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Associations of low-carbohydrate diets patterns with the risk of hyperuricemia: a national representative cross-sectional study in Korea

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Abstract

Background The association between low-carbohydrate diets and hyperuricemia risk, a significant risk factor for gout and cardiometabolic morbidities, remains inconclusive, partly due to differing effects of replacing carbohydrates with animal- or plant-based macronutrients. This study examined associations between low-carbohydrate diet patterns and hyperuricemia risk in 39,880 adults in the Korea National Health and Nutritional Examination Study 2016–2022.

Methods Diet was assessed via a 24-hour dietary recall. The overall, animal-rich, and plant-rich low-carbohydrate diet score (LCDS) was calculated based on percent energy derived from protein and fat in animal and plant food sources. Hyperuricemia was defined as serum uric acid levels > 7.0 mg/dL for men and > 6.0 mg/dL for women. Multivariate-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression models to estimate the risk of hyperuricemia across quintiles of LCDS.

Results A significantly greater risk of hyperuricemia was observed among individuals with higher overall LCDS (OR for quintile 5 vs. quintile 1 [Q5vs.Q1]: 1.41, 95%CI:1.22–1.63, P-trend: <0.001) and animal-rich LCDS ($OR_{Q5vs.Q1}$: 1.28, 95%CI:1.12–1.47, P-trend: <0.001), but not with plant-rich LCDS ($OR_{Q5vs.Q1}$: 1.00, 95%CI: 0.87–1.16). These positive associations for overall LCDS and animal-rich LCDS were evident in overweight individuals (OR_{Q5vsQ1}: 1.53, 95%CI: 1.29–1.82 for overall LCDS; and 1.39, 95%CI: 1.19–1.63 for animal-rich LCDS; all P-trends < 0.001), but not in non-overweight individuals (all P-interactions: <0.001).

Conclusions In our study, animal-based low-carbohydrate diets were associated with a greater risk of hyperuricemia, while no association was observed for plant-based low-carbohydrate diets. Larger cohort studies are warranted to replicate these findings.

Keywords Hyperuricemia, Low-carbohydrate diet, Animal-rich low-carbohydrate diet, Plant-rich low-carbohydrate diet

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Introduction

Hyperuricemia, a condition characterized by an elevated serum uric acid level, is emerging as a significant global public health concern [1]. Hyperuricemia constitutes a primary risk factor for gout, the most prevalent form of inflammatory arthritis, which affects approximately 56.47 million worldwide as of 2021 [1–3]. Moreover, hyperuricemia frequently coexists with various cardiometabolic and cardiovascular disorders [4–6], and is recognized as an independent risk factor for renal pathologies [7], obesity [8], hypertension [9], diabetes mellitus [9], nonalcoholic fatty liver disease [10], and mortality [4, 11]. Nonetheless, preventive and therapeutic strategies for hyperuricemia remain suboptimal, exacerbating its rising prevalence [1, 12].

Uric acid is the end product of purine metabolism that can rise due to either excessive production or inefficient excretion, both of which can be influenced by diet [13–15]. The low-carbohydrate diet, widely adopted for weight loss and cardiometabolic health [16], has recently been investigated for its role managing uric acid levels [1, 2, 5, 9, 17]. However, it contrasts with traditional guideline to limit protein intake, a major purine source, as the low-carbohydrate diet typically increases protein and fat intake [13, 16]. Studies on low-carbohydrate diets and serum uric acid levels also have yielded mixed results [18–23]. A meta-analysis of six randomized controlled trials (RCT) [18] and other trial [19] reported no association [18, 19], while other RCTs [20–22] and another trial [23] found decreases [20, 21, 23] and increases [22] in serum urate levels following a low-carbohydrate diet.

The explanation behind the controversial results, though limited, remains unclear. However, growing evidence suggests that the selection of food sources of fats and proteins to replace carbohydrates does matter than the quantity of micronutrition composition in a low-carbohydrate diet [24, 25]. In a Health Professionals Follow-up Study, high intake of meat or seafood intake was associated with a 41% and 51% greater risk of gout, respectively [26]. However, such associations were not seen with purine-rich vegetables or total protein [26]. Subsequent analyses also found higher urate levels with greater consumption of animal protein, red meat, and seafoods, while increasing consumption of purine-vegetable or plant protein was associated with lower urate levels [27–33]. Collectively, these findings imply the impact of low-carbohydrate diets on uric acid levels may vary depending on the composition of food sources rather than merely the quantity of macronutrients replaced. This perspective may help reconsider the role low-carbohydrate diets in the context of hyperuricemia, where they have traditionally been discouraged.

However, to date, no studies have yet investigated how low-carbohydrate diet patterns could influence hyperuricemia risk. Therefore, we examined associations between the overall low-carbohydrate diets–differentiating those rich in animal versus plant foods–and the risk of hyperuricemia in the general Korean adult population, who typically consume carbohydrate-rich diets [34] and are at higher hyperuricemia risk [35], capitalizing on a nationally representative data from the Korea National Health and Nutrition Examination Survey (KNHANES) [36].

Materials & methods

Study design and study population

This study analyzed data from the KNHANES study 2016–2022 [36]. The KNHANES is an ongoing, nationwide, population-based, annual cross-sectional study conducted by the Korea Centers for Disease Control and Prevention (KCDC). The KNHANES aims to assess the health and nutritional status of civilian, non-institutionalized Koreans. The survey employs a complex, stratified, multi-stage clustered probability sampling methods to ensure a representative sample and enrolled Koreans aged ≥ 1 years, selected from 600 districts across cities and provinces in Korea. The KNHANES comprises a health interview, a health examination, and a nutrition survey, all conducted by trained interviewers or laboratory technicians. It provides extensive data on participants' demographic, socioeconomic, anthropometric, dietary, health-related lifestyles, medical conditions, and medical history. All KNHANES protocols were approved by the institutional review boards of the KCDC, and participants provided written informed consent. This study adheres to the principles of the Helsinki Declaration was approved by the institutional Review Board of Ewha Womans University (IRB no. ewha-202409-0011-01).

