness	0.0007 (0.0013)	0.6261	0.6316
	Observed ASVs	−3.4097 (1.8160)	0.0606	0.1212
	Faith's PD	−0.3263 (0.1416)	0.0213	0.0852
Protein intake (%E)	Shannon's diversity	0.0259 (0.0156)	0.0964	0.1285
	Pielou's evenness	0.0006 (0.0013)	0.6485	0.6485
	Observed ASVs	5.2976 (1.7285)	0.0022	0.0044
	Faith's PD	0.4266 (0.1349)	0.0016	0.0044
Fat intake (%E)	Shannon's diversity	0.0018 (0.0167)	0.9132	0.9132
	Pielou's evenness	−0.0009 (0.0014)	0.5004	0.6672
	Observed ASVs	2.5624 (1.8515)	0.1665	0.3330
	Faith's PD	0.2521 (0.1444)	0.0810	0.3240

ASV, amplicon sequence variant; BMI, body mass index; FDR, false discovery rate; KMS, Korean Microbiome Study; LCD, low–carbohydrate diet; PD, phylogenetic diversity

All values were obtained from the multivariate generalized linear model after adjusting for age, sex, BMI, education level, household income, drinking status, smoking status, physical activity, total energy intake, and examination site

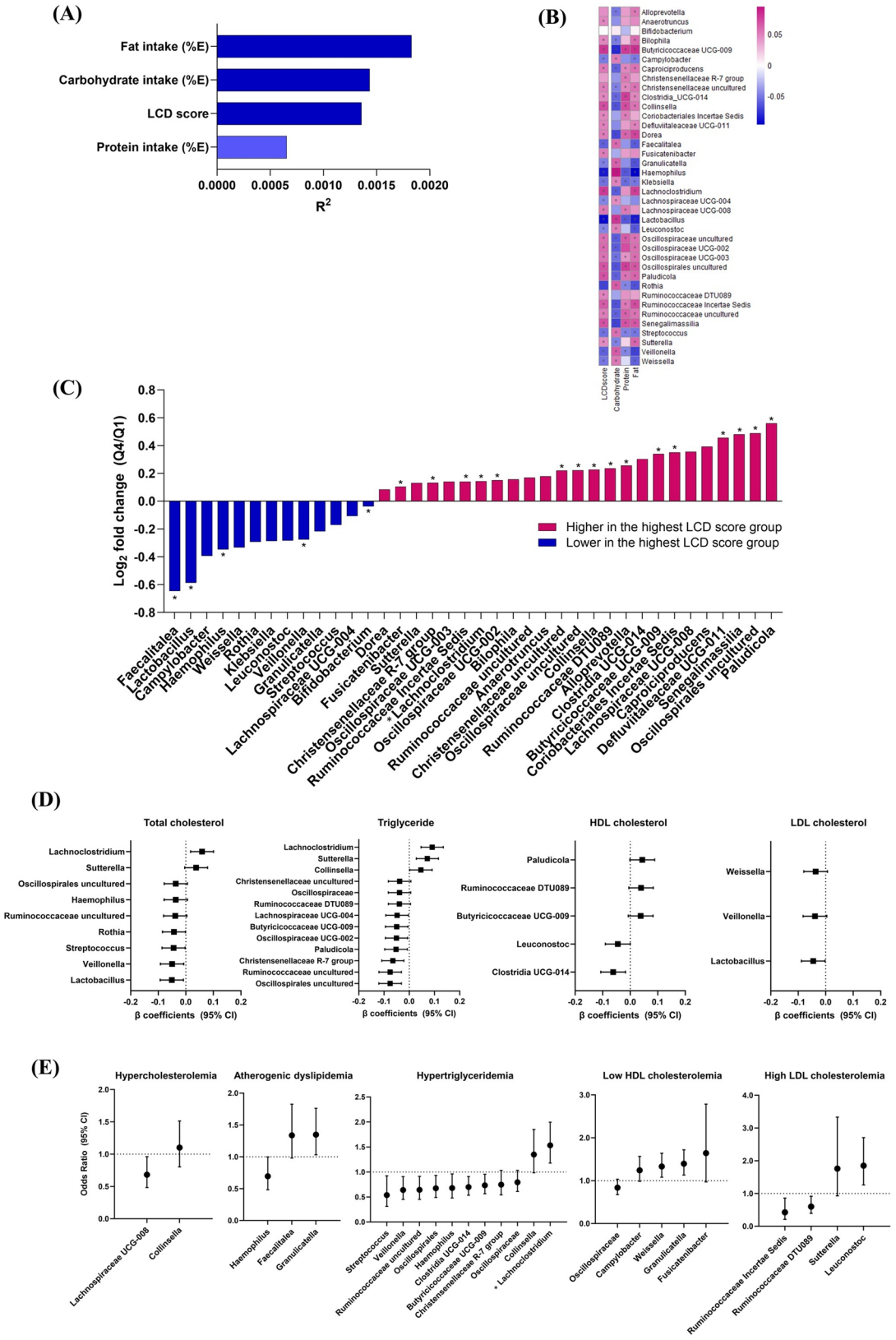

Fig. 3 (See legend on next page.)

