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Joint Effect of Inflammatory Dietary Patterns and Physical Activity on the Risk of Depressive Symptoms: A Nation-Wide Cross-Sectional Study

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Purpose: Depression is a major global public health concern. Diet and physical activity are major modifiable lifestyle factors associated with depression; however, their joint effects have not been fully addressed. This cross-sectional study aimed to quantitatively examine the interaction between physical activity and inflammatory nutrients in depression and utilized Bayesian kernel machine regression (BKMR) models to compare the effects of inflammatory nutrients on depression in individuals with and without physical activity.
Materials and Methods: The inflammatory diet was assessed using the dietary inflammatory index (DII), while physical activity levels were measured using the Global Physical Activity Questionnaire, with sufficient physical activity defined as achieving 600 metabolic equivalent task minutes per week. Depression was defined as a 9-item Patient Health Questionnaire score of ≥10. We used multiple logistic regression and BKMR models to investigate the associations between the DII and depression, with all models adjusted for covariates.
Results: A total of 4110 participants from the 2020 Korea National Health and Nutrition Examination Survey were included in this study. Notably, participants with higher total DII scores were more likely to have depressive symptoms, and the additive interaction between insufficient physical activity and inflammatory nutrients was attributed to a 36% risk of depression. Moreover, BKMR analyses showed that individuals with insufficient physical activity exhibited a greater risk of depression posed by pro-inflammatory dietary patterns and did not benefit from anti-inflammatory dietary patterns with regard to the risk of depression.
Conclusion: Comprehensive plans for diet control and increased physical activity are essential to help prevent depression.

Key Words: Dietary inflammatory index, physical activity, depression, Bayesian kernel machine regression approach

INTRODUCTION

Depression is a major public health concern, affecting approximately 320 million people worldwide.[1] It is one of the leading causes of non-fatal health loss and premature death,[2] and its prevalence has rapidly increased over the years; however, only modest advances in its treatment have been made.[3] Therefore, preventive measures against depression are urgently required. As low-grade inflammation is an important aetiology of depression,[4] lifestyle modifications that can downregulate the inflammatory process may represent a viable measure to prevent depression.

A daily diet containing pro-inflammatory and anti-inflammatory nutrients has the ability to modify the risk of depression by altering the production of inflammatory cytokines, such as interleukin (IL)-6, IL-10, tumour necrosis factor alpha, and C-reactive protein.[4] These inflammatory cytokines can cross the blood-brain barrier to enter the brain and affect neurotrans-

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mission, neurogenesis, and the activity of the hypothalamic-pituitary-adrenocortical (HPA) axis.[4] Notably, recent studies have identified an association between depression and the dietary inflammatory index (DII), a novel parameter that reflects the inflammatory potential of nutrients.[4-7] However, most previous studies have mainly focused on the impact of a few individual nutrients (e.g., vitamin D and omega-3) without considering their interactions in the entire diet.[8] Moreover, although the association between depression and some dietary patterns, such as the Mediterranean and Dietary Approaches to Stop Hypertension diets, has previously been examined, strict adherence to these diets is often challenging. As a result, the findings may not fully reflect the typical diet of individuals.[4] These gaps in the current knowledge could potentially be resolved by the recent development of the Bayesian kernel machine regression (BKMR) model, a novel statistical tool for analyzing high-dimensional exposure-outcome functions considering the interactions among various exposures and covariates.[9] Compared to linear regression analysis, the BKMR method can account for the multicollinearity among nutrients by estimating their joint effects without the need to assume linear relationships.[9]

Another potential modifiable factor in the prevention of depression is physical activity, which influences a wide range of the biological and psychological pathways involved in depressive symptoms.[10] In fact, recent evidence has emphasized the ability of exercise to downregulate various inflammatory mediators, significantly reducing the risk of depression.[10,11]

Thus far, it has been well-documented that both physical activity and nutrient intake modify the risk of depression by altering the inflammatory process;[4,10,11] however, the interaction between these two factors remains unclear.

Therefore, in the current study, we aimed to quantitatively examine the interaction between physical activity and nutrient intake with regard to the risk of depression and utilize BKMR models to compare the impact of dietary inflammatory properties on the risk of depression between individuals with sufficient physical activity and those with insufficient physical activity.

MATERIALS AND METHODS

Study population

We selected participants from the 2020 Korea National Health and Nutrition Examination Survey (KNHANES) for inclusion in this study. The KNHANES is a cross-sectional survey of a nationwide representative sample of South Korea,[12] comprising three domains: health interviews, health examinations, and nutritional surveys. All procedures were performed by the Korea Center for Disease Control and Prevention (KCDC).[12]

From the 7359 participants in the 2020 KNHANES, we selected adult participants aged 18 years and older who completed the 9-item Patient Health Questionnaire (PHQ-9), 24-h dietary recall interview, and Global Physical Activity Questionnaire (GPAQ). Of the 4165 selected participants, we excluded 55 with missing data on their main demographic characteristics [age, sex, body mass index (BMI), education level, employment status, smoking, and alcohol consumption]. As a result, 4110 participants were included in the final analysis.