For this study, out of 43,900 participants with survey sampling weights from the KNHANES 2016–2022 cycles, we excluded those who met the following exclusion criteria: individuals who were aged less than 19 years (N = 8,140), pregnant or breastfeeding women (N = 237), those who reported no dietary data or implausible energy intake (< 500 kcal/day or > 5000 kcal/day; N = 587), and those who did not have a measurement of serum uric acid (N = 976). Consequently, a total of 33,960 participants were included in the analysis (Fig. 1).

Assessment of low-carbohydrate diets

Diet was assessed by a 24-hour recall. Trained staff conducted face-to-face interviews and obtained the participants' food and beverage intake consumed during the day prior to the staffs' visit. Daily nutrient intakes from each food item were calculated based on the national standard food composition Table [37] and total daily nutrients intakes for each participant were estimated by summing the nutrient intake from all consumed food items.

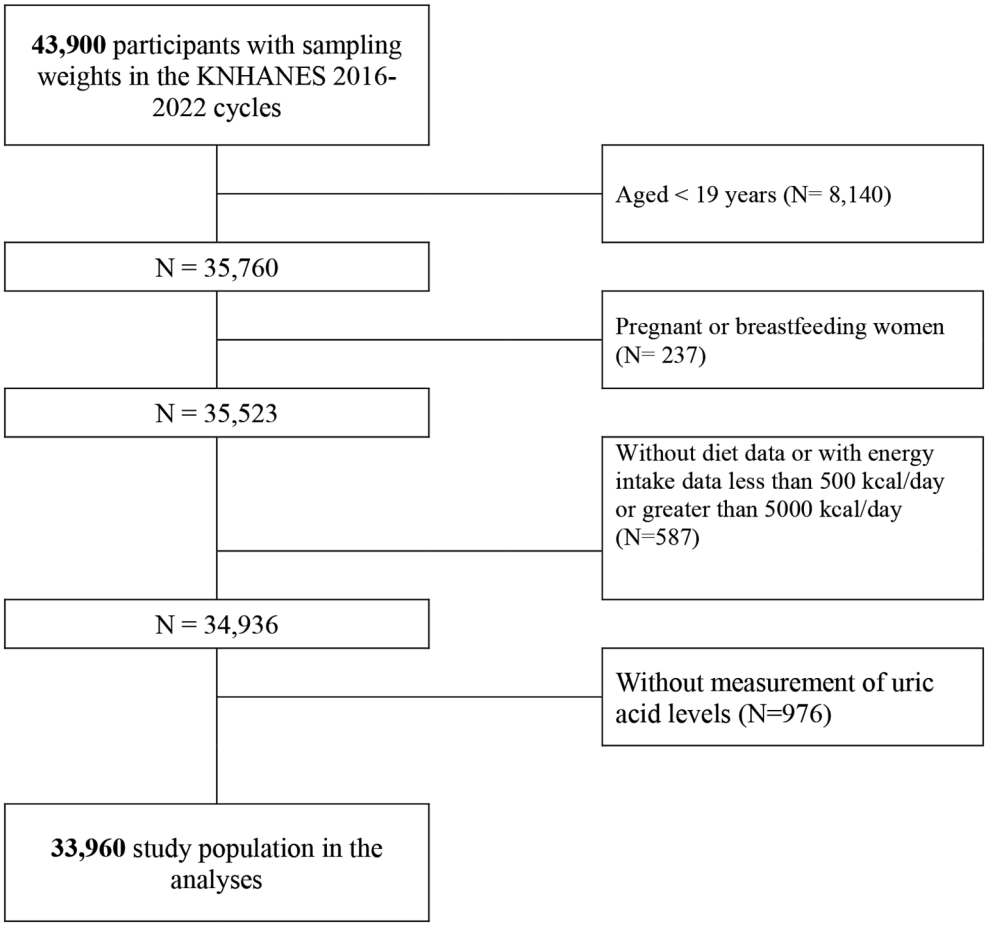

Fig. 1 Flow chart of study population, *Abbreviation*: KNHANES, Korea National Health and Nutrition Examination Survey

This study assessed the adherence to the low-carbohydrate diets by calculating the low-carbohydrate diet score (LCDS) [38]. In brief, the LCDS is a low-carbohydrate diet score algorithm that integrates ranks of energy contribution from macronutrients [38]. Participants were divided into 11 equal strata based on the energy percentage from carbohydrates, proteins, or fats. Macronutrient specific scores were then calculated as follows: for protein and fat scores, 0 point was assigned to participants in the lowest stratum and 10 points to those in the highest stratum. The carbohydrate score was assigned in reverse, with 0 point for those in the highest stratum and 10 points for those in the lowest stratum. The three scores were then summed to calculate the overall LCDS, ranging from 0 (lowest for fat or protein, highest for carbohydrates) to 30 (highest for fat or protein, lowest for carbohydrates). A higher LCDS represents a greater likelihood of consuming low-carbohydrates in the diet. Additionally, animal- and plant- based LCDSs were calculated using animal-derived fats and proteins and plant-derived fats and proteins, respectively, to displace total fats and proteins.