(See figure on previous page.)

Fig. 3 Association of dietary factors and dyslipidemia with the gut microbiome. (**A**) Gut microbiome community variation with dietary factors based on the KMS. Values represent the adjusted proportion of variance explained (R^2) for β–diversity obtained from the Bray–Curtis distance and Adonis method adjusted for confounding variables (Dark navy: $p = 0.001$ and FDR = 0.0013; Light navy: $p = 0.010$ and FDR = 0.0100). (**B, C**) Association of LCD score and gut microbial genera in the KMS. We identified 38 gut microbial genera associated with LCD score. (**B**) Data are beta coefficients estimated using a multivariate generalized linear model ($^*p < 0.05$ and FDR < 0.2). (**C**) Differences in the relative abundance of the highest and lowest LCD score group. The relative abundance is represented as a fold change on the log2 scale and significances were estimated using a multivariate generalized linear model among all groups ($^*p < 0.05$ and FDR < 0.2). (**D, E**) Association of LCD score–associated gut microbial genera and dyslipidemia in the KMS. (**D**) Associations of gut microbial genus and lipid parameters are shown as beta coefficients estimated using a multivariate generalized linear model. (**E**) Data are ORs and 95% CIs for dyslipidemia in each presence group of genus compared with the absence group obtained from the multivariate logistic regression. All values were obtained after adjusting for age, sex, BMI, education level, household income, drinking status, smoking status, physical activity, total energy intake, and examination site. CI, confidence interval; HDL, high density lipoprotein; KMS, Korean Microbiome Study; FDR, false discovery rate; LCD, low–carbohydrate diet; LDL, low density lipoprotein; OR, odds ratio* Data are shown in the high relative abundance group (third and fourth quartile groups) compared with the low relative abundance group (first and second quartile groups) for *Lachnoclostridium* due to low proportion of absence group (< 0.1%)

S10). Several genera showed significant associations with the prevalence of dyslipidemia in the presence group compared with the absence group. For example, the presence of *Collinsella* (OR: 1.35; 95% CI: 0.98–1.85) or *Weissella* (OR: 1.33, 95% CI: 1.08–1.64) was associated with an increased odds ratio of hypertriglyceridemia and low HDL cholesterolemia, respectively, compared with the absence of the genera.

Association of fat and carbohydrate intake according to AMDR with dyslipidemia

As described in Fig. 4 and Table S11, the association between fat and carbohydrate intake according to AMDR (fat: 15–30% of energy intake from fat; carbohydrate: 55–65% of energy intake from carbohydrate) and dyslipidemia was estimated in the KMS and verified in the KNHANES to confirm the association of dyslipidemia with macronutrient intake at the same level. The associations showed a similar trend in both studies. Similar to LCD score, fat intake was negatively associated with low–HDL cholesterolemia in both studies (p for trend = 0.0057 in KMS; p for trend = 0.0112 in KNHANES). Fat intake within the AMDR was associated with a reduced prevalence of atherogenic dyslipidemia in both studies (OR: 0.69, 95% CI: 0.52–0.91 in the KMS; OR: 0.83, 95% CI: 0.73–0.94 in the KNHANES). Moreover, fat intake was marginally positively associated with hypercholesterolemia in both studies (OR: 2.00, 95% CI: 1.12–3.57 [in the fat intake > AMDR], p for trend = 0.0596 in the KMS; OR: 1.19, 95% CI: 0.98–1.45 [in the fat intake > AMDR], p for trend = 0.0210 in the KNHANES). In contrast, hypertriglyceridemia (p for trend = 0.0023) and high–LDL cholesterolemia (p for trend = 0.0403) were negatively and positively associated with fat intake, respectively, only in the KNHANES.

Hence, low carbohydrate intake was associated with a decreased prevalence of low–HDL cholesterolemia in both studies (p for trend = 0.0076 in the KMS; p for trend < 0.0001 in the KNHANES). Low carbohydrate intake showed downward trends with atherogenic dyslipidemia in the KMS (p for trend = 0.0081) and KNHANES (p for trend = 0.0004).

Interactive association between fat intake and dyslipidemia by LCD score–associated genera

We quantitatively estimated the interactive effect of LCD score–associated genera and fat intake on dyslipidemia using a multivariate generalized linear model in the KMS. Consequently, among the 38 LCD score–associated genera, those who had *Bifidobacterium* (p for interaction = 0.0017) showed stronger inverse associations between percentage of energy intake from fat and TG level compared with those who did not have the genus (Fig. 5A). Those with *Lachnospiraceae UCG–004* (p for interaction = 0.0482) showed stronger protective associations between percentage of energy intake from fat and HDL–C level compared with those who did not have the genus (Fig. 5B).