Dietary measurement

We used the DII to evaluate the inflammatory potential of the participants' diets. The DII can be calculated using data from several assessment tools, including 24-h recall interviews, food frequency questionnaires, and food records.[13] In the present study, we used input data from a validated 24-h recall interview to calculate the DIIs of 22 dietary nutrients, including carbohydrates, protein, fiber, total fat, cholesterol, saturated fat, monounsaturated fat, polyunsaturated fat, n-6 fatty acid, n-3 fatty acid, vitamin A, β-carotene, vitamin B1, vitamin B2, niacin, folate, vitamin C, vitamin D, vitamin E, iron, magnesium, and zinc. The DII links personal nutrient intake with the national representative database, which provides reliable means and standard deviations for each nutrient.[13,14] First, we calculated the standardized z-score by subtracting the "standard mean" from the individual's nutrient intake and dividing this value by its "standard deviation". Subsequently, the z-score was converted to a percentile score, multiplied by 2, and subtracted by 1 to obtain a symmetrical distribution centred at 0. The centered percentile score of each nutrient was then multiplied by a corresponding inflammatory effect score adapted according to the research by Shivappa, et al.[13] For each nutrient, a positive DII mean or median value indicated a pro-inflammatory pattern, whereas a negative value indicated an anti-inflammatory pattern. For each participant, the DIIs of all 22 dietary nutrients were summed to obtain the overall DII score, which represented the inflammatory potential of their entire diet.

Physical activity measurement

The 2020 KNHANES used the GPAQ—introduced by the World Health Organization—to collect participants' physical activities in the following three domains: activities at work, leisure activities, and travelling (walking/cycling).[15] Using this GPAQ data, we calculated the participants' metabolic equivalent task minutes (MET-minutes). We assigned MET values of 8 and 4 for high-intensity and moderate-intensity physical activity or walking/cycling from place to place, respectively.[15] Subsequently, we multiplied the MET value by the duration of physical activity (in minutes) per week to obtain the MET-minutes/week. Sufficient physical activity was considered to be achieved if an individual reached at least 600 MET-minutes/week.

Depressive symptoms

Depressive symptoms or depression were evaluated using the PHQ-9. The PHQ-9 is a reliable and valid screening tool for assessing the severity of depression,[16] consisting of nine questions that examine the participants' symptoms over the past 2 weeks.

Each question represents a criterion for diagnosing major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. Each question was scored from 0 (no symptoms at all) to 3 (symptoms occurred almost every day), and the total score of the nine questions ranged from 0 to 27, with higher scores indicating more severe depression.[16] In this study, we defined depression as having a PHQ-9 score of ≥10. This cut-off value demonstrated a sensitivity of 88% and a specificity of 88% for major depressive disorder diagnosis and was preferred in most previous studies.[16]

Covariables

Age (years), BMI (kg/m^2), sex (male/female), education level (primary, secondary, high school, and college), employment status (employed/unemployed), smoking status (present/absent), alcohol drinking status (present/absent), and daily energy intake (kcal/day) were selected as covariates. The selection of these covariates was based on the findings of previous studies on DII and depression.[5] The smoking status was determined according to participants' answers in the survey and their urinary cotinine test (having ≥50 ng/mL cotinine), while alcohol consumption was defined as consumption of at least 12 alcoholic drinks per year.

Statistical analysis

All statistical analyses were performed using R software version 4.3.2. We performed descriptive analyses to describe participants' demographic characteristics, with continuous variables presented as mean±SD or median (interquartile range) and categorical variables presented as numbers and percentages. For continuous variables, we used the independent Student's t-test or Mann–Whitney U test to compare the two groups. In contrast, for categorical variables, the chi-square test or Fisher's exact test was performed to compare the two groups. All statistical tests were two-tailed, with the significance level set at $p<0.05$.

Multiple logistic regression was conducted to examine the association between the total DII scores and depression, and odds ratios (OR) were calculated. Additionally, we performed subgroup analyses of individuals with and without sufficient physical activity to examine whether insufficient physical activity altered the association between DII and depression. All logistic regression models were adjusted for all covariates, and to examine the effect of physical activity on the relationship between total DII score and depression, we calculated the ratio of ORs to identify significant differences between the ORs found in the subgroup analyses.[17]

To further evaluate the effects of the interaction between physical activity and an inflammatory diet on depression, we performed interaction analyses, including the relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and synergy index (SI). These three indicators were calculated as follows:[18] $RERI=RR_{11}-RR_{10}-RR_{01}+1$; $AP=(RR_{11}-RR_{10}-RR01+1)/RR_{11}=RERI/RR_{11}$; and $SI=(RR_{11}-1)/[(RR_{01}-1)+(RR_{10}-1)]$.

RR_{ab} was defined as the relative risk (RR) in the group with exposures "a" (insufficient physical activity) and "b" (the most pro-inflammatory diet, defined as the total DII score in the 4th quartile) when compared with the non-exposed group (1=exposed, 0=not exposed). In this study, we used ORs from logistic regression models to approximate the RR since the prevalence of depression was low and our sample size was relatively large.

In our analyses, an RERI and AP of 0 indicated no interaction, whereas a positive value for the RERI or AP indicated a positive interaction. Moreover, an SI of 1 indicated no interaction and an SI >1 indicated a positive interaction.[18]

Finally, BKMR models were used to estimate the effects of individual nutrients and the entire diet (all nutrients at the same time) on the risk of depression prevalence (presence vs. absence) in individuals with and without sufficient physical activity. In each subgroup, we used two separate BKMR models for nutrients with pro-inflammatory and anti-inflammatory patterns. BKMR analyses also identified interactions among the different nutrients in an individual's diet.[9] All BKMR models used in this study underwent 20000 iterations using the Markov chain Monte Carlo method and were adjusted for all covariates. However, since the BKMR model does not test the null hypothesis as other classical statistical methods do, we should refrain from any conventional discussions on statistical power or specific cut-off values.[19] Therefore, in our study, we determined the effects of individual nutrients and the entire diet using the median and 95% confidence intervals (CIs) as reference points.