Ascertainment of hyperuricemia

Blood samples were collected from participants who fasted ≥ 8-hours overnight, then immediately centrifuged and transferred to the central laboratory within 24 h (Neodin Medical Institute, Seoul, Korea). The serum uric acid levels were determined by colorimetry with the uricase–catalase system (Hitachi automatic analyzer 7600–210, Japan). Individuals were determined to have hyperuricemia if their serum uric acid level was > 7.0 mg/dL for men and > 6.0 mg/dL for women [39]. As a result, a total of 3,347 hyperuricemia cases were determined in this study.

Assessment of other covariates

A standardized, self-reported questionnaire was administered to gather detailed information on socio-demographics (age, sex, education, and household income), health-related lifestyle factors (physical activity, smoking status, and alcohol consumption), and medical history [36]. Participants reported the frequency and average intensity of their smoking and alcoholic drinking behavior. Physical activity was assessed by using the global physical activity questionnaire. The total physical activity

level was estimated by multiplying the average number of hours and frequencies of each physical activity spent per week with the specific metabolic equivalent task value and summing those across all activities. Weight and height were measured, and body mass index (BMI) was calculated as weight (kg)/height (m^2). The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration Eqs. [40, 41], which incorporates sex, age, race, and serum level of creatinine. The presence of diabetes was determined if participants had a fasting serum glucose level ≥ 126 mg/dl, received a diagnosis of physician or used oral hypoglycemic drugs or insulin injections [42]. Hypertension was defined if participants had ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic blood pressure (BP) from the average of two BP readings or used an antihypertensive medicine [42]. Hypercholesterolemia was determined if participants had a fasting serum cholesterol level ≥ 240 mg/dL or used cholesterol lowering agents [42].

Statistical analyses

In our descriptive analyses of population characteristics, we estimated the means and standard deviations for continuous variables and the proportions for categorical variables across quintiles of overall LCDS. We primarily investigated the association between low-carbohydrate diet patterns and the risk of hyperuricemia using a logistic regression model, and we calculated the multivariable-adjusted odds ratio (MVOR) and 95% confidence interval (95% CI) across quintiles of overall, animal-rich, and plant-rich LCDS. The multivariable-model adjusted for well-established risk factors and potential confounding factors of hyperuricemia [1, 39], including age (quintiles, years), sex (men, women), household income (low, middle-low, middle-high, high), educational level (elementary school, middle school, high school, college or higher), smoking status (never, past, current), alcoholic consumption (never, past, current, < 2 times/week, ≥ 2 times/week), physical activity (quintiles, MET-min/week), BMI (< 18.5, ≥ 18.5-<23.0, ≥ 23.0-<25.0, ≥ 25.0 kg/m^2), eGFR (continuous, ml/min/1.73 m^2), hypertension (yes, no), diabetes (yes, no), hypercholesterolemia (yes, no) and intake of total energy (quintiles, kcal/day) and fruits and vegetables (quintiles, kcal/day). A missing indicator was used for covariates with missing data, where applicable. The trend p-value was calculated by modelling the median value within each quintile of LDSC as a continuous term.

In sensitivity analyses, the robustness of the results was tested by including fiber or water or restricting the analysis to participants without reduced kidney function, defined as eGFR less than 60 ml/min/1.73 m^2 [40, 41]. We also performed subgroup analyses to evaluate heterogeneity in the associations across strata of BMI [43], age [32], sex [32], total energy intake [18, 43] and the presence of diabetes [43]. The interaction significance was tested by including the product term between the LCDS and stratification factors.

Secondarily, we conducted substitution analyses to estimate the effects of replacing carbohydrate-derived energy with equivalent energy from total fat, total protein, and macronutrients from specific food sources, applying the nutrition density model [44, 45]. The substitution models included the percent of energy from total fat and protein along with the total energy and other covariates in the primary LCDS model. To estimate the substitution effects for animal or plant-derived macronutrients, we simultaneously adjusted for the percent of energy from both animal and plant sources in the model. The coefficient from the substitution analysis can be interpreted as the estimated isocaloric effect of replacing carbohydrates with specific macronutrients with the same energy percentage.

All analyses were analyzed at a two-tailed alpha level of 0.05 using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA) and applied the sampling weights to account for the multistage sampling design of KNHANES and to generate unbiased national estimates.

Results

Table 1 presents the characteristics of the study population according to quintiles of LCDS. Participants in the higher quintiles of LDCS tended to be younger, more likely male, and had higher income and education levels. These individuals were also more likely to be current smokers, consume alcohol, and engage in physically activity. Moreover, they had a higher total energy intake, but consumed less fiber and fewer fruits and vegetables. The prevalence of diabetes, hypertension, and hypercholesterolemia decreased with higher LCDS. The distribution of other variables remained similar across the quintiles of LCDS.

