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Title Page

Low-carbohydrate and low-fat diets, genetic susceptibility, and long-term risk of dementia: A prospective cohort study

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Abstract

Background

Low-carbohydrate and low-fat diets (LCDs and LFDs) are promoted for cardiometabolic prevention.

Objective

This study examined associations of LCDs and LFDs with incident dementia and evaluated modification by genetic susceptibility.

Methods

We included 5301 dementia-free adults aged ≥55 years from the Health and Retirement Study. Overall LCD and LFD indices were constructed based on macronutrient composition rankings assessed using a food frequency questionnaire in 2013-2014. Plant-based, animal-based, healthy, and unhealthy sub-scores were derived to characterize macronutrient sources and quality. Incident dementia was defined using the Langa-Weir algorithm through 2022. Genetic susceptibility was assessed using *APOE* genotype and Alzheimer disease polygenic risk score (AD-PRS). Cox models estimated hazard ratios (HRs).

Results

During the 9-year follow-up, 506 participants developed dementia. Greater LCD score was associated with lower dementia risk (HR per SD increment 0.90, 95% CI, 0.82, 0.99), whereas an overall LFD was not (1.05, 95% CI, 0.96, 1.15). Plant-based and healthy LCDs showed stronger inverse associations (0.85, 95% CI, 0.78, 0.94 and 0.82, 95% CI, 0.74, 0.90), while higher animal-based (1.10; 95% CI, 1.00, 1.20) and unhealthy LFDs (1.13; 95% CI, 1.04, 1.24) were linked to higher dementia risk. Associations were consistent across *APOE* genotype and AD-PRS strata. Higher plant-based and healthy LCDs were also associated with better global and domain-specific cognitive performance.

Conclusion

Adherence to LCDs, particularly plant-based and higher-quality LCDs, was associated with lower dementia risk, consistently across genetic susceptibility strata. These findings underscored the importance of macronutrient quality, in addition to quantity, in promoting cognitive health.

Keywords

Dietary pattern, dementia, cohort study, macronutrients, APOE.

Abbreviations

AD: Alzheimer's disease
AD-PRS: Alzheimer's disease polygenic risk score
ADGC: Alzheimer Disease Genetics Consortium
AHEI: Alternative Healthy Eating Index
AIC: Akaike information criterion
APOE: apolipoprotein E
BMI: body mass index
CES-D: Center for Epidemiologic Studies Depression Scale
CI: confidence interval
CIND: cognitive impairment no dementia
DASH: Dietary Approaches to Stop Hypertension
EADI: European Alzheimer's Disease Initiative
FFQ: food frequency questionnaire
GWAS: genome-wide association study
HCAP: Harmonized Cognitive Assessment Protocol
HR: hazard ratio
HRS: Health and Retirement Study
IADLs: instrumental activities of daily living
IGAP: International Genomics of Alzheimer's Project
LCD: low-carbohydrate diet
LCDs: low-carbohydrate diets
LFD: low-fat diet
LFDs: low-fat diets
MV: multivariable adjusted model
NHANES: National Health and Nutrition Examination Survey
NTB: neuropsychological test battery
SD: standard deviation

Introduction

Dementia is a growing public health challenge and currently affects over 55 million people worldwide.[1,2] It imposes profound personal, societal, and economic burdens. Given the limited curative treatments for most forms of dementia, identifying modifiable factors for dementia and cognitive decline is of critical importance.[3] Diet is a key modifiable factor of cognitive health.[4] Accumulating evidence linked healthy dietary patterns, such as the Mediterranean and DASH diets to slower cognitive decline and lower dementia risk,[4] despite inconsistent findings across populations. [5–9] While overall dietary quality has been extensively investigated,[4,10] the role of dietary macronutrient structure in cognitive health is less understood.

Over the past two decades, low-carbohydrate diets (LCDs) and low-fat diets (LFDs) have each been promoted for weight loss and cardiometabolic health.[11,12] However, their long-term cardiometabolic effects remain debated,[13,14] and evidence on their roles in cognitive health is even scarce. Macronutrient composition and quality can influence insulin resistance, lipid metabolism, adiposity, systemic inflammation, endothelial function, and vascular health,[13,14] all of which have been implicated in cerebrovascular impairment and neurodegeneration.[1] Existing studies on macronutrients and cognitive outcomes have primarily focused solely on macronutrient quantity,[15,16] while the roles of different sources and quality of carbohydrates and fats remained unclear.[4] Given the brain's high metabolic demands and reliance on efficient energy utilization, cognitive function could be influenced by both the quantity and quality of macronutrient intake.[17] In addition, genetic susceptibility may shape individual vulnerability to diet-related dementia risk. *Apolipoprotein E* (*APOE*) ε4, the strongest common genetic risk factor for late-onset Alzheimer disease (AD), may influence lipid transport, amyloid-β metabolism, neuroinflammation, and

vascular integrity, whereas polygenic risk scores (PRS) capture cumulative inherited susceptibility across multiple AD-related loci.[18,19] A recent study reported that higher glycemic index and glycemic load are both associated with higher dementia risk, especially in *APOE* ε4 carriers.[20] Further evaluating whether *APOE* ε4 carrier status and AD-PRS modify the associations between LCDs and LFDs and dementia risk may further provide clues for targeted recommendations.

To address these gaps, we investigated the associations of LCD and LFD, accounting for macronutrient sources and quality, with incident dementia and cognitive function in a nationally representative cohort of US adults. We hypothesized that the LCD, especially healthy LCD, was associated with a lower risk of dementia and better cognitive function, while the unhealthy types were related to higher risk of dementia and worse cognitive function. We further explored whether these associations were modified by AD genetic susceptibility.