Ethics

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the Institutional Review Board of the KCDC (approval no. 2018-01-03-2C-A). Written informed consent was obtained from all subjects.

RESULTS

Baseline characteristics of the participants

A total of 4110 Korean adults from the 2020 KNHANES database were included in this study. The median age of the participants was 53.0 (38.0–65.0) years, with females accounting for 56.7% of the sample population. Overall, 219 (5.3%) out of 4110 participants were diagnosed with depressive symptoms. The baseline characteristics of all participants are presented in Table 1. Notably, the proportions of participants that were female or unemployed were significantly higher among individuals with depression than among those without depression. Furthermore, individuals with depressive symptoms had

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Table 1. Baseline Characteristics of 4110 Korean Adults Included in the Study

Characteristics	Total (n=4110)	Depressed (n=219)	Non-depressed (n=3891)	*p* value
Age	53.0 (38.0–65.0)	48.0 (32.0–64.0)	53.0 (39.0–65.0)	0.050
Sex				<0.001
Male	1779 (43.3)	67 (30.6)	1712 (44.0)	
Female	2331 (56.7)	152 (69.4)	2179 (56.0)	
BMI (kg/m^2)	23.9 (21.7–26.3)	24.1 (21.7–27.4)	23.9 (21.7–26.3)	0.130
Educational level				<0.001
Primary school	692 (16.8)	49 (22.4)	643 (16.5)	
Secondary school	410 (10.0)	28 (12.8)	382 (9.8)	
High school	1428 (34.7)	90 (41.1)	1338 (34.4)	
College	1580 (38.5)	52 (23.7)	1528 (39.3)	
Employment status				<0.001
Unemployed	1672 (40.7)	137 (62.6)	1535 (39.5)	
Employed	2438 (59.3)	82 (37.4)	2356 (60.5)	
Smoking status				0.004
Yes	1635 (39.8)	108 (49.3)	1527 (39.2)	
No	2475 (60.2)	111 (50.7)	2364 (20.8)	
Alcohol drinking				0.140
Yes	2857 (69.5)	142 (64.8)	2715 (69.8)	
No	1253 (30.5)	77 (35.2)	1176 (30.2)	
Physical activity				0.140
Sufficient	1747 (42.5)	83 (37.9)	1665 (42.8)	
Insufficient	2363 (57.5)	136 (62.1)	2226 (57.2)	
Daily energy intake (kcal/day)	1705.5 (1272.9–2230.4)	1542.8 (1043.6–2027.7)	1711.4 (1283.3–2238.1)	<0.001

BMI, body mass index.
Data are presented as median (Interquartile range) or n (%).

a lower daily energy intake and a higher proportion of smokers.

The median total DII score of Korean adults in our study was 0.539 (-0.893, 1.581). Supplementary Table 1 (only online) shows the median DII for 22 individual nutrients and the total DII score. Notably, of the 22 dietary nutrients, 16 were considered to have pro-inflammatory patterns (DII >0), including vitamin C, folate, niacin, vitamin B2, vitamin B1, β-carotene, vitamin E, vitamin D, vitamin A, zinc, magnesium, fibre, n-6 fatty acid, n-3 fatty acid, polyunsaturated fatty acid, and monounsaturated fatty acid. The other six nutrients (protein, iron, carbohydrates, cholesterol, saturated fatty acids, and total fat) showed anti-inflammatory patterns.

Association between the total DII and depression

We found that participants with higher total DII scores were more likely to have depressive symptoms (OR 1.18, 95% CI 1.04–1.33, *p*=0.008). Moreover, upon subgroup analysis, the risk of depression increased significantly with the total DII score in individuals with insufficient physical activity (OR 1.20, 95% CI 1.01–1.42, *p*=0.040). In contrast, a higher total DII score did not significantly increase the risk of depression in individuals with sufficient physical activity (OR 1.14, 95% CI 0.95–1.39, *p*=0.160). Nevertheless, the difference between the two estimates was not statistically significant (OR 0.95, 95% CI 0.74–1.23, *p*=0.730).

Joint effect of inflammatory dietary nutrients and physical activity on depression

Notably, we observed positive values of RERI and SI >1 when assessing the additive interaction between insufficient physical activity and the highest quartile of the total DII [RERI: 1.21 (-0.01–2.44, *p*=0.030); SI: 2.09 (0.93–4.67), *p*=0.040]. By calculating the AP, we found that 36% of the risk of depression was attributable to the interaction between these two risk factors (Table 2).

Effect of pro-/anti-inflammatory nutrients on depression in individuals with and without sufficient physical activity

BKMR analyses of both unadjusted (Supplementary Figs. 1 and 2, only online) and adjusted models (Figs. 1 and 2) showed that increased intake of all nutrients with pro-inflammatory patterns significantly increased the risk of depression in individuals with and without sufficient physical activity. However, the adjusted BKMR models showed that the estimated depression risk was greater in participants with insufficient physical activity than in those with sufficient physical activity when the same quartile of the nutrient mixture was reached (Figs. 1A and 2A). The posterior inclusion probabilities of individual nutrients were also higher in the BKMR model for the sedentary participants (Figs. 1B and 2B).