In the multivariable-adjusted analyses of low-carbohydrate diet patterns, overall LCDS was significantly associated with a higher risk of hyperuricemia (Table 2). The OR of hyperuricemia comparing the highest versus lowest quintiles of overall LCDS was 1.41 (95% CI: 1.22–1.63; P-trend < 0.001). This positive association was observed to vary by the sources of macronutrients in the LCDS. The animal-rich LCDS was significantly associated with a greater risk of hyperuricemia (OR for quintile 5 vs. quintile 1 [Q5 vs. Q1]: 1.28, 95% CI: 1.12–1.47, P-trend < 0.001). In contrast, plant-rich LCDS had no association ($OR_{Q5\ vs.Q1}$: 1.00, 95% CI: 0.87–1.16, P-trend: 0.75). These findings of overall, animal-rich, and plant-rich LCDS did not change materially in sensitivity analyses adjusting for fiber (Supplementary Table 1) or water

Table 1 Population characteristics across quintiles of low carbohydrate diet scores in KNHANES 2016–2022 ($N = 33,960$)

	Quintiles of overall low-carbohydrate diet score				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
Socio-demographic factors					
Age, years	59.9 ± 0.28	51.2 ± 0.27	47.0 ± 0.25	44.1 ± 0.23	41.1 ± 0.25
Sex					
Men	2,472 (40.1)	3,327 (50.9)	3,352 (53.6)	3,123 (52.3)	2,282 (50.2)
Women	4,416 (59.3)	4,117 (49.1)	3,895 (46.4)	3,805 (47.7)	3,171 (49.8)
Education					
Elementary school	2,542 (29.3)	1,410 (12.9)	788 (7.0)	515 (4.7)	293 (3.2)
Middle school	1,022 (13.5)	899 (9.7)	703 (7.1)	459 (4.8)	294 (3.7)
High school	1,543 (25.6)	2,085 (29.1)	2000 (27.6)	1,779 (24.2)	1,295 (22.2)
College or higher	1,276 (24.5)	2,656 (43.5)	3,441 (54.2)	3,898 (62.2)	3,404 (67.7)
Household income					
Low	2,567 (30.9)	1,684 (17.9)	1,104 (12.0)	828 (9.9)	570 (8.7)
Middle-low	1,791 (25.8)	1,956 (24.9)	1,802 (23.5)	1,584 (21.1)	1,163 (20.1)
Middle-high	1,357 (22.7)	1,933 (28.1)	2,099 (30.9)	2,043 (30.8)	1,638 (30.6)
High	1,141 (19.9)	1,843 (28.8)	2,227 (33.3)	2,453 (37.9)	2,077 (40.5)
Health-related behaviors					
Body mass index, kg/m^2					
<18.5	242 (3.8)	272 (4.2)	291 (4.2)	281 (4.3)	245 (4.7)
18.5-<23.0	2,431 (36.0)	2,707 (36.5)	2,760 (37.1)	2,713 (38.7)	2,118 (37.6)
23.0-<25.0	1,637 (23.4)	1,764 (23.5)	1,632 (22.5)	1,533 (21.3)	1,172 (21.5)
≥25.0	2,483 (35.6)	2,632 (35.1)	2,514 (35.7)	2,356 (35.1)	1,891 (35.7)
Smoking status					
Never	4,598 (64.2)	4,500 (56.7)	4,387 (57.0)	4,266 (58.6)	3,617 (62.4)
Past	1,364 (20.0)	1,575 (21.9)	1,557 (21.8)	1,371 (19.9)	1,056 (20.8)
Current	815 (14.1)	1,301 (20.5)	1,256 (20.5)	1,243 (20.9)	761 (16.5)
Alcohol consumption					
Never	1,479 (18.0)	961 (9.9)	652 (6.6)	517 (6.0)	329 (4.5)
Past	1,606 (22.3)	1,397 (16.7)	1,175 (14.1)	1,049 (13.8)	779 (12.4)
Current, < 2 times/wk	2,780 (43.4)	3,413 (49.3)	3,704 (53.9)	3,750 (56.1)	3,212 (61.0)
Current, ≥ 2 times/wk	923 (14.7)	1,607 (23.2)	1,670 (24.7)	1,568 (23.5)	1,115 (21.7)
Physical activity, METs-min/wk	728.5 ± 21.8	922.8 ± 25.5	921.6 ± 21.5	1004.7 ± 24.6	1158.5 ± 28.8
Dietary intake					
Energy intake	1,588.6 ± 10.7	1,836.8 ± 10.7	1,957.5 ± 11.2	2,054.8 ± 11.8	2,106.2 ± 14.9
Carbohydrate, %E	78.0 ± 0.07	66.8 ± 0.15	60.2 ± 0.13	54.0 ± 0.12	44.7 ± 0.14
Protein, %E	10.8 ± 0.03	12.8 ± 0.04	14.4 ± 0.05	16.2 ± 0.06	19.4 ± 0.07
Animal protein, %E	2.6 ± 0.03	5.0 ± 0.04	7.0 ± 0.05	9.3 ± 0.06	13.3 ± 0.08
Plant protein, %E	8.2 ± 0.03	7.8 ± 0.03	7.4 ± 0.03	6.9 ± 0.03	6.0 ± 0.04
Fat, % E	10.3 ± 0.06	15.6 ± 0.07	20.5 ± 0.08	25.6 ± 0.10	33.9 ± 0.12
Plant fat, %E	3.0 ± 0.04	5.9 ± 0.05	8.7 ± 0.07	12.6 ± 0.10	19.6 ± 0.17
Animal fat, %E	7.3 ± 0.06	9.8 ± 0.07	11.8 ± 0.09	13.0 ± 0.11	13.3 ± 0.01
Fruit and vegetable, g/d	489.0 ± 6.2	470.2 ± 5.1	447.8 ± 4.7	429.4 ± 4.3	393.3 ± 4.8
Fiber, g/d	26.1 ± 0.27	26.0 ± 0.20	25.7 ± 0.18	25.0 ± 0.18	22.9 ± 0.21
Medical condition					
eGFR, ml/min/1.73 m^2	93.3 ± 0.28	98.8 ± 0.26	102.0 ± 0.24	103.8 ± 0.23	105.9 ± 0.26
Uric acid, mg/dL	5.0 ± 0.02	5.2 ± 0.02	5.3 ± 0.02	5.3 ± 0.02	5.4 ± 0.02
Diabetes, %	1,358 (17.4)	1,156 (13.0)	861 (10.1)	673 (8.2)	457 (7.1)
Hypertension, %	3,333 (43.0)	2,845 (32.7)	2,255 (27.4)	1,744 (21.6)	1,140 (18.3)
Hypercholesterolemia, %	2,052 (28.1)	2,000 (23.7)	1,721 (21.4)	1,555 (19.7)	1,142 (18.4)