Methods

Study design and participants

We conducted a prospective cohort study using data from the Health and Retirement Study (HRS), a nationally representative longitudinal survey of US adults aged 50 years and older.[21] The HRS collects information on sociodemographic characteristics, health behaviors, medical history, and cognitive function through biennial interviews, with dietary assessments conducted in 2013 and neuropsychological test batteries (NTB) in 2016. Details of the HRS design and sampling procedures have been described previously.[21] The HRS was approved by the University of Michigan Health Sciences/Behavioral Sciences Institutional Review Board (protocol HUM00061128). All participants provided written informed consent before participation. The current analysis was approved by School of Public Health, Zhejiang University.

For the present study, we used data from the 2013-2014 wave, when dietary intake was assessed via a validated food frequency questionnaire (FFQ).[22] Participants were eligible for inclusion if they were ≥55 years at baseline, had complete dietary data, and were free of dementia at the time of dietary assessment. We excluded individuals with implausible total energy intake (<500 or >4,000 kcal/day for female; <800 or >4,200 kcal/day for male), a history of stroke at baseline, incident dementia within the first 2 years of follow-up, or incomplete follow-up for dementia status (**Figure S1**). The final analytic sample included 5,301 dementia-free participants for incident dementia analyses. A subsample of participants who underwent comprehensive cognitive testing in the 2016 wave was included for the cross-sectional analyses of dietary indices and cognitive performance.

Dietary assessment

Dietary intake was assessed in 2013-2014 using a validated FFQ that collected information on participants' usual frequency of intake of 163 food items over the past year. Daily nutrient and energy intakes were calculated by multiplying the reported consumption frequency of each item by its nutrient and energy content (based on pre-specified portion sizes) and summing across all items. The validity and reproducibility of macronutrient calculated from this FFQ was reported previously.[22,23] In the validation study, the rank intraclass correlation coefficients were 0.68 for total fat, 0.73 for carbohydrate, and 0.62 for protein. Compared with 7-day dietary records, the deattenuated Spearman correlation coefficients were 0.67 for total fat, 0.69 for carbohydrate, and 0.54 for protein. These findings suggest high reproducibility and relative validity for assessing and ranking participants by carbohydrate and fat intake.[22]

Following previously published studies,[24–26] we derived five LCD scores and five LFD scores to capture both the composition and quality of macronutrients (**Table S1**). Overall LCD and LFD scores were derived by ranking participants into 11 categories based on the percentage of total energy from carbohydrates, fats, and proteins, with component scores summed to yield a total score (range, 0-30), where higher values indicated greater adherence. Plant-based and animal-based versions were further created by distinguishing macronutrient sources.[26]

To distinguish sources of three macronutrients, plant-based and animal-based LCD and LFD scores were calculated, respectively.[25] Animal-based LCD score positively ranked categories of animal-sourced proteins and fats and reversely ranked categories of total carbohydrates, whereas the plant-based LCD score positively ranked plant-sourced proteins and fats. To further account for quality of three macronutrients, quality-specific LCD and LFD scores were created. The healthy LCD score was based on the plant-based LCD with further emphasis on lower

carbohydrate intake from unhealthy sources, such as added sugar and refined grains.[25] The unhealthy LCD score was based on the animal-based LCD with further emphasis on lower carbohydrate intake from healthy sources, such as whole grains. For LFDs, the healthy version summed ranks for vegetable protein and healthy carbohydrates, with the reverse rank of animal fats, whereas the unhealthy version summed the ranks for animal proteins and low-quality carbohydrates, with the reverse rank of vegetable fats. In a sensitivity analysis, we defined saturated fat and proteins from red/processed meat, whole-fat dairy, and sweets and pastries as unhealthy, while unsaturated fat and proteins from other sources as healthy.[27]

The distributions of the LCD and LFD scores were presented in **Figure S2**, and their correlations with five *a priori* defined healthy dietary pattern scores were presented in **Table S2**. Notably, the healthy LCD showed the highest correlations with *a priori* defined healthy dietary patterns. **Figure S3** further displayed the correlations of the diet scores with energy-adjusted intake levels of food groups.

Incident dementia and cognitive function

Incident dementia was identified using the Langa-Weir classification, based on cognitive performance measures collected during the core interviews for self-respondents and from proxy interviews.[28] Langa-Weir classification was based on cognitive performance measures collected during the core interviews for self-respondents and from proxy interviews, which was applied to five waves of the Health and Retirement Study: 2014, 2016, 2018, 2020, and 2022.[28] For self-respondents, a 27-point cognition score was derived from immediate and delayed word recall, serial 7 subtraction, and backward counting from 20. A cognition score of 0-6 indicates dementia. For proxy respondents, an 11-point score was constructed from information on instrumental

activities of daily living (IADLs), the proxy's rating of the respondent's memory, and the interviewer's assessment of the respondent's cognition. A proxy-based score of 6-11 was indicative of dementia. Detailed procedures for this classification are described elsewhere. The follow-up period was from 2013 Health Care and Nutrition Study (HCNS, late November 2013 through early May 2014) to the 2022 wave (March 2022 to December 2023).