Furthermore, the prevalence of dyslipidemia according to the AMDR of fat intake, as recommended for Korean adults, was assessed using a multivariate logistic regression model stratified by the presence or absence of each genus in the KMS. Among individuals with *Bifidobacterium*, fat intake within the AMDR was associated with a lower prevalence of hypertriglyceridemia (OR: 0.75; 95% CI: 0.56–0.99) compared to those with fat intake below the AMDR. In contrast, this association was not significant among individuals without *Bifidobacterium* (p for interaction = 0.0060) (Fig. 5A and Table S12). Similarly, among individuals with *Lachnospiraceae UCG–004*, fat intake above the AMDR was associated with a lower prevalence of low-HDL cholesterolemia (OR: 0.46; 95% CI: 0.24–0.85; p for trend = 0.0033), compared to intake below the AMDR. No significant association was observed among individuals without *Lachnospiraceae UCG–004*; however, the interaction was not statistically significant (p for interaction = 0.0910) (Fig. 5B and Table S12).

In contrast, *Oscillospirales* uncultured and *Weissella* showed positive interactive effects with fat intake and dyslipidemia (Fig. 5C and D; Table S12). Among individuals carrying uncultured *Oscillospirales*, fat intake was positively associated with hypercholesterolemia (OR: 5.45; 95% CI: 1.81–16.42; p for interaction = 0.0050). Among those without *Weissella*, fat intake was negatively

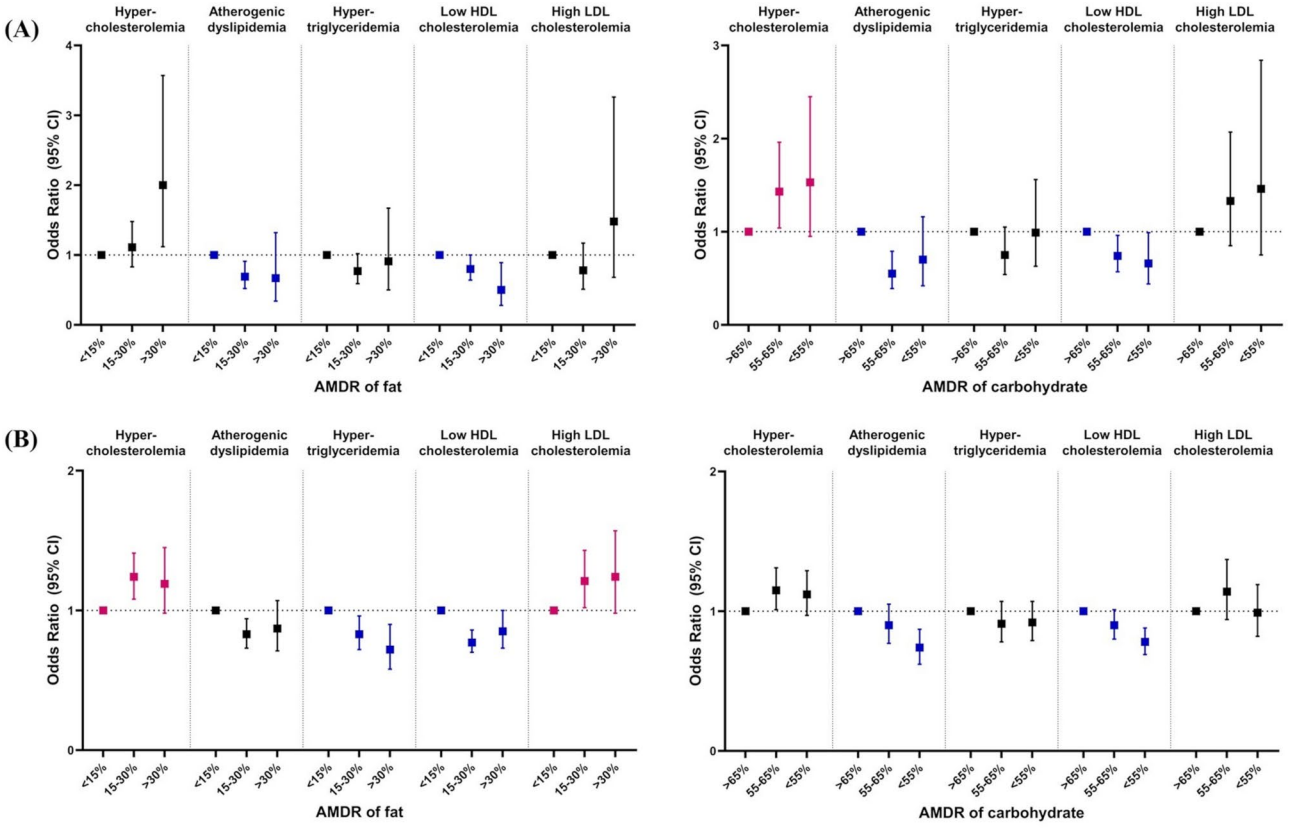

Fig. 4 Associations of fat and carbohydrate intake according to the AMDR and dyslipidemia in the (**A**) KMS and (**B**) KNHANES. ORs, 95% CIs, and p values for trends were obtained from the multivariate logistic regression after adjusting for age, sex, BMI, education level, household income, drinking status, smoking status, physical activity, total energy intake, and examination site (only for KMS). Navy: negatively associated, p for trend < 0.05; Magenta: positively associated, p for trend < 0.05; AMDR, acceptable macronutrient distribution range; CI, confidence interval; HDL, high density lipoprotein; KMS, Korean Microbiome Study; KNHANES, Korea National Health and Nutrition Examination Survey; LCD, low–carbohydrate diet; LDL, low density lipoprotein; OR, odds ratio