Abbreviation: E, energy; eGFR, estimated glomerular filtration rate, METs, metabolic equivalent tasks; Q, quintile

Values are means (SD) for continuous variables or frequencies (percentages) for categorical variables

Table 2 Age- and multivariable[1]–adjusted odds ratios (OR) and 95% confidence intervals (CIs) of hyperuricemia according to quintiles of low-carbohydrate diet scores

	Quintiles (Q) of diet scores					*P*-trend[2]
	Q1	Q2	Q3	Q4	Q5	
Overall low-carbohydrate diet score						
Median	4	11	16	21	26	
N. cases/ N. non-cases	718/6,170	894/6,550	848/6,399	822/6,106	750/4,703	
Age-adjusted OR (95% CIs)	1.00 (ref)	1.28 (1.13–1.45)	1.28 (1.13–1.45)	1.18 (1.04–1.34)	1.42 (1.24–1.63)	< 0.001
MV-adjusted OR (95% CIs)	1.00 (ref)	1.21 (1.06–1.38)	1.22 (1.07–1.40)	1.13 (0.99–1.30)	1.41 (1.22–1.63)	< 0.001
Animal-rich low-carbohydrate diet score						
Median	4	11	16	21	26	
N. cases/ N. non-cases	809/6,863	734/6,209	743/5,702	874/5,586	872/5,568	
Age-adjusted OR (95% CIs)	1.00 (ref)	1.07 (0.95–1.22)	1.17 (1.03–1.33)	1.34 (1.19–1.52)	1.35 (1.19–1.53)	< 0.001
MV-adjusted OR (95% CIs)	1.00 (ref)	1.06 (0.93–1.21)	1.16 (1.01–1.33)	1.31 (1.15–1.50)	1.28 (1.12–1.47)	< 0.001
Plant-rich low-carbohydrate diet score						
Median	8	12	15	18	23	
N. cases/ N. non-cases	887/6,472	783/5,698	790/5,825	950/7,175	622/4,758	
Age-adjusted OR (95% CIs)	1.00 (ref)	1.00 (0.88–1.21)	1.00 (0.89–1.23)	0.98 (0.87–1.10)	0.95 (0.83–1.08)	0.42
MV-adjusted OR (95% CIs)	1.00 (ref)	0.97 (0.85–1.11)	0.96 (0.84–1.09)	1.02 (0.90–1.16)	1.00 (0.87–1.16)	0.75

[1] Multivariable model was adjusted for age (quintiles, years), sex (men, women), household income (low, middle-low, middle-high, high), educational level (elementary school, middle school, high school, college or higher), smoking status (never, past, current), alcoholic consumption (never, past, < 2 times/week, ≥ 2 times/week), physical activity (quintiles, MET-min/week), BMI (< 18.5, ≥ 18.5-<23.0, ≥ 23.0-<25.0, ≥ 25.0 kg/m^2), eGFR (continuous, ml/min/1.73 m^2), hypertension (yes, no), diabetes (yes, no), hypercholesterolemia (yes, no) and intakes of total energy (quintiles, kcal/day) and fruits and vegetables (quintiles, g/day)

[2] P-trend was calculated by including the median value within each quintile of low-carbohydrate diet scores as a continuous term

(Supplementary Table 2) or when excluding participants with reduced kidney function (Supplementary Table 3).

In substitution analyses (Table 3), an increasing percentage of energy intake from animal fat substituting for carbohydrates was associated with a suggestive, though non-significant, higher risk of hyperuricemia. ($OR_{Q5\ vs.Q1}$: 1.13, 95% CI: 0.97–1.31, P-trend: 0.03). Conversely, replacing carbohydrates with the percentage of energy intake from plant protein was marginally significantly associated with a lower risk of hyperuricemia ($OR_{Q5\ vs.Q1}$: 0.85, 95% CI: 0.73-1.00, P-trend: 0.07). No associations were observed for total fat, plant fat, total protein, or animal protein intakes.

Notably, the associations between overall LCDS and animal-rich LCDS with hyperuricemia risk exhibited significant heterogeneity by BMI (All P-interactions: <0.001) (Table 4). The positive association was pronounced and evident in the overweight group ($MVOR_{Q5\ vs.Q1}$: 1.53, 95% CI: 1.29–1.82 for overall LCDS and 1.39, 95% CI: 1.19–1.63, for animal-rich LCDS, all P-trends < 0.001). In contrast, the positive associations were attenuated and became no longer significant in the non-overweight group. No other substantial heterogeneity was observed across other subgroups stratified by age, sex, energy intake, and diabetes (Supplementary Tables 4–6).

Discussion

In this large national study of Korean adults, greater adherence to overall and animal-rich low-carbohydrate diets was associated with a greater risk of hyperuricemia, whereas plant-rich low-carbohydrate diets exhibited no such association. Likewise, substituting animal fat for carbohydrates appeared to be associated with higher risk of hyperuricemia, while substituting it for plant protein was associated with a lower risk, though these results were not statistically significant. Theses associations were stronger among overweight individuals, with no significant associations observed in non-overweight individuals. No considerable heterogeneity in associations were detected across subgroups by age, sex, energy intakes, or diabetes.