Table 2. Inflammatory Diet and Insufficient Physical Activity as Risk Factors for Depression: Single Effects, Joint Effect, and Measures of Interaction on Additive Scales

	Inflammatory diet (absent)			Inflammatory diet (present)			Effect of inflammatory diet within the strata of insufficient physical activity		
	OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value
Insufficient physical activity (absent)	1	Reference		1.87	1.28–2.73	0.001	1.87	1.28–2.73	0.001
Insufficient physical activity (present)	1.25	0.86–1.80	0.240	3.33	2.29–4.86	<0.001	2.67	1.75–4.07	<0.001
Effect of insufficient physical activity within the strata of inflammatory diet	1.25	0.86–1.80	0.240	1.78	1.16–2.75	0.009			
Multiplicative scale									
RERI	1.21	-0.01–2.44	0.030						
AP	0.36	0.08–0.65	0.007						
SI	2.09	0.93–4.67	0.040						

OR, odds ratio; CI, confidence interval; RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction; SI, synergy index.

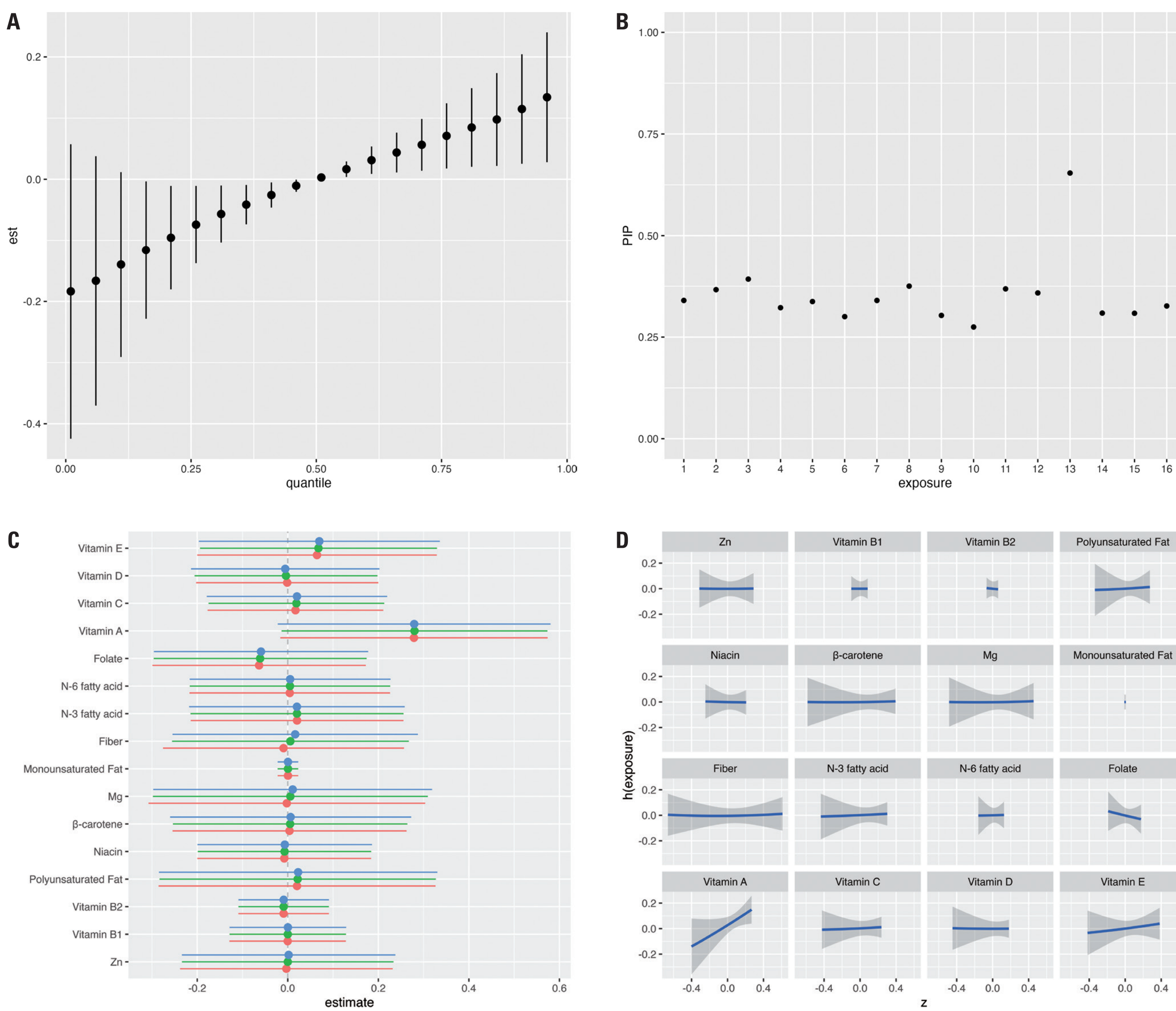

Fig. 1. Association between depression and nutrients with pro-inflammatory patterns in individuals with sufficient physical activity, according to the BKMR model. (A) The risk of depression when all nutrients were at a particular percentile compared to when all nutrients were at their 50th percentile (estimates and 95% CIs). (B) Posterior inclusion probability of the individual nutrients. (C) The single-nutrient effect (estimates and 95% CIs) when all the remaining nutrients were fixed to a particular percentile (25th, red line; 50th, green line; and 75th, blue line). (D) The univariate relationship between individual nutrients and the risk of depression, where all the other nutrients were fixed to a particular percentile. BKMR, Bayesian kernel machine regression; CI, confidence interval; PIP, posterior inclusion probability.