associated with low-HDL cholesterolemia (OR: 0.23; 95% CI: 0.10–0.56; p for interaction = 0.0210). Associations involving other genera—such as *Campylobacter*, *Rothia*, *Veillonella*, *Klebsiella*, *Granulicatella*, and *Butyricicoccaceae UCG–009*—and fat intake in relation to dyslipidemia are detailed in Figure S2 and Table S12.

Interactive association between carbohydrate intake and dyslipidemia by LCD score–associated genera

We applied the same multivariate statistical model used in the fat intake analysis to investigate carbohydrate intake. Interactive effects between specific gut microbial genera and carbohydrate intake on dyslipidemia were also observed. The presence of *Collinsella* was associated with a protective effect against hypertriglyceridemia among individuals whose carbohydrate intake fell within the AMDR (OR: 0.69; 95% CI: 0.48–1.01; p for interaction = 0.0470). In addition, low carbohydrate intake was strongly and positively associated with the prevalence of hypercholesterolemia among individuals with a high abundance of *Lachnoclostridium* (OR: 3.79; 95% CI: 2.01–7.17; p for interaction < 0.0001) (Fig. 5E and F; Table S12). An association involving another genus, such as *Granulicatella*, in relation to carbohydrate intake and dyslipidemia is presented in Figure S2 and Table S12.

Interactive association between fat and carbohydrate intake and dyslipidemia by LCD score–associated ASVs

Interactive effects were also observed at the ASV level for genera previously identified as significant in genus-level analyses. As shown in Fig. 6A, individuals carrying *Bifidobacterium* ASV1 exhibited a stronger negative association between the percentage of energy derived from fat and TG levels compared to those without this ASV (p for interaction = 0.0197). Among these individuals, fat intake within the AMDR was inversely associated with the prevalence of hypertriglyceridemia (OR: 0.69; 95% CI: 0.50–0.96; p for interaction = 0.0340), compared to fat intake below the AMDR. Similarly, fat intake was negatively associated with the prevalence of low-HDL cholesterolemia among individuals carrying *Lachnospiraceae UCG–004* ASV3 (p for interaction = 0.0320),