Cognitive function was further assessed in a subsample during the 2016 Harmonized Cognitive Assessment Protocol (HCAP) sub-study, which administered a comprehensive battery of standardized tests.[29] The 2016 HCAP evaluated both global cognitive performance and domain-specific abilities, including memory, executive function, language, visuospatial processing, and orientation. For the present analysis, we used previously developed standardized z-scores for each cognitive domain and for global cognition, which demonstrated strong structural validity in earlier work.[29]

Genetic susceptibility

The AD-PRS was derived from a 2019 meta-analysis by the International Genomics of Alzheimer's Project (IGAP), which confirmed 20 previously identified late-onset AD risk loci and discovered five novel genome-wide loci.[30] For the present study, we used the AD-PRS provided by the HRS,[31] which included only variants with an association p-value <0.01 in the GWAS. At this threshold, the AD-PRS including APOE-region variants comprised 18,393 SNPs in participants of European ancestry, 18,395 SNPs in participants of African ancestry, and 18,391 SNPs in participants of Hispanic ancestry. The score was calculated as the weighted sum of risk alleles, with weights derived from GWAS effect estimates reported by Kunkle et al. The posted HRS AD-PRSs were standardized within each ancestry group to a standard normal distribution,

213 with a mean of 0 and standard deviation of 1. Full SNP-level details are available from the HRS
214 genetic data documentation and the source GWAS.[30,31] Two versions of the score were employed:
215 one excluding the *APOE/TOMM40* genomic region and one retaining this region. The PRS
216 excluding the *APOE/TOMM40* region was used to capture polygenic susceptibility independent of
217 the major *APOE*-related signal, whereas the PRS including this region was used to represent
218 overall genetic susceptibility incorporating both *APOE/TOMM40*-related and non-*APOE*
219 polygenic risk. To account for population stratification, the AD-PRS was median-dichotomized
220 separately by ancestry.

221 To further assess the influence of *APOE* genotype, we used data from a TaqMan allelic
222 discrimination SNP assay for *rs7412* and *rs429358*, which define the three isoforms (ε2, ε3, and
223 ε4). For participants without direct genotyping, *APOE* status was imputed from existing genome-
224 wide array data using best-guess genotypes.[32] For this analysis, participants were classified as ε4
225 carriers or non-ε4 carriers to ensure adequate statistical power.

226

227 Covariates

228 We collected information on multiple covariates for confounding adjustment based on the previous
229 literature, including sociodemographic, lifestyle, clinical factors, and total energy intake.[6,19,33,34]
230 Sociodemographic confounders included age, sex defined by self-identity, race (White, Black or
231 others), and duration of formal education (college and above or below college). In the public-use
232 masked file, the released race categories were collapsed to White/Caucasian, Black/African
233 American, and Other, where "Other" includes American Indian, Alaskan Native, Asian, Native
234 Hawaiian, and Pacific Islander, and Hispanic ethnicity was categorized as Hispanic or non-
235 Hispanic. We also included a set of lifestyle variables including smoking status (never, former or

current), alcohol drinking status (never, former or current), frequency of moderate-to-vigorous physical activity (<1 time/week, <3 times/week or ≥3 times/week), body mass index (BMI) categories (< 25.0 kg/m^2, 25.0 -< 30.0 kg/m^2, or ≥ 30.0 kg/m^2; calculated as weight in kilograms divided by height in meters squared). Clinical factors as binary categorical variables included hypertension (yes or no), heart disease (yes or no), and type 2 diabetes (yes or no). The Center for Epidemiologic Studies Depression Scale (CES-D) score was adjusted to account for depressive symptoms. We adjusted for total energy intake calculated from the FFQ to reduce measurement errors.

Statistical Analysis

We described baseline characteristics of participants according to adherence to overall LCD and LFD scores, expressed as means (standard deviations) for continuous variables and as counts (percentages) for categorical variables. Missing values in covariates were addressed using multiple imputation by chained equations. We generated five imputed datasets with five iterations for each imputation procedure. The primary analytic models were fitted separately in each imputed dataset, and the resulting estimates and standard errors were pooled according to Rubin's rules.

For the primary analysis, we used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for incident dementia in relation to LCD and LFD adherence. Follow-up time was calculated from baseline to the date of dementia diagnosis, death, loss to follow-up, or the end of follow-up, whichever occurred first. Models were sequentially adjusted for demographic, socioeconomic, lifestyle, health-related covariates, and total energy intake. Tests for linear trend across tertiles of dietary scores were performed by assigning the median value of each tertile to participants within that tertile and modeling this tertile-specific median value as a

continuous variable in the fully adjusted Cox proportional hazards model. Proportional hazards assumptions were verified using Schoenfeld residuals. To evaluate potential non-linear associations, we conducted both tertile-based and restricted cubic spline analyses, with number of knots determined by AIC criteria.

To examine whether the associations between LCD/LFD adherence and dementia risk differed by genetic susceptibility to Alzheimer's disease (AD), we conducted stratified analyses by Alzheimer's disease polygenic risk score (AD-PRS; high versus low) and *APOE* genotype (ε4-carrier versus non-carrier). Multiplicative interaction terms (diet score × genetic risk) were tested in fully adjusted models, and stratified estimates were presented where significant interactions were observed ($P<0.05$ for interaction). To assess whether the diet-dementia associations differed by study subgroups, stratified analyses were conducted by age group (<65 versus ≥65 years), sex, and education level (college and above versus below college). Effect modification was formally tested using interaction terms between the dietary score and subgroup variable in fully adjusted models.

As a secondary analysis to assess whether LCDs and LFDs were related to cognitive performance, we used linear regression models to assess their associations with global cognitive function and domain-specific scores. Sensitivity analyses included: (1) excluding participants with baseline diabetes to reduce confounding by dietary change due to diabetes diagnosis; (2) excluding participants with baseline cognitive impairment no dementia (CIND) to reduce reverse causation; and (3) additionally adjusting for overall diet quality measured as the Alternative Healthy Eating Index (AHEI) to further account for overall diet quality; (4) mutually adjusting LCD and LFD scores to evaluate whether associations were independent of the alternate macronutrient pattern; (5) using alternative definitions for healthy/unhealthy scores to test robustness to score

construction; (6) adjusting the models for LCDs for red meat intake to evaluate whether the associations were driven by red meat intake; (7) using Fine-Gray models to calculate subdistribution HR (sHR), with death before dementia diagnosis treated as a competing event, to account for the potential competing risk of death.