The low-carbohydrate diet, which restricts carbohydrate intake while increasing protein and fat consumption [46], has gained considerable attention since the mid-19 century due to the carbohydrate-insulin axis hypothesis, which suggests that reducing carbohydrate intake lowers insulin levels, affecting glycemic control, lipid metabolism, adiposity, and cardiometabolic function. Since then, the low-carbohydrate diet has been widely adopted for weight loss, metabolic enhancement, and glycemic management. Indeed, a recent large systematic review of 121 RCTs with 21,942 overweight adults confirmed its short-term greater efficacy in achieving modest weight loss and improvements in cardiovascular risk factors, compared to standard or popular alternative diets, though its long-term effects remain uncertain [16]. Another subsequent review of 51 RCTs with 4,164 adults also found greater benefits of low-carbohydrate diet over low-fat diets over low-fat diets on inflammatory markers [47].

Table 3 Age- and multivariable- adjusted[1] odds ratios (OR) and 95% confidence intervals (CIs) of hyperuricemia according to quintiles of specific types of dietary fat and dietary protein substituting for carbohydrate intakes

	Quintiles (Q) of intake					*P*-trend[1]
	Q1	Q2	Q3	Q4	Q5	
Total fat, % of energy						
Median, %	8.8	14.4	19.0	24.2	32.8	
N. cases/ N. non-cases	852/5,940	759/6,033	765/6,027	787/6,005	869/5,923	
Age-adjusted OR (95% CI)	1.00 (ref)	0.88 (0.78-1.00)	0.94 (0.83–1.08)	0.89 (0.78–1.01)	0.91 (0.80–1.04)	0.42
MV-adjusted OR (95% CI)[2]	1.00 (ref)	0.93 (0.81–1.07)	1.04 (0.90–1.20)	0.98 (0.84–1.13)	1.09 (0.94–1.26)	0.12
Animal fat, % of energy						
Median, %	1.1	4.4	7.5	11.5	19.9	
N. cases/ N. non-cases	796/5,996	753/6,039	783/6,009	822/5,970	878/5,914	
Age-adjusted OR (95% CI)	1.00 (ref)	0.94 (0.82–1.06)	1.02 (0.89–1.17)	1.06 (0.93–1.21)	1.01 (0.88–1.16)	0.49
MV-adjusted OR (95% CI)[3]	1.00 (ref)	0.95 (0.83–1.10)	1.08 (0.94–1.25)	1.15 (1.00-1.32)	1.13 (0.97–1.31)	0.03
Plant fat, % of energy						
Median, %	4.0	6.7	9.5	12.9	19.4	
N. cases/ N. non-cases	888/5,904	801/5,991	818/5,974	730/6,062	795/5,997	
Age-adjusted OR (95% CI)	1.00 (ref)	0.93 (0.82–1.05)	0.94 (0.83–1.06)	0.82 (0.72–0.94)	0.86 (0.75–0.94)	0.01
MV-adjusted OR (95% CI)[4]	1.00 (ref)	1.00 (0.88–1.14)	1.02 (0.89–1.17)	0.92 (0.80–1.06)	1.03 (0.89–1.19)	0.93
Total protein, % of energy						
Median, %	10.0	12.3	14.0	16.0	19.8	
N. cases/ N. non-cases	856/5,936	741/6,051	783/6,009	806/5,986	846/5,946	
Age-adjusted OR (95% CI)	1.00 (ref)	0.86 (0.76–0.97)	0.97 (0.86–1.11)	1.04 (0.91–1.18)	1.05 (0.93–1.19)	0.04
MV-adjusted OR (95% CI)[5]	1.00 (ref)	0.88 (0.76–1.01)	0.98 (0.85–1.13)	1.06 (0.92–1.21)	1.01 (0.88–1.16)	0.22
Animal protein, % of energy						
Median, %	2.0	6.3	7.4	8.6	10.4	
N. cases/ N. non-cases	772/6,020	736/6,056	780/6,012	853/5,939	891/5,901	
Age-adjusted OR (95% CI)	1.00 (ref)	1.02 (0.88–1.17)	1.05 (0.92–1.21)	1.16 (1.01–1.33)	1.14 (0.98–1.32)	0.04
MV-adjusted OR (95% CI)[6]	1.00 (ref)	1.06 (0.92–1.24)	1.06 (0.91–1.24)	1.12 (0.96–1.30)	1.07 (0.91–1.26)	0.50
Plant protein, % of energy						
Median, %	4.6	6.3	7.4	8.6	10.4	
N. cases/ N. non-cases	1,011/5,781	827/5,965	718/6,074	772/6,020	704/6,088	
Age-adjusted OR (95% CI)	1.00 (ref)	0.80 (0.72–0.91)	0.74 (0.65–0.84)	0.81 (0.72–0.93)	0.76 (0.66–0.89)	< 0.001
MV-adjusted OR (95% CI)[7]	1.00 (ref)	0.88 (0.77-1.00)	0.80 (0.70–0.92)	0.90 (0.77–1.03)	0.85 (0.73-1.00)	0.07

Abbreviation: Q, quintile

[1] P-trend was calculated by including the median value within each quintile of energy percent of macronutrient as a continuous term

[2] Model adjusted for variables in the multivariable-model in Table 2 and additionally adjusted for total protein (quintiles, % energy)

[3] Model adjusted for variables in the multivariable-model in Table 2 and additionally adjusted for total protein (quintiles, % energy) and plant fat (quintiles, % energy)

[4] Model adjusted for variables in the multivariable-model in Table 2 and additionally adjusted for total protein (quintiles, % energy) and animal fat (quintiles, % energy)