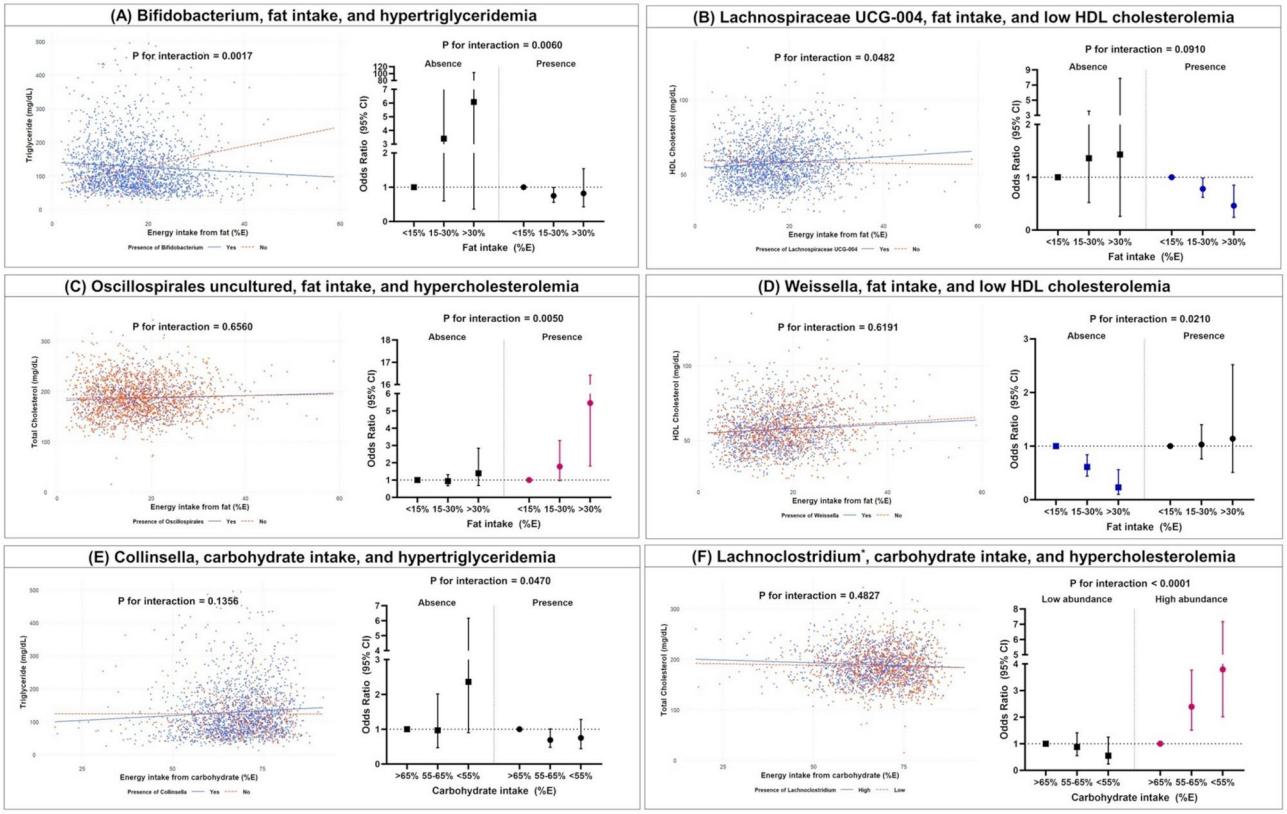

Fig. 5 LCD score-associated gut microbial genera showing interactive effects with fat and carbohydrate intake on dyslipidemia. (**A, B**) Protective effects with fat intake. (**C, D**) Unfavorable effects with fat intake. (**E**) Protective effects with carbohydrate intake. (**F**) Unfavorable effects with carbohydrate intake. A multivariate generalized linear model was used for assessment of interactive effects of genus and fat intake on lipid level (left graph). ORs and 95% CIs for dyslipidemia according to genus carriage and fat AMDR levels were obtained from the multivariate logistic regression (right graph). All values were adjusted for age, sex, BMI, education level, household income, drinking status, smoking status, physical activity, total energy intake, and examination site. Navy: negatively associated, p for trend < 0.05; Magenta: positively associated, p for trend < 0.05; AMDR, acceptable macronutrient distribution range; CI, confidence interval; HDL, high density lipoprotein; KMS, Korean Microbiome Study; LCD, low-carbohydrate diet. OR, odds ratio * Data are shown in the high relative abundance group (third and fourth quartile groups) compared with the low relative abundance group (first and second quartile groups) for Lachnoclostridium due to low proportion of absence group (< 0.1%)

whereas no significant association was observed in individuals without this ASV (Fig. 6B and Table S13). Associations involving other ASVs—such as *Veillonella* ASV4, *Butyricicoccaceae UCG–009* ASV5, *Collinsella* ASV2, and *Granulicatella* ASV6—and dietary intake in relation to dyslipidemia are described in Figure S3 and Table S13. Characteristics of the ASVs are summarized in Table S14.

Discussion

We investigated the association of LCD score and macronutrient intake with dyslipidemia and then the interactive effect of macronutrient intake with the gut microbiome on dyslipidemia among a Korean population using two population–based studies among Koreans, the KMS and KNHANES. The association of LCD score and macronutrient intake with dyslipidemia was estimated in the KMS and KNHANES. A total of 38 gut microbial genera associated with LCD score and macronutrient intake were identified in the KMS. A high LCD score was associated with reduced prevalence of atherogenic dyslipidemia and low–HDL cholesterolemia in both studies. The level of significance for associations between hypercholesterolemia and fat and carbohydrate intake according to the AMDR differed slightly between the two studies. The association of hyperlipidemic parameters with macronutrient intake varied along with gut microbiome carriage in the KMS. Our findings suggest that the gut microbiomes may regulate dyslipidemia with macronutrient intake in the general Korean population.

The association of LCD and dyslipidemia has been investigated in numerous studies. Consistent with our results, a low carbohydrate and high fat intake was related to TC, TG, and HDL–C levels. The LCD score was positively associated with hypercholesterolemia [40, 41] or negatively associated with hypertriglyceridemia or low–HDL cholesterolemia [41, 42] in Chinese and Korean populations. In a meta–analysis of 62 studies conducted among Koreans, fat intake was positively associated with