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Regarding the effects of individual nutrients, insufficient vitamin A intake was associated with an increased the risk of depression in the sufficient physical activity group; however, this association did not reach statistical significance (Fig. 1C and D). Notably, anti-inflammatory nutrients had an overall protective effect against depression in participants with sufficient physical activity in both unadjusted and adjusted models (Supplementary Fig. 3A, only online and Fig. 3A). The unadjusted BKMR model detected this protective effect on participants with insufficient physical activity (Supplementary Fig. 4A, only online). However, in the unadjusted model, the individual effects of total fat and carbohydrate were the main contributors to the overall effect (Supplementary Fig. 4C and D, only online). These two components usually constitute a high proportion of total daily energy; thus, when we adjusted for covariates, including total daily energy, these effects were diminished (Fig. 4). No interactions were found among the 16 nutrients with pro-inflammatory patterns or the six nutrients with anti-inflammatory patterns (Supplementary Fig. 5, only online).

DISCUSSION

This study demonstrated that the total DII of dietary nutrients

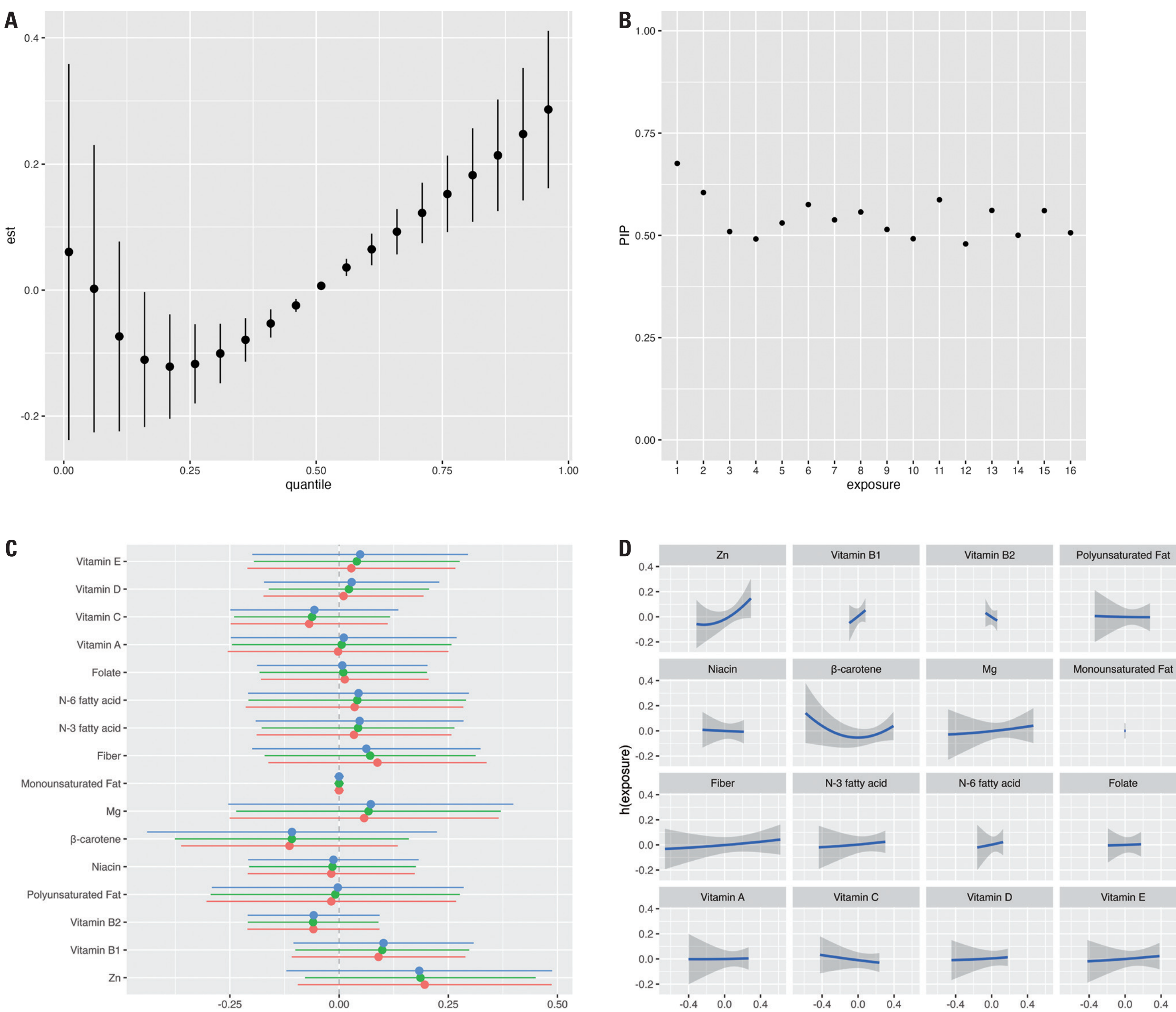

Fig. 2. Association between depression and nutrients with pro-inflammatory patterns in individuals with insufficient physical activity, according to the BKMR model. (A) The risk of depression when all the nutrients were at a particular percentile compared to when all nutrients were at their 50th percentile (estimates and 95% CIs). (B) Posterior inclusion probability of the individual nutrients. (C) The single-nutrient effect (estimates and 95% CIs) when all the remaining nutrients were fixed to a particular percentile (25th, red line; 50th, green line; and 75th, blue line). (D) The univariate relationship between individual nutrients and the risk of depression, where all the other nutrients were fixed to a particular percentile. BKMR, Bayesian kernel machine regression; CI, confidence interval; PIP, posterior inclusion probability.