All analyses were conducted using *R* version 4.4.0 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided *P*-values <0.05 were considered statistically significant. We applied false discovery rate correction for the primary analyses using the Benjamini-Hochberg method.

289 **Results**

290 Baseline characteristics

291 Among the 5,301 study participants, the mean age was 68.6 years, and 59.2% were female (**Table**
292 **1**). Participants in the highest tertile of overall LCD score tended to be younger (67.5 years versus
293 69.3 years) and have higher educational attainment compared with those in the lowest tertile. They
294 consumed a lower proportion of energy from carbohydrates (42.4% versus 57.7%) and a higher
295 proportion from fats (38.5% versus 28.1%) and proteins (18.0% versus 13.9%). In contrast,
296 participants in the highest tertile of overall LFD score were slightly older (68.9 years versus 68.5
297 years), more likely to be female, and consumed more carbohydrates (57.4% versus 44.0%) and
298 less fats (26.9% versus 38.7%) than those in the lowest tertile.

299

300 LCDs, LFDs and incident dementia

301 During the 9-year follow-up, 506 participants developed dementia. In the fully-adjusted models
302 (**Table 2**), higher overall LCD score was associated with lower dementia risk (HR per SD = 0.90;
303 95% CI: 0.82, 0.99; P-trend = 0.035), with stronger associations for plant-based (0.85; 95% CI,
304 0.78, 0.94; P-trend = 0.003) and healthy LCDs (0.82; 95% CI, 0.74, 0.90; P-trend < 0.001).
305 Animal-based (0.94; 95% CI, 0.85, 1.02) or unhealthy LCD (1.01; 95% CI, 0.92, 1.11) was not
306 significantly associated with dementia risk. For LFDs, while overall LFD score showed no
307 association with dementia risk (1.05; 95% CI, 0.96, 1.15), higher animal-based (1.10; 95% CI,
308 1.00, 1.20) and unhealthy LFDs (1.13; 95% CI, 1.04, 1.24) scores were linked to higher dementia
309 risk. Plant-based and healthy LFD scores showed non-significant associations. Restricted cubic
310 spline analyses confirmed linear inverse associations for plant-based and healthy LCD scores and
311 linear positive associations for unhealthy LFD scores, with no evidence of non-linearity for these

patterns (**Figure 1**). Most of the associations passed FDR-adjusted significance threshold, except for overall LCD (FDR-corrected P-trend = 0.087).

Subgroup analyses by age, sex, and education showed broadly consistent associations (**Table S3**; **Figure S4**). However, the inverse associations of plant-based and healthy LCD scores with dementia risk appeared stronger among participants with higher education (e.g., healthy LCD HR = 0.69; 95% CI, 0.59, 0.81) than among those below college level (0.90; 95% CI, 0.80, 1.02), with significant interactions (P-interaction = 0.03 for plant-based LCD; P-interaction = 0.04 for healthy LCD). Sensitivity analyses yielded similar results (**Table S4**). The plant-based and healthy LCD associations were slightly attenuated after adjusting for AHEI, but remained significant, and the positive association for unhealthy LFD persisted. The associations between LCD scores and dementia risk were similar after red meat intake was taken into account. In the Fine-Gray competing-risk models, the inverse associations for plant-based and healthy LCDs persisted (sHR: 0.88, 95%CI: 0.80, 0.97 for plant-based LCD and sHR: 0.85, 95%CI: 0.77, 0.94 for healthy LCD), whereas the positive association for unhealthy LFD was attenuated and not statistically significant (sHR: 1.07, 95%CI: 0.98, 1.17).

Effect modification by genetic susceptibility

Associations between plant-based and healthy LCD scores and dementia risk were consistent across strata of AD-PRS and *APOE* ε4 status, with no significant multiplicative interactions (all P-interaction > 0.05; **Table S5**; **Figure 2**). Among participants with higher AD-PRS, higher plant-based LCD score tended to show stronger associations with lower dementia risk (HR 0.79; 95%

CI: 0.68, 0.91 for higher AD-PRS without *APOE/TOMM40* region), although the interaction was not significant. Moreover, the interaction between plant-based LFD and AD-PRS was borderline significant (P-interaction = 0.05), and the HRs for higher plant-based LFD were 1.13 (95% CI: 0.97, 1.31) among participants with higher AD-PRS and 0.93 (95% CI: 0.79, 1.09) among those with lower AD-PRS. Given the confidence intervals crossing the null, this finding should be interpreted cautiously.

LCDs, LFDs and cognitive function

In the HCAP subsample (N = 1,321), LCD score was modestly associated with global cognition (β per SD = 0.06; 95%CI: 0.01, 0.11) and memory (0.08; 95% CI, 0.02, 0.13). Each SD higher plant-based and healthy LCD scores were associated with better global cognition by 0.10 (95%CI: 0.05, 0.14) and 0.10 (0.06, 0.15), respectively. Similar associations were shown for two domain-specific cognitive z-scores: memory (0.10; 95% CI, 0.05, 0.16 and 0.10; 95% CI, 0.05, 0.15), executive function (0.09; 95% CI, 0.04, 0.14 and 0.08; 95% CI, 0.03, 0.13). In addition to these domains, healthy LCD score was further associated with better language and fluency performances (0.08; 95% CI, 0.02, 0.13). Animal-based and unhealthy LCD scores were not associated with global cognition (**Table S6**; **Figure 3**).