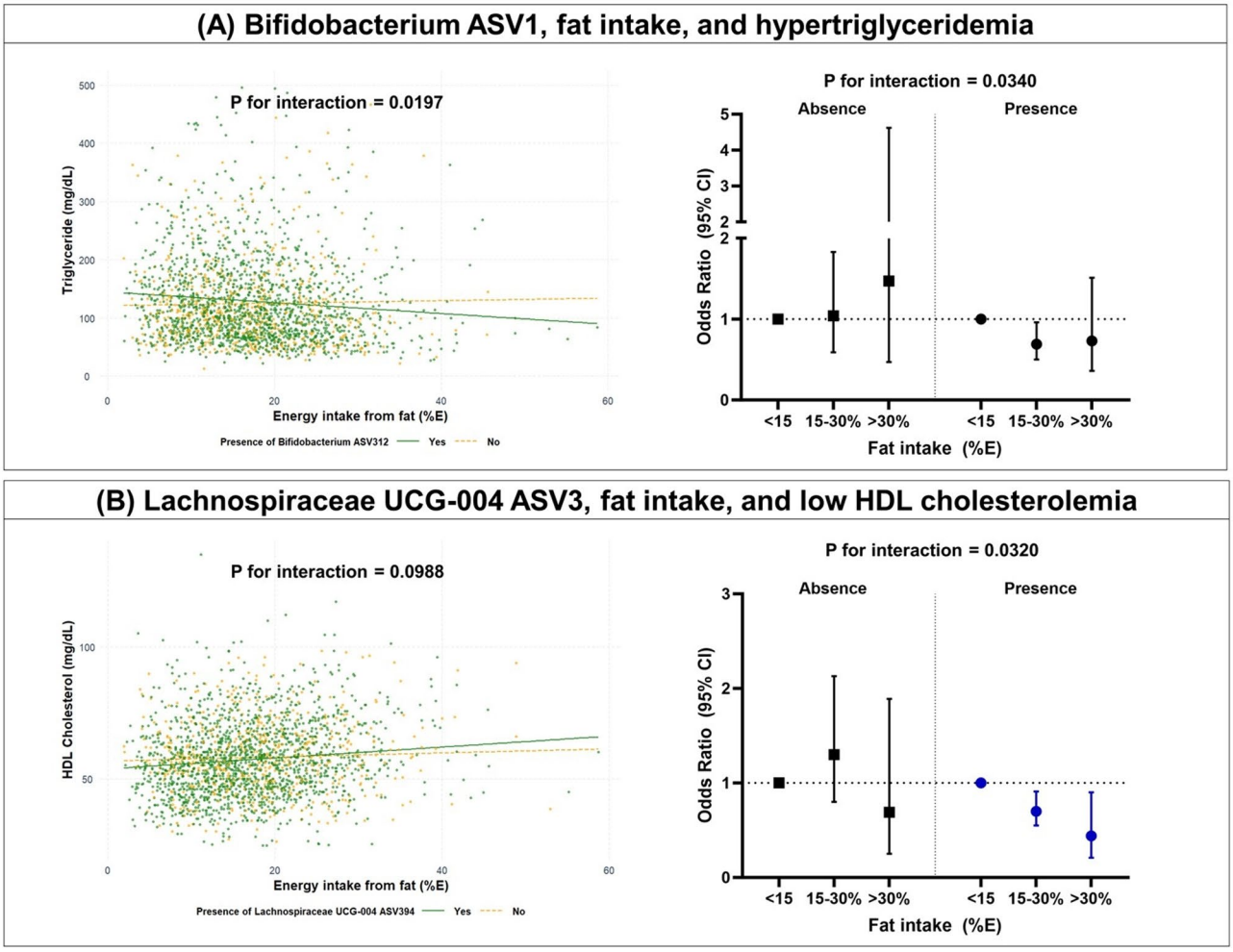

Fig. 6 LCD score-associated gut microbial ASVs showing protective interactive effects with fat intake on dyslipidemia. A multivariate generalized linear model was used for assessment of interactive effects of ASV and fat intake on lipid level. ORs and 95% CIs for dyslipidemia according to ASV carriage and fat AMDR levels were obtained from the multivariate logistic regression. All values were adjusted for age, sex, BMI, education level, household income, drinking status, smoking status, physical activity, total energy intake, and examination site. Navy: negatively associated, p for trend < 0.05; AMDR, acceptable macronutrient distribution range; ASV, amplicon sequence variant; CI, confidence interval; HDL, high density lipoprotein; KMS, Korean Microbiome Study; LCD, low-carbohydrate diet. OR, odds ratio

high TC levels, whereas LCD score was negatively associated with high TG and low HDL–C levels [43]. In another meta–analysis of randomized controlled trials for individuals with dyslipidemia, a long–term carbohydrate–restricted diet improved TC, TG, and HDL–C levels in individuals with dyslipidemia [44].

Alpha diversity was positively associated with LCD score and fat and carbohydrate intake were strongly associated with microbial community structure in the current study. In contrast, non–significant changes in alpha–diversity after an LCD intervention were reported in previous studies [26, 27]. However, it was found that a high–fat diet induced an increase in microbial diversity compared with a low fat diet in a mouse model [45]. Microbiome composition is influenced by various dietary factors, including macronutrient intake and the amount and consumption frequency of a variety of foods [46]. The discrepancies in microbial diversity between clinical trials and the current study may be owing to different meal settings. Individuals in clinical trials are provided with fixed meals, whereas those in cross–sectional studies ingest more diverse foods in their daily lives. Thus, it is important to evaluate microbiome composition and macronutrient intake level in conjunction with overall food consumption patterns.