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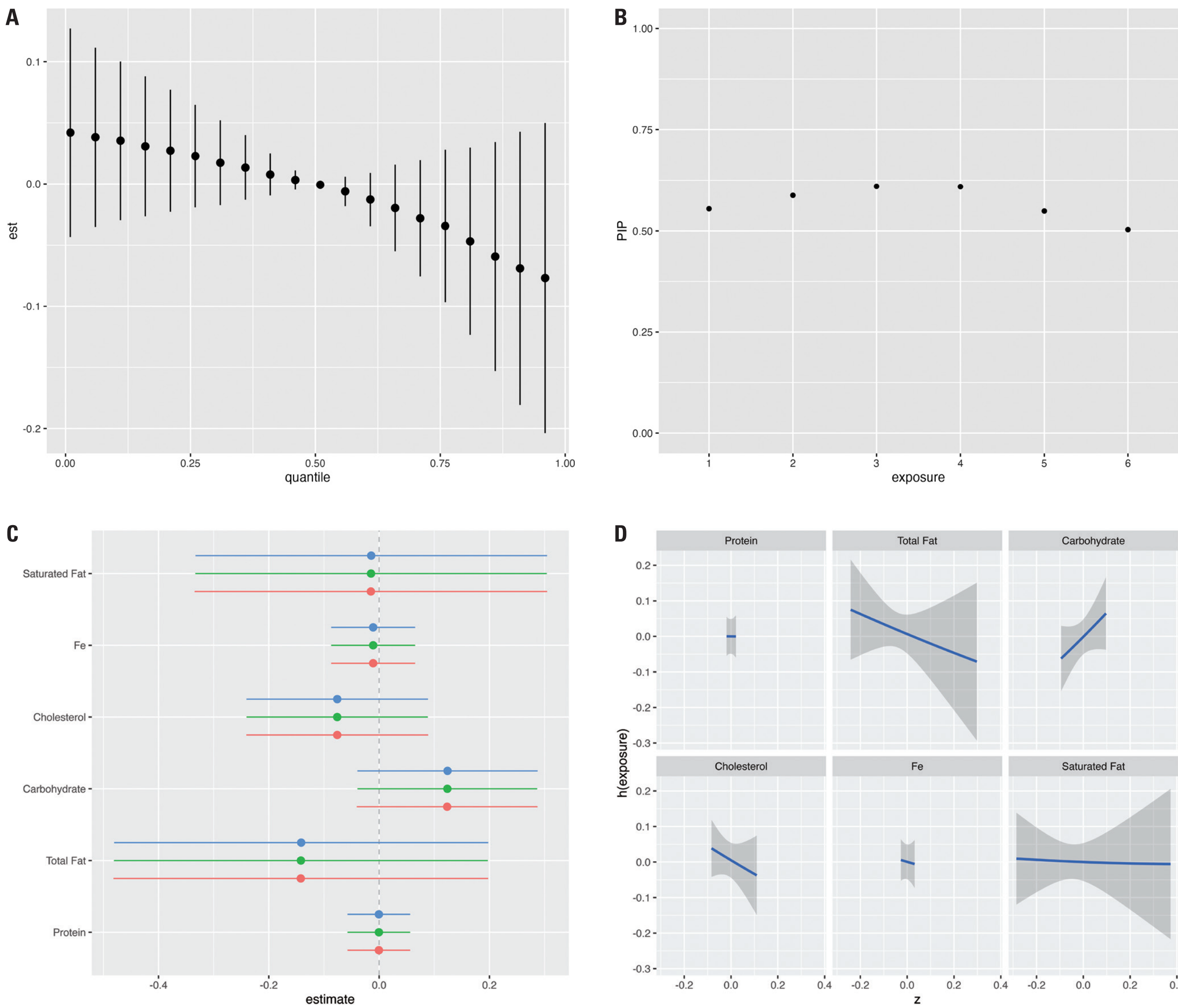

Fig. 3. Association between depression and nutrients with anti-inflammatory patterns in individuals with sufficient physical activity, according to the BKMR model. (A) The risk of depression when all the nutrients were at a particular percentile compared to when all the nutrients were at their 50th percentile (estimates and 95% CIs). (B) Posterior inclusion probability of the individual nutrients. (C) The single-nutrient effect (estimates and 95% CIs) when all the remaining nutrients were fixed to a particular percentile (25th, red line; 50th, green line; and 75th, blue line). (D) The univariate relationship between individual nutrients and the risk of depression, where all the other nutrients were fixed to a particular percentile. BKMR, Bayesian kernel machine regression; CI, confidence interval; PIP, posterior inclusion probability.

is positively associated with the risk of depression in Korean adults. We found that nutrients with pro-inflammatory patterns increased the risk of depression, while nutrients with anti-inflammatory patterns were protective against depression. Moreover, compared with active individuals, those with a sedentary lifestyle suffered from a more remarkable impact of pro-inflammatory nutrients and fewer protective effects of anti-inflammatory nutrients. We demonstrated the effect of additive interactions between the highest quartile of the total DII and insufficient physical activity on the risk of depression. To the best of our knowledge, this study is the first to quantify the synergistic effects of dietary nutrients and physical activity on the risk of depression using additive and BKMR models.