[5] Model adjusted for variables in the multivariable-model in Table 2 and additionally total fat (quintiles, % energy)

[6] Model adjusted for variables in the multivariable-model in Table 2 and additionally total fat (quintiles, % energy) and plant protein (quintiles, % energy)

[7] Model adjusted for variables in the multivariable-model in Table 2 and additionally total fat (quintiles, % energy) and animal protein (quintiles, % energy)

However, whether the short-term metabolic benefits of a low-carbohydrate diet extend to modulate uric acid levels remains unclear. The conventional guideline for hyperuricemia recommends restricting high-protein foods because of their purine content, conflicting with the high protein nature of low-carbohydrate diets [48]. Indeed, a Japanese study reported purine concentrations 1.5 times above the recommended threshold in a low-carbohydrate diet [49]. Our findings of an increased hyperuricemia risk with greater adherence to a low-carbohydrate diet al.ign with these guidelines. Similarly, two RCTs of 349 overweight adults [19] and 20 healthy adults [22] found significant elevations of serum uric acid levels at 5 [22] and 70 days [19] on low-carbohydrate diets, although these effects diminished after one year [19]. Conversely, an RCT of 235 obese adults [20] and a pilot study of 13 gout patients [23] reported reductions in serum urate at 6 and 12 months, respectively, following a low-carbohydrate diet intervention. A meta-analysis of six RCTs of 39 to 55 overweight adults on ketogenic diet – a very strict form of low carbohydrate diet – over 8 to 16 week found no significant uric acid alterations [18].

The reason for discrepancies between previous studies and our findings are unclear. However, many prior

Table 4 Multivariable-adjusted[1] odds ratios (OR) and 95% confidence intervals (CIs) of hyperuricemia according to the quintiles of low-carbohydrate diet score stratified by body mass index

Stratification factors	*N.* case /*N.* non-cases	Quintiles of diet scores					*P*-trend[2]	*P*-interaction[3]
		Q1	Q2	Q3	Q4	Q5		
		Overall low-carbohydrate diet score						
Body mass index, kg/m^2								
< 23.5	845/13,215	1.00 (ref)	1.18 (0.90–1.53)	1.22 (0.92–1.60)	1.09 (0.83–1.43)	1.13 (0.84–1.52)	0.67	< 0.001
≥ 23.5	3,133/16,481	1.00 (ref)	1.24 (1.06–1.45)	1.25 (1.07–1.48)	1.18 (1.00-1.39)	1.53 (1.29–1.82)	< 0.001	
		Animal-rich low-carbohydrate diet score						
Body mass index, kg/m^2								
< 23.5	845/13,215	1.00 (ref)	0.96 (0.73–1.26)	0.95 (0.72–1.27)	1.19 (0.89–1.56)	1.08 (0.81–1.44)	0.28	< 0.001
≥ 23.5	3,133/16,481	1.00 (ref)	1.12 (0.96–1.30)	1.26 (1.07–1.47)	1.39 (1.19–1.63)	1.39 (1.19–1.63)	< 0.001	
		Plant-rich low-carbohydrate diet score						
Body mass index, kg/m^2								
< 23.5	845/13,215	1.00 (ref)	0.85 (0.66–1.11)	0.90 (0.68–1.19)	0.81 (0.62–1.05)	0.80 (0.60–1.08)	0.13	0.70
≥ 23.5	3,133/16,481	1.00 (ref)	1.03 (0.88–1.20)	0.99 (0.85–1.15)	1.11 (0.95–1.29)	1.09 (0.92–1.29)	0.18	

Abbreviation: Q, quintile

[1] Multivariable model was adjusted for age (quintiles, years), sex (men, women), household income (low, middle-low, middle-high, high), educational level (elementary school, middle school, high school, college or higher), smoking status (never, past, current), alcoholic consumption (never, past, < 2 times/week, ≥ 2 times/week), physical activity (quintiles, MET-min/week), BMI (< 18.5, ≥ 18.5-<23.0, ≥ 23.0-<25.0, ≥ 25.0 kg/m^2), eGFR (continuous, ml/min/1.73 m^2), hypertension (yes, no), diabetes (yes, no), hypercholesterolemia (yes, no) and intakes of total energy (quintiles, kcal/day) and fruits and vegetables (quintiles, g/day)

[2] P-trend was calculated by including the median value within each quintile of low-carbohydrate diet score as a continuous term

[3] P-interaction was tested by including the product term between stratification factors and low-carbohydrate diet score

studies were small and short-term small feeding trials predominantly focused on low-calorie, low-carbohydrate diets (600 and 1,800 kcal/day), often resulting in weight loss and metabolic improvements in glucose, insulin, and lipids [18–23]. Furthermore, unlike our study of general population, earlier studies were secondary analyses of RCTs involving individuals with obesity, gout, or hyperuricemia, who may benefited more from metabolic improvements due to their pre-existing elevated uric acid levels [18–23]. This complicates disentangling whether the mixed results were attributable to the diet al.one, weight loss or other health benefits, or a combination of both. Large studies using isocaloric, low-carbohydrate diets in health populations are required to clarify these inconsistencies.