For LFDs, overall and animal-based LFD scores were inversely associated with global cognition (-0.05; 95% CI, -0.10, -0.00 and -0.07; 95% CI, -0.12, -0.02) and memory (-0.06; 95% CI, -0.11, -0.01 and -0.08; 95% CI, -0.14, -0.03). Higher unhealthy LFD score was associated with poorer global cognition (-0.07; 95% CI, -0.12, -0.03), memory (-0.07; 95% CI, -0.13, -0.02), language

356 and fluency (-0.06; 95% CI, -0.11, -0.01), and orientation (-0.07; 95% CI, -0.11, -0.02). No
357 significant associations were observed for plant-based or healthy LFD scores.

Discussion

In this cohort of middle-aged and older U.S. adults, higher adherence to LCDs, especially plant-based and healthy LCDs emphasizing plant-sourced proteins and fats, was associated with a lower risk of dementia and better performance across multiple cognitive domains, including global cognition, memory, and executive function. In contrast, adherence to unhealthy LFDs, characterized by higher intakes of animal-sourced proteins and low-quality carbohydrates, was linked to higher dementia risk and poorer cognitive performance. These associations were not significantly modified by genetic susceptibility of AD or *APOE* genotype.

Previous research has examined the associations of established dietary patterns with dementia and cognitive outcomes. Adherence to the Mediterranean, DASH, and MIND diets has been linked to slower cognitive decline and reduced dementia risk in observational studies. [5,6,8] However, a recent trial among older adults with a family history of dementia did not show additional cognitive benefits of the MIND diet in addition to the caloric-restricted diet.[7] Other evidence suggests that the Mediterranean and MIND diet could potentially improve metabolic and inflammatory profiles,[35,36] improve cerebral perfusion and cerebrospinal fluid AD biomarker profile,[37] and reduce brain atrophy.[38] In contrast, evidence on LCDs and LFDs, which emphasize macronutrient distribution, remains limited. A previous study indicated a U-shaped association between overall LCD and cognitive performance,[39] but it did not differentiate macronutrient sources or quality and is limited by the cross-sectional design. In the UK Biobank, a 13-year cohort study observed that higher glycemic index and glycemic load are both associated with higher dementia risk; although no significant *APOE*-interaction with was observed, this study reported that the association was only significant in *APOE* ε4 carriers.[20] Nevertheless, it is important to note that absolute

381 macronutrient distributions in the current study largely fell within established Acceptable
382 Macronutrient Distribution Range: the highest overall LCD tertile consumed a mean of 42.4%
383 energy from carbohydrate, 38.5% from fat, and 18.0% from protein, and the highest LFD tertile
384 consumed a mean of 57.4% energy from carbohydrate, 26.9% from fat, and 16.5% from protein.
385 Therefore, these findings should not be interpreted as effects of extreme fat or carbohydrate
386 restriction. Evidence on extreme dietary restrictions, including the very low-carbohydrate
387 ketogenic diet proposed for neurodegenerative disease prevention or treatment, [40–42] remains
388 preliminary and requires further confirmation.

389

390 Additionally, our study highlighted that the sources and quality of macronutrients are critical for
391 cognitive function. Prior research has suggested the potential benefits of unsaturated fatty acids,
392 especially omega-3 fatty acids, for cognition and dementia.[43] In contrast, higher intakes of
393 saturated and trans-unsaturated fats have been linked to a higher risk of dementia.[44] Carbohydrate
394 quality also appears relevant: high-quality carbohydrates (e.g., whole grains) have been associated
395 with better cognitive function,[45] whereas refined carbohydrates (e.g., added sugars) have been
396 related to higher risk, although the findings were mixed.[6,46] To our knowledge, our study is the
397 first to comprehensively evaluate the roles of sources, and quality of macronutrients in cognitive
398 health, rather than solely focusing on overall composition. We found that greater intakes of healthy
399 and plant-sourced proteins and fats were associated with lower dementia risk, underscoring the
400 importance of nutrient quality rather than quantity. Interestingly, the healthy LCD had many
401 similarities with a high-fat modified Mediterranean ketogenic diet, which showed potential benefit
402 among adults with mild cognitive impairment in a randomized controlled trial.[47]

While the exact mechanisms of LCDs and LFDs on brain aging remain to be explored, our findings could be explained with existing literature on cardiometabolic outcomes, which have demonstrated that high-quality macronutrient sources improve body weight[48], blood pressure[49], glucose and lipid regulation[50], and reduce premature mortality.[24] The plant-based and healthy low-carbohydrate diet scores, which were associated with lower dementia risk, generally reflected a more favorable nutritional profile, including greater contributions from healthier sources of fat and protein and lower contributions from refined carbohydrates. These findings suggest that the observed associations may not be attributable to lower carbohydrate intake alone, but may also depend on the quality and food sources of the macronutrients replacing carbohydrates. Our observation that overall LCD was related to lower risk of dementia suggests potential cognitive-specific pathways which may involve lipid metabolism,[51] may influence cognitive health. Collectively, these findings emphasize the importance of macronutrient quality in cardiometabolic health, which may further influence brain vascular function and pathological changes.[4,52]

These results reinforce the importance of macronutrient quality and sources in maintaining cognitive health with important clinical and public health implications. Compared with the well-established glycemic index and load, the low-carbohydrate diet and low-fat diet scores characterize broader macronutrient patterns, and our findings suggest that dementia prevention strategies may also need to consider the overall macronutrient profile and the nutritional quality of replacement nutrients. The potential benefits for plant-based and healthy LCDs, if further confirmed by randomized controlled trials, suggest that dietary guidance may move beyond macronutrient quantity to emphasize nutrient sources. Given the absence of evidence on effect modification by

genetic risk, such dietary strategies could be broadly beneficial across the population, including people with high genetic susceptibility. Future research should explore additional mechanistic pathways, including gut microbiome composition, neuroimaging biomarkers of cerebrovascular health, and longitudinal inflammatory profiles. Randomized controlled trials with diverse populations and long follow-up are also needed to establish causality and inform dietary recommendations for dementia prevention.