Microbial diversity and composition have been associated with cardiometabolic health [47, 48] and microbial composition may affect responsiveness to individual diets [49]. In the current study, 38 gut microbiome genera including *Bifidobacterium*, *Lachnospiraceae UCG–004*, *Lachnoclostridium*, *and Collinsella*—which are associated with LCD score—exhibited an interplay with fats

or carbohydrates, and affected dyslipidemia in a Korean population. Several genera such as *Bifidobacterium* and *Colinsella* had favorable effects on hypertriglyceridemia with moderate fat and carbohydrate intake within the AMDR. These findings suggest that the gut microbiome has a stronger impact on dyslipidemia with appropriate nutrient intake.

An interaction between several bacteria—including *Bifidobacterium*, *Bifidobacterium* ASV1, *Lachnospiraceae UCG–004*, and *Lachnospiraceae UCG–004* ASV3—and fat intake was negatively associated with dyslipidemia, demonstrating protective effects against hypertriglyceridemia and low HDL cholesterolemia in this study. The protective effect of *Bifidobacterium* on CVD risk factors such as dyslipidemia is already well documented [50]. *Bifidobacterium* treatment has been shown to not only decrease plasma TG levels but also to modulate gut microbiota composition in both humans and mice fed a high-fat diet [51–53]. The association between *Lachnospiraceae UCG–004* and CVD-related risk factors has also been explored in previous studies. In a Chinese ethnic population, the abundance of *Lachnospiraceae UCG–004* was lower among individuals with hypertension, and the *Lachnospiraceae* family was positively associated with HDL-C levels [54]. Furthermore, reduced abundance of *Lachnospiraceae UCG–004* has been observed in patients with coronary heart disease [55] and acute ischemic attack [56], compared to healthy individuals, and was negatively associated with the OR for coronary heart disease [55].

Although the direct interactive roles of these genera—classified as short-chain fatty acid (SCFA)–producing bacteria—with dietary fat and lipid metabolism (TG and HDL-C) remain insufficiently elucidated, a previous clinical trial reported that supplementation with omega-3 polyunsaturated fatty acids led to an increased abundance of butyrate-producing bacterial genera [57]. It is assumed that SCFA-producing bacteria mitigate inflammation, which plays a role in the pathogenesis of CVD [58–60]. Butyrate, the most abundant SCFA, has been reported to elevate serum HDL-C levels by stimulating ApoA-IV gene expression [61]. Specifically, *Bifidobacterium* may improve CVD outcomes by participating in immunomodulatory processes through butyrate production, maintaining intestinal barrier integrity, and inhibiting lipopolysaccharide translocation [50].

Additional evidence suggests that the gut microbiome mediates the effect of fat intake on dyslipidemia. A high intake of saturated fatty acids promotes lipopolysaccharide translocation across the intestinal barrier via chylomicron formation, consequently triggering inflammation [62–64]. In contrast, conjugated linoleic acid, abundant in animal-derived foods, has been shown to increase *Bifidobacterium* abundance and reduce body weight, fat mass, TG levels, and TC levels in mice, potentially through preferential microbial utilization of this fatty acid [65].

In this study, low carbohydrate intake was associated with increased odds of hypercholesterolemia among participants harboring *Lachnoclostridium*. The abundance of *Lachnoclostridium* was positively correlated with serum TC levels, and its role in promoting atherosclerosis as a trimethylamine-producing bacterium has been demonstrated using data from the Human Microbiome Project and validated in both in vitro and in vivo models [66]. Although the mechanisms underlying the interaction between carbohydrate intake and *Lachnoclostridium* in hypercholesterolemia remain unclear, a 2-week crossover clinical trial reported that a low carbohydrate diet in high resistant starches was positively associated with plasma trimethylamine-*N*-oxide levels [67]. Furthermore, a mouse model showed that high saturated fat intake accompanied by low carbohydrate intake increased *Lachnoclostridium* abundance [68].

Carbohydrate intake has also been shown to modify or even reverse the association between specific bacterial genera and dyslipidemia. In the present study, participants carrying *Collinsella* exhibited a higher prevalence of hypertriglyceridemia compared to those without. Similar associations between *Collinsella* and cardiovascular risk have been reported in earlier studies [69, 70]. However, in contrast to these findings, the interactive effect of *Collinsella* and carbohydrate intake appeared to be protective against hypertriglyceridemia. Future studies should further investigate the potential interaction between *Collinsella* and carbohydrate intake in relation to dyslipidemia.

Certain genera have been shown to abrogate the effect of dietary intake on dyslipidemia. For instance, the carriage of *Weissella* with fat intake showed a non-significant association with low-HDL cholesterolemia, whereas non-carriage of this genus was negatively associated with fat intake. Several studies have reported that *Weissella*, typically isolated from fermented foods, exerts favorable effects on cholesterol levels, primarily in animal models. However, infections caused by specific *Weissella* strains have also been documented [71–73].