Notably, increasing evidence suggests that food sources, rather than merely the quantities of protein and fat, are pivotal to health outcomes [24, 25]. A meta-analysis of 12 cohort studies with 483,615 adults and 68,876 mortality events found no association between total protein and overall mortality [50], but identified an 8% reduction for all-cause mortality and 5% for cardiovascular disease (CVD) mortality with high plant protein intake, whereas animal protein intake increased CVD mortality by 11%. Similarly, a prospective study of 407,531 adults with 185,111 overall deaths and 58,526 CVD deaths found a 9% and 14% risk reduction in overall and CVD mortality with high plant fat intake. Conversely, high animal fat intake increased these risks by 16% and 14%, respectively [51]. These suggest that discrepancies in hyperuricemia risk associated with low-carbohydrate diets may stem from dietary source variation in the low-carbohydrate diet rather than micronutrient composition alone.

To our knowledge, this study is the first to examine how different low-carbohydrate diet patterns affect hyperuricemia. We found that low-carbohydrate diets with animal-based sources were more strongly associated with higher risk of hyperuricemia than those with plant-based sources. Supporting this finding, a meta-analysis of ten cohorts and nine cross-sectional studies showed that animal-derived foods, particularly from red meat and seafood, raised hyperuricemia risk by 29%~31%, whereas soy foods and purine rich vegetables were associated with a reduction in risk by 15 ~ 16% [27]. These findings were corroborated by subsequent pooled analyses of five large cohorts [28], one cohort [33]. and three cross-sectional studies [29–31]. Additionally, some nutrient analyses, though not all [52], support these findings, reporting associations of animal protein with increased risk [32, 53] and plant protein with an inverse [32] or no association [53].

Our finding of greater risk of hyperuricemia from animal-rich low-carbohydrate diets, compared to plant-rich ones, aligns with several evidence. Animal-derived foods, such as animal meats or processed meats, typically contain purine levels two to ten times higher than plant foods. Moreover, over half of these purines are in forms of hypoxanthine, which rapidly converts to uric acids, whereas plant-based purines predominantly consist of adenine and guanine, which exert minimal impact on uric acid levels [14]. Additionally, animal foods are high

in saturated fats, which may exacerbate inflammation, oxidative stress, and kidney dysfunction, the primary organ responsible for approximately 80% of uric acid excretion [54]. In contrast, plant-based foods are rich in phytochemicals and antioxidants, which may inhibit uric acid reabsorption and formation, while mitigating metabolic disturbances [25]. Taken together, our findings confirm the varying effect of food sources on health risks and further suggest that the type of low-carbohydrate diet-animal-based or plant-based - can have distinct effects on hyperuricemia risk.

In the sub-group analyses, positive association between low-carbohydrate diets and the risk of hyperuricemia was stronger among overweight individuals than non-overweight adults. Though the precise mechanism remains elusive, insulin resistance, frequently associated with adiposity, has been documented to exhibit anti-uricosuric properties by disturbing glycolysis and impeding renal uric acid clearance [55–57]. Additionally, a previous study found that sugar-sweetened beverages exert a more deleterious effect on serum urate among adults with higher BMI [58]. Our results might indicate that individuals with excess body weight is more susceptible to the adverse effects of animal-rich low-carbohydrate diets on uric acid levels [55].

Our study had several limitations. The cross-sectional design limits causal inference. We examined only moderate low-carbohydrate diets (highest category: 44.7%) and were unable to assess stricter versions like the Akins diet. The 24-hour recall dietary data may introduce random error, but macronutrient variability is relative minimal [59]. A single measurement of uric acid may limit precision, but its reliability is generally high (intra class classification: 0.8–0.9 [60, 61]. Residual and unmeasured confounding, such as use of uric acid-lowering agents or diuretics, cannot be ruled out, but is unlikely in this healthy population. Finally, the results generalization to other races needs caution due to high carbohydrate consumption and genetic predisposition to hyperuricemia in Asian [35].

Notwithstanding this limitation, this is the first study to explore the differential effects of macronutrient substitutions in low-carbohydrate diets on hyperuricemia risk, utilizing a large, nationally representative sample of the general adult population. Rigorous data collection conducted by trained on diets, lifestyles, anthropometrics, laboratory markers, and medical histories and extensive adjustments for confounders, along with subgroup analyses, enhance the robustness of our findings.

Conclusion

In conclusion, in this nationally representative cross-sectional study of Korean adults, greater adherence to a low-carbohydrate diet, particularly one characterized by a predominance of animal-based foods, not plant-based foods, was associated with a higher risk of hyperuricemia. This association appeared to be more pronounced in overweight individuals, compared to non-overweight counterparts. Although low-carbohydrate diets have gained considerable popularity for managing overweight and cardiometabolic disorders, their role in lowering uric acid remains contentious. Further large-scale cohort studies are warranted to determine whether the composition of food sources within low-carbohydrate diets may influence the risk of hyperuricemia.

Abbreviations

BMI	Body mass index
BP	Blood pressure
CVD	Cardiovascular disease
LCDS	Low-carbohydrate diet score
eGFR	Estimated glomerular filtration rate
KCDC	Korea Centers for Disease Control and Prevention
KNHENAS	Korea National Health and Nutrition Examination Study
%E	Percent energy
RCT	Randomized controlled trial

Supplementary Information

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Supplementary Material 1

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Not applicable.

Author contributions

SJ designed, conducted statistical analyses, drafted and revised the paper. Y.J.P. critically reviewed the manuscript and contributed to the interpretation of data. SJ had primary responsibility for final content. All authors reviewed and approved the final manuscript.

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Data availability

The datasets analyzed during the current study are available in the KNHANES website, https://knhanes.kdca.go.kr

Declarations

Ethical approval

All KNHANES protocols were approved by the institutional review boards of the KCDC, and participants provided written informed consent. This study the study adheres to the principles of the Helsinki Declaration and was approved by the institutional Review Board of Ewha Womans University (IRB no. ewha-202409-0011-01).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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