The strengths of this study include its relatively large sample size, nationally representative design, and detailed dietary scoring system that incorporated both the source and quality of macronutrients. The availability of genetic and biomarker data provided opportunities to explore effect modifications. However, several limitations should be noted. First, dietary intake was self-reported and collected at a single time point, which may introduce measurement error and limit the ability to capture long-term dietary changes, although the non-differential measurement error likely biases the results toward the null. Second, although we adjusted for a comprehensive set of confounders, residual confounding cannot be ruled out. In this observational study, lower-carbohydrate / higher-fat patterns are still within usual intake range, so the effect estimates may not extend to extreme restrictions. In addition, all-cause dementia was identified using survey-based algorithms rather than clinical adjudication, and we were unable to examine associations with specific dementia subtypes, despite the lack of effect modification by AD-PRS. Finally, despite the nationally representative sampling frame, selective attrition and missing data may introduce bias, particularly among older and socioeconomically disadvantaged participants, and the generalizability of the findings warrants further examinations in other populations.

In conclusion, this study suggests that adherence to an overall LCD was associated with a lower risk of dementia, with stronger associations observed for plant-based and healthy LCDs. These relationships were independent of genetic susceptibility. Our findings underscore the importance of the sources and quality of macronutrients, rather than focusing solely on their quantity, in supporting cognitive health in aging populations. Future studies should incorporate repeated dietary assessments, more granular dementia phenotyping, and mechanistic investigations to further elucidate the biological pathways linking macronutrient quality to cognitive aging.

Declarations

Consent for publication: Not applicable.

Availability of data and materials: The Health and Retirement Study data could be accessed from its website at http://hrs.isr.umich.edu upon request.

Competing interests: The authors declare that they have no competing interests.

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Tables and Figures

Table 1. Baseline characteristics of study participants

		Low-carbohydrate diet		Low-fat diet	
Variable	Overall	Tertile 1	Tertile 3	Tertile 1	Tertile 3
N	5301	1954	1694	1939	1583
Age (mean (SD))	68.6 (9.4)	69.3 (9.7)	67.5 (8.6)	68.5 (9.0)	68.9 (9.8)
Female (%)	3139 (59.2)	1180 (60.4)	1022 (60.3)	1077 (55.5)	1012 (63.9)
Race (%)					
White	4124 (78.0)	1396 (71.7)	1415 (83.6)	1616 (83.5)	1128 (71.5)
Black	807 (15.3)	365 (18.8)	198 (11.7)	234 (12.1)	298 (18.9)
Other races	359 (6.8)	185 (9.5)	79 (4.7)	86 (4.4)	152 (9.6)
College and above (%)	2762 (52.1)	879 (45.0)	959 (56.6)	1064 (54.9)	755 (47.7)
Smoking status (%)					
Never	2456 (46.3)	964 (49.3)	755 (44.6)	795 (41.0)	830 (52.4)
Former	2307 (43.5)	807 (41.3)	760 (44.9)	899 (46.4)	632 (39.9)
Current	538 (10.1)	183 (9.4)	179 (10.6)	245 (12.6)	121 (7.6)
Drinking status (%)					
Never	2272 (42.9)	921 (47.1)	689 (40.7)	724 (37.3)	796 (50.3)
Former	834 (15.7)	316 (16.2)	266 (15.7)	271 (14.0)	307 (19.4)
Current	2195 (41.4)	717 (36.7)	739 (43.6)	944 (48.7)	480 (30.3)
Frequency of exercise (%)					
<1 time/week	1322 (24.9)	526 (26.9)	395 (23.3)	495 (25.5)	393 (24.8)
<3 times/week	2125 (40.1)	781 (40.0)	706 (41.7)	764 (39.4)	620 (39.2)
>=3 times/week	1854 (35.0)	647 (33.1)	593 (35.0)	680 (35.1)	570 (36.0)
BMI category (%)					
Normal	1417 (26.7)	566 (29.0)	397 (23.4)	508 (26.2)	429 (27.1)
Overweight	1973 (37.2)	778 (39.8)	586 (34.6)	718 (37.0)	616 (38.9)
Obesity	1911 (36.0)	610 (31.2)	711 (42.0)	713 (36.8)	538 (34.0)
Total energy intake, kcal/d (mean (SD))	1764.7 (677.0)	1761.7 (689.5)	1736.4 (648.5)	1852.0 (682.8)	1649.8 (666.1)
Carbohydrate intake, %TEI (mean (SD))	50.3 (8.1)	57.7 (5.9)	42.4 (4.8)	44.0 (6.0)	57.4 (6.3)
Fat intake, %TEI (mean (SD))	33.1 (6.2)	28.1 (4.4)	38.5 (4.7)	38.7 (4.8)	26.9 (3.5)
Protein intake, %TEI (mean (SD))	15.9 (3.2)	13.9 (2.4)	18.0 (2.8)	15.4 (3.0)	16.5 (3.4)
CES-D score (mean (SD))	1.3 (1.9)	1.4 (2.0)	1.2 (1.9)	1.2 (1.8)	1.4 (2.0)
Type 2 diabetes (%)	1192 (22.5)	416 (21.3)	442 (26.1)	433 (22.3)	359 (22.7)
Hypertension (%)	3138 (59.2)	1182 (60.5)	977 (57.7)	1114 (57.5)	956 (60.4)
Heart disease (%)	1168 (22.0)	436 (22.3)	343 (20.2)	403 (20.8)	368 (23.2)

SD, standard deviation; BMI, body mass index; TEI, total energy intake; CES-D score, the Center for Epidemiologic Studies Depression Scale score.