The findings of the current study are consistent with those of previous reports.[6,7,20,21] For example, we found that a higher total DII score was associated with an 18% increase in the odds of depression, which was similar to the findings of previous studies by Shakya, et al.,[7] Luo, et al.,[20] and Zhao, et al.[6] Meanwhile, few studies have examined the effects of physical activity on the relationship between nutrient intake and depression. A study by Wang, et al.[21] found that individuals with both a pro-inflammatory diet and insufficient physical activity had a significantly higher risk of depression than individuals with just one or none of these two risk factors. However, to the best of our knowledge, no previous study has quantitatively examined the additive effects of these two lifestyle-modifiable fac-

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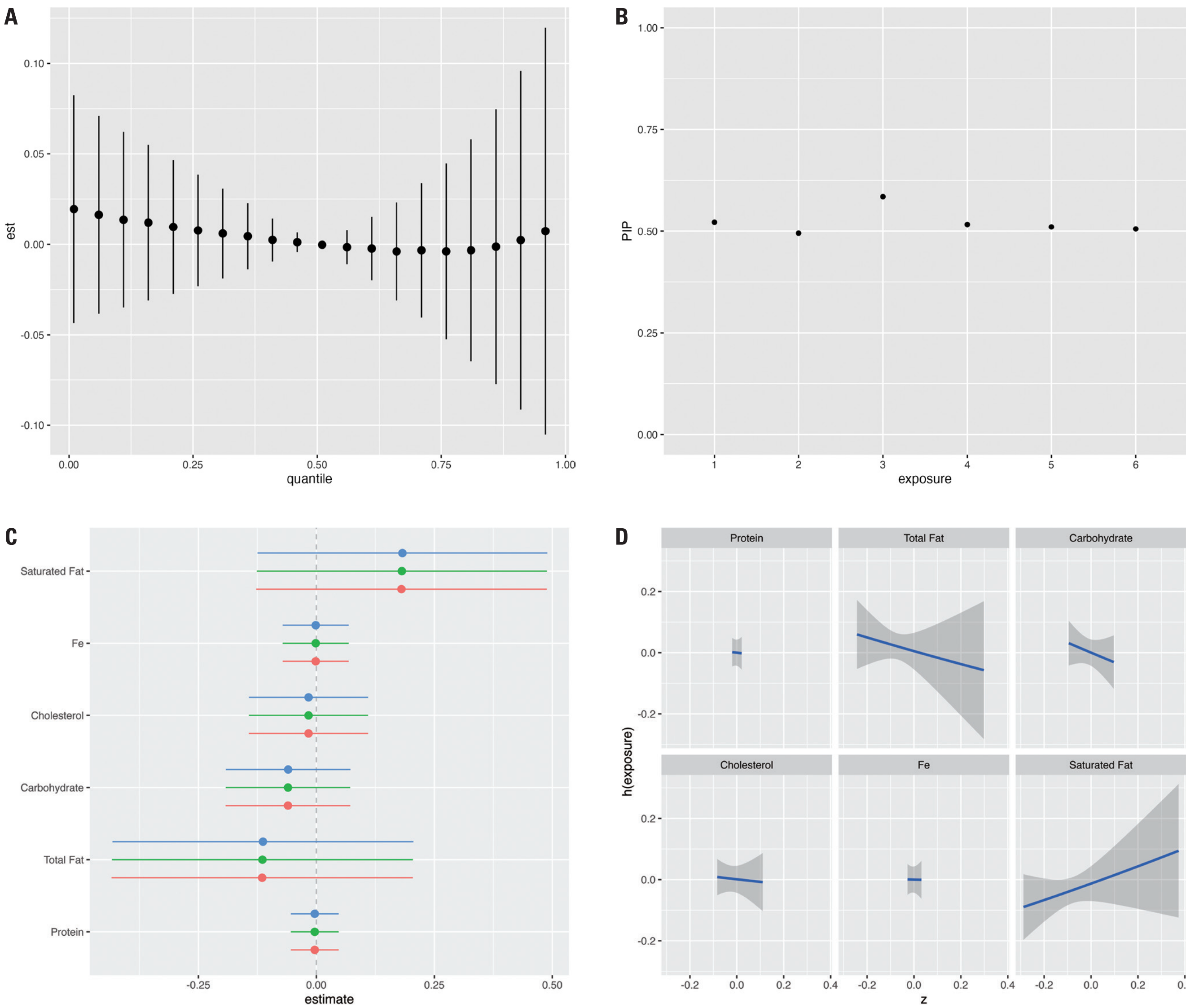

Fig. 4. Association between depression and nutrients with anti-inflammatory patterns in individuals with insufficient physical activity, according to the BKMR model. (A) The risk of depression when all the nutrients were at a particular percentile compared to when all the nutrients were at their 50th percentile (estimates and 95% CIs). (B) Posterior inclusion probability of the individual nutrients. (C) The single-nutrient effect (estimates and 95% CIs) when all the remaining nutrients were fixed to a particular percentile (25th, red line; 50th, green line; and 75th, blue line). (D) The univariate relationship between individual nutrients and the risk of depression, where all the other nutrients were fixed to a particular percentile. BKMR, Bayesian kernel machine regression; CI, confidence interval; PIP, posterior inclusion probability.

tors on depression risk. Therefore, our study demonstrated a novel finding of an additive interaction between insufficient physical activity and the highest quartile of the total DII, with a 36% risk of depression attributable to the additive interaction. Considering this additive interaction and the high odds of depression in individuals with both risk factors, it is critical to maintain at least an active lifestyle or a healthy eating habit with a limited intake of pro-inflammatory nutrients to prevent depression. In fact, a previous study by You, et al.[22] indicated that a more pro-inflammatory diet tends to attenuate the protective effects of leisure physical activity against depression. Interestingly, in the current study, sufficient physical activity was likely to buffer the negative impact of a pro-inflammatory diet on the development of depressive symptoms. A higher total DII score—representing a more inflammatory diet—was significantly associated with a higher risk of depression in inactive individuals but not in active individuals, though we did not find a significant risk difference between the two groups.