Additionally, we evaluated the association between dyslipidemia and carbohydrate quality using the HLCD score. However, the influence of HLCD score on dyslipidemia varied between the KMS and KNHANES datasets. While hypercholesterolemia showed a positive association with the HLCD score in both studies, hypertriglyceridemia was negatively associated with the HLCD score only in KNHANES. Similarly, high LDL cholesterolemia was positively associated with the HLCD score exclusively in KNHANES. The HLCD score—which reflects lower intake of unhealthy carbohydrates and higher

intake of vegetable protein and fat—has previously been associated with reduced weight gain, whereas the total LCD score, which includes total carbohydrate, protein, and fat intake, was associated with weight gain in three large U.S. prospective studies [74]. Collectively, these findings suggest that carbohydrate quality may play a beneficial role in health and is potentially linked to the gut microbiome. However, direct comparisons between KMS and KNHANES were limited due to differences in dietary assessment tools; the KMS used a FFQ, while KNHANES utilized 24-hour dietary recall. Additionally, the number and type of food items differed between the two methods. Future large-scale studies investigating the association between carbohydrate quality, dyslipidemia, and the gut microbiome are warranted.

This study has several limitations. First, the cross-sectional design precludes causal inference regarding the effects of dietary intake and the gut microbiome on dyslipidemia. Despite adjusting for potential covariates associated with diet, microbiome composition, and lipid profiles, residual confounding cannot be excluded. Second, differences in dietary intake between the two studies may have arisen due to variation in dietary assessment methods—FFQ in KMS versus 24-hour dietary recall in KNHANES. This methodological discrepancy also hindered comparisons of specific nutrient intakes, such as fatty acids and sugars, due to differences in the underlying nutrient databases. Saturated and unsaturated fatty acids—critical for evaluating fat quality—should be incorporated into future LCD scoring systems to improve interpretability. Although some nutrient intake differences were present, the overall trends between LCD score, macronutrient intake, and dyslipidemia remained consistent across the two studies. Third, the generalizability of these findings to non-Asian populations should be approached cautiously. Asians generally consume higher levels of carbohydrates compared to non-Asians [7, 8], which may limit extrapolation of these results. Comparative studies that account for population-level differences in carbohydrate intake are warranted. Finally, the mechanisms by which the gut microbiome affects dietary metabolism and further influences biological metabolism were not investigated, and limited taxonomic resolution existed owing to 16S rRNA gene sequencing. Further analysis using metagenome shotgun sequencing, providing information on a higher resolution of the microbial community and functional genes, is warranted. Nevertheless, this study provides new insights into the potential role of the gut microbiome in regulating dyslipidemia through interaction with macronutrient intake in the Korean population via linkage with the KNHANES, which ensures generalizability to the Korean population.

Conclusions

In conclusion, a higher LCD score was associated with a lower prevalence of atherogenic dyslipidemia and HDL cholesterolemia, whereas higher fat intake was associated with a higher prevalence of hypercholesterolemia among Korean adults. Several gut microbial genera and ASVs, such as *Bifidobacterium*, *Bifidobacterium* ASV1, *Lachnospiraceae UCG–004*, *Lachnospiraceae UCG–004* ASV3, and *Lachnoclostridium* may regulate hypertriglyceridemia, low–HDL cholesterolemia, and hypercholesterolemia via interactions with fat or carbohydrate intake in the Korean population.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12937-025-01188-4.

Supplementary Material 1

Supplementary Material 2

Author contributions

SC conducted data analysis and wrote the first draft. JHS and YDN curated data explanation. SC, JHK, KBK, and MYL edited the manuscript. MYL was in charge of overall research supervision. All authors have read and approved the final manuscript.

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Data availability

Data of KNHANES are available in a public, open access repository [https://knhanes.kdca.go.kr/knhanes/eng/main.do]. Data of the 16S rRNA gene sequencing used in this study are available in the European Nucleotide Archive under accession numbers PRJEB33905 and PRJEB87500 [https://www.ebi.ac.uk/ena/].

Declarations

Ethics approval and consent to participate

The KMS was approved by the Institutional Review Board (IRB) of Chung–Ang University Hospital (Seoul, Republic of Korea) (approval number: 1750–002–281) and Chungbuk Hospital (Chungbuk, Republic of Korea) (approval number: 2019–04–014). The protocols for data collection of KNHANES were approved by the IRB of the KDCA (approval numbers: 2018–01–03–P–A, 2018–01–03–C–A, and 2018–01–03–2 C–A). All participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Abbreviations

ASV, amplicon sequence variant.
HDL–C, high–density lipoprotein–cholesterol.
KMS, Korean Microbiome Study.
KNHANES, Korea National Health and Nutrition Examination Survey.
LCD, low carbohydrate diet.
LDL–C, low–density lipoprotein–cholesterol.
TC, total cholesterol.
TG, triglyceride.

Clinical trial number
Not applicable.

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