Table 2. Hazard ratios (HRs) and 95% confidence intervals (CIs) of incident dementia by low-fat and low-carbohydrate diet scores (N=5301)

Dietary score	Outcome measurement	Hazard ratios (95% CIs)			Nominal P-trend	FDR corrected P-trend	Hazard ratios Per SD (95% CIs)
		Tertile 1	Tertile 2	Tertile 3			
LCD	Cases/P-Ys	233 / 14088	146 / 12169	127 / 12716	NA	NA	NA
	HR (95%CI)	1.00 (Ref)	0.81 (0.65, 0.99)	0.80 (0.64, 1.00)	0.035	0.087	0.90 (0.82, 0.99)
Animal-based LCD	Cases/P-Ys	203 / 12953	169 / 13359	134 / 12661	NA	NA	NA
	HR (95%CI)	1.00 (Ref)	0.95 (0.77, 1.17)	0.89 (0.71, 1.11)	0.31	0.44	0.94 (0.85, 1.02)
Plant-based LCD	Cases/P-Ys	217 / 12863	191 / 15082	98 / 11028	NA	NA	NA
	HR (95%CI)	1.00 (Ref)	0.84 (0.69, 1.02)	0.69 (0.54, 0.89)	0.0032	0.016	0.85 (0.78, 0.94)
Healthy LCD	Cases/P-Ys	227 / 13270	146 / 12520	133 / 13183	NA	NA	NA
	HR (95%CI)	1.00 (Ref)	0.71 (0.57, 0.87)	0.70 (0.56, 0.87)	<0.001	0.006	0.82 (0.74, 0.90)
Unhealthy LCD	Cases/P-Ys	214 / 14532	138 / 11557	154 / 12885	NA	NA	NA
	HR (95%CI)	1.00 (Ref)	0.90 (0.72, 1.11)	1.03 (0.83, 1.28)	0.49	0.55	1.01 (0.92, 1.11)
LFD	Cases/P-Ys	174 / 14329	163 / 13180	169 / 11465	NA	NA	NA
	HR (95%CI)	1.00 (Ref)	1.03 (0.83, 1.28)	1.10 (0.88, 1.38)	0.4	0.5	1.05 (0.96, 1.15)
Animal-based LFD	Cases/P-Ys	165 / 14221	165 / 13769	176 / 10983	NA	NA	NA
	HR (95%CI)	1.00 (Ref)	1.04 (0.84, 1.30)	1.23 (0.98, 1.53)	0.076	0.15	1.10 (1.00, 1.20)
Plant-based LFD	Cases/P-Ys	165 / 13450	158 / 12871	183 / 12653	NA	NA	NA
	HR (95%CI)	1.00 (Ref)	1.03 (0.82, 1.28)	1.00 (0.80, 1.25)	0.99	0.99	1.01 (0.93, 1.11)
Healthy LFD	Cases/P-Ys	181 / 14223	183 / 13426	142 / 11324	NA	NA	NA
	HR (95%CI)	1.00 (Ref)	0.99 (0.81, 1.23)	0.89 (0.71, 1.12)	0.0081	0.027	0.93 (0.85, 1.02)
Unhealthy LFD	Cases/P-Ys	188 / 15475	149 / 12503	169 / 10995	NA	NA	NA
	HR (95%CI)	1.00 (Ref)	0.92 (0.74, 1.14)	1.30 (1.05, 1.61)	0.098	0.16	1.13 (1.04, 1.24)

The hazard ratios (HRs) were adjusted for age at baseline, sex, total energy intake, race, education level, smoking status, alcohol drinking status, frequency of exercise, BMI category, CES-D score, type 2 diabetes, hypertension, and heart disease. False discovery rate (FDR) correction was applied using the Benjamini-Hochberg method.

Figure 1. Associations of low-fat and low-carbohydrate diet scores with risk of incident dementia (N=5301)

Panel (a) shows the hazard ratios (HRs) per standard deviation (SD) increment in low-fat and low-carbohydrate diet scores. The HRs were adjusted for age at baseline, sex, total energy intake (in multivariable adjusted model 1, MV1), race, education level, smoking status, alcohol drinking status, frequency of exercise, BMI category (in MV2, based on MV1), Center for Epidemiologic Studies-Depression (CES-D) score, type 2 diabetes, hypertension, and heart disease (in MV3, based on MV2).