To date, only a few studies have used BKMR to estimate the combined effects of dietary nutrients.[5] A previous study by Li, et al.[5] found a cumulative inflammatory effect of nutrients on the risk of depression and no interaction among the 11 nutrients included in the BKMR model. Our findings on 22 nutrients (16 with pro-inflammatory patterns and six with anti-inflammatory patterns) were consistent with the results of Li, et al.[5] Moreover, we found that the inflammatory effects of nutri-

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ents on depression were mediated by physical activity. Higher quantiles of all nutrients with pro-inflammatory patterns resulted in a higher risk of depression in both subgroups, but the overall effect was more remarkable in inactive participants than in active participants. Similarly, the impact of individual nutrients on depression, as indicated by the higher posterior inclusion probability in the models, was more consistently significant in the inactive group than in the active group. In contrast, nutrients with anti-inflammatory patterns demonstrated a protective effect against depression in individuals with sufficient physical activity, but not in individuals with insufficient physical activity. These findings imply that physical activity is necessary to optimize the effects of an anti-inflammatory diet in preventing depression. Therefore, our results reaffirm the application of comprehensive lifestyle changes, including regular exercise and a higher intake of anti-inflammatory nutrients and/or a lower intake of pro-inflammatory nutrients, to help prevent depression.

Previous studies have indicated that both an inflammatory diet and an inactive lifestyle can upregulate low-grade inflammatory processes.[4,10] This could potentially explain the additive effects of the two factors. Another possible explanation may be related to the increase in body weight and decrease in fatty acids released from adipose tissues caused by both an inflammatory diet and inactivity.[4,10,23] This, in turn, may lead to the upregulation of adipose-induced chronic low-grade inflammation,[4,10,23] which is believed to cause depressive symptoms by altering neurotransmission, neurogenesis, and the HPA axis.[23,24] Inflammation affects neurotransmission by reducing the synaptic availability of serotonin, noradrenaline, and dopamine.[23,24] Furthermore, it decreases the production of brain-derived neurotrophic factor (BDNF), which is required for neurogenesis.[23,24] A reduction in synaptic monoamines and BDNF is believed to be the main pathophysiological mechanism of depression.[24] In addition, inflammatory cytokines stimulate immune cells and further activate the HPA axis, which is the preferred mechanism of cytokine-induced depression.[23,24] However, further research is required to clarify the biological mechanisms underlying this synergistic effect.

To our knowledge, our study is the first to thoroughly investigate the association between an inflammatory diet, physical activity, and depression using a nationally representative sample from Korea. We used the BKMR model to estimate the risk of depression following exposure to a mixture of pro-inflammatory and anti-inflammatory nutrients. This is considered more realistic than the conventional approach, which only investigates single nutrients or dietary patterns. The BKMR model also increased the credibility of our findings by identifying both linear and non-linear relationships between individual nutrients and depression, while considering all possible interactions among the consumed nutrients.

However, this study had some limitations. First, this was a cross-sectional study; therefore, there is a possibility of a reverse association between an inflammatory diet and depression. Second, our findings may not be generalizable since the study was limited to a Korean population. However, we found similar findings in previous studies conducted in China and the United States.[5,6,21] Despite the well-known national representativeness of the KNHANES, selection bias may have occurred as individuals who were isolated and depressed due to COVID-19 were less likely to participate in the KNHANES 2020 survey. However, the prevalence of depression was significantly higher in the KNHANES 2020 than in the KNHANES 2018;[25] therefore, we assumed that the potential bias may not have distorted our results. Third, depression was defined using the PHQ-9 rather than a specialist diagnosis. However, the PHQ-9 score has been widely validated in several studies, and a cut-off value of 10 demonstrated a sensitivity of 88% and a specificity of 88% for the diagnosis of major depressive disorder.[16] Finally, we included only 22 nutrients instead of all nutrients from the diet, and the DII was calculated from the results of the 24-h recall interview, which could not completely reflect the long-term eating habits of an individual.

In summary, we found that an inflammatory diet increased the risk of depression in Korean adults. Moreover, individuals with insufficient physical activity exhibited a substantially greater risk of depression posed by pro-inflammatory dietary patterns and did not benefit from anti-inflammatory dietary patterns in terms of the risk of depression. Furthermore, insufficient physical activity and inflammatory nutrients had additive effects on the risk of depression. Therefore, while diet control is essential for preventing depression, its full potential can only be realized when combined with regular physical activity.

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AUTHOR CONTRIBUTIONS

Conceptualization: Kim Thai Thien Nguyen and Jaelim Cho. Data curation: Kim Thai Thien Nguyen and Jaelim Cho. Formal analysis: Kim Thai Thien Nguyen. Methodology: all authors. Project administration: Juyeon Ko and Jaelim Cho. Resources: Jaelim Cho. Supervision: Jaelim Cho. Validation: Jaelim Cho. Visualization: Kim Thai Thien Nguyen and Jaelim Cho. Writing—original draft: Kim Thai Thien Nguyen. Writing—review & editing: all authors. Approval of final manuscript: all authors.

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