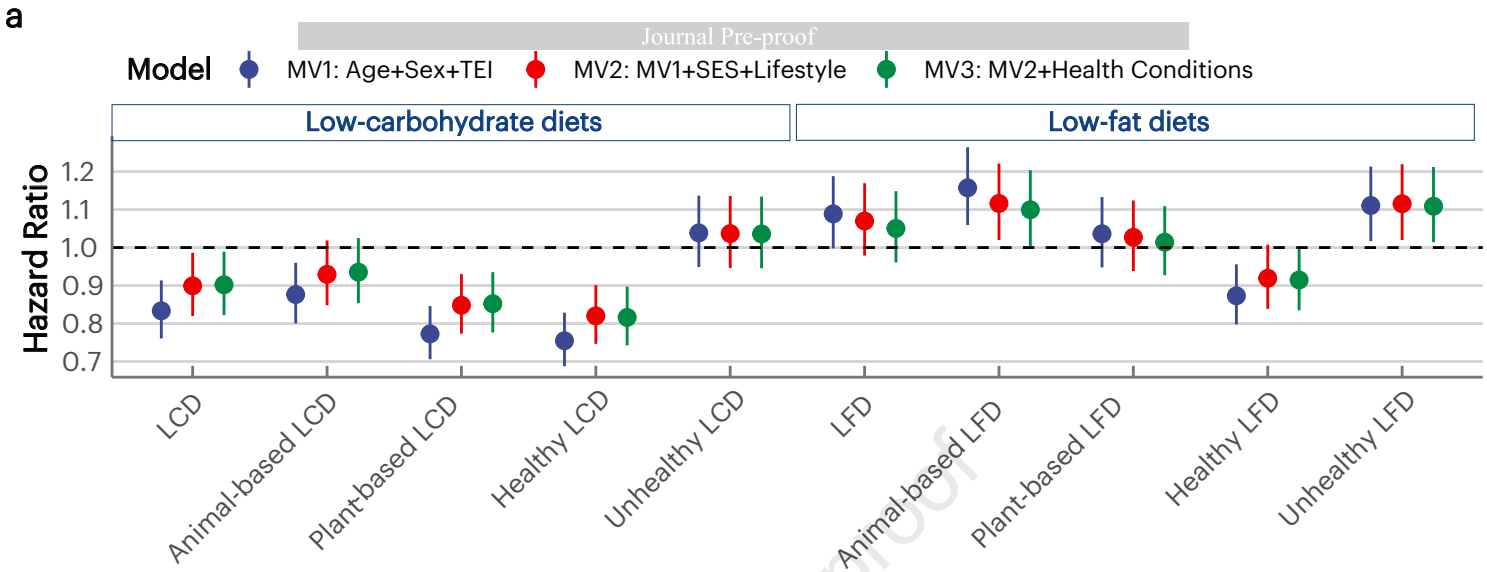
Panel (b) shows the HRs modelled using restricted cubic splines for these associations, adjusted for all covariates mentioned above.

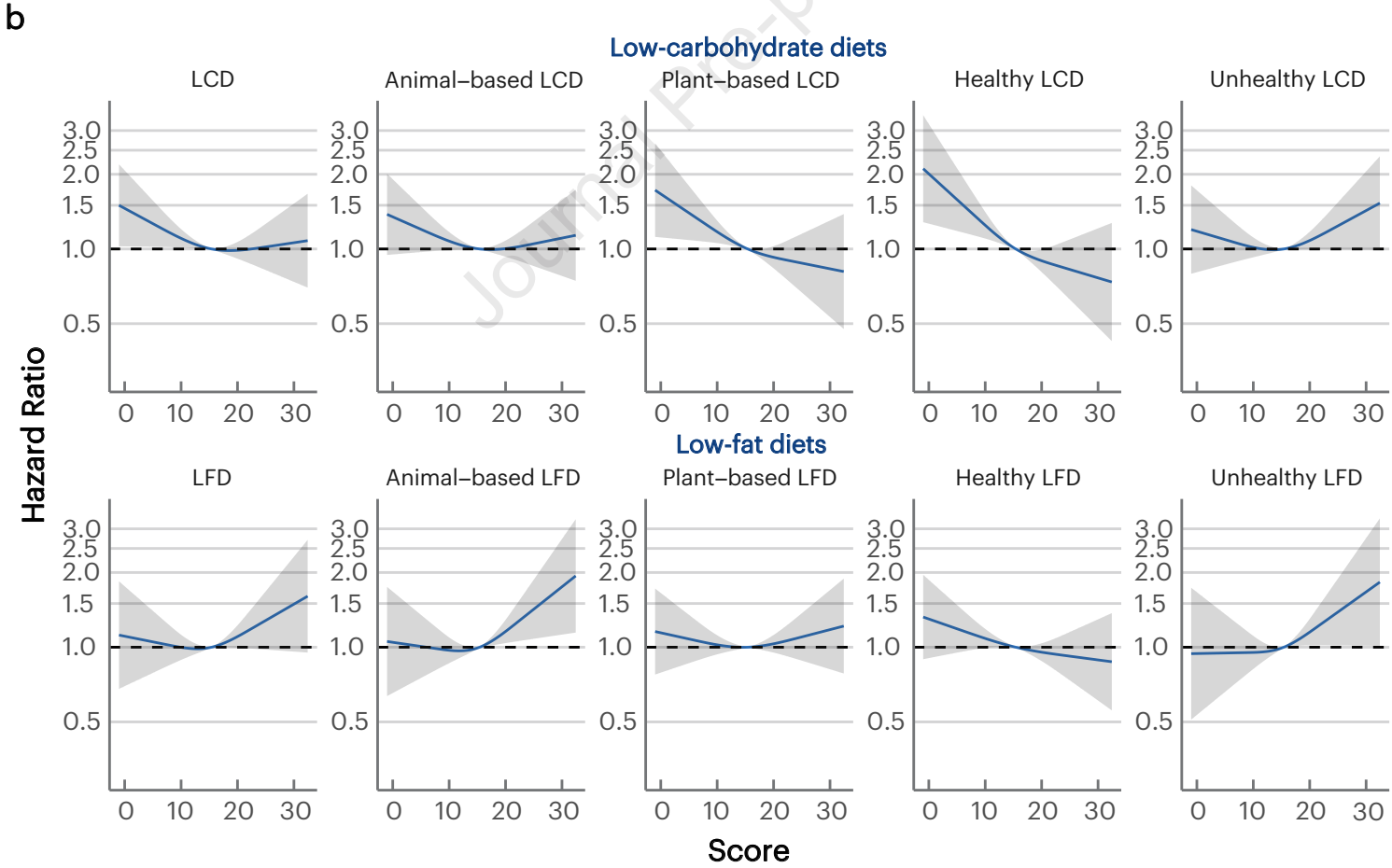
Figure 2. Associations of low-fat and low-carbohydrate diet scores with risk of incident dementia by *APOE* genotype (N=4466) and genetic risk scores of Alzheimer's disease (N=3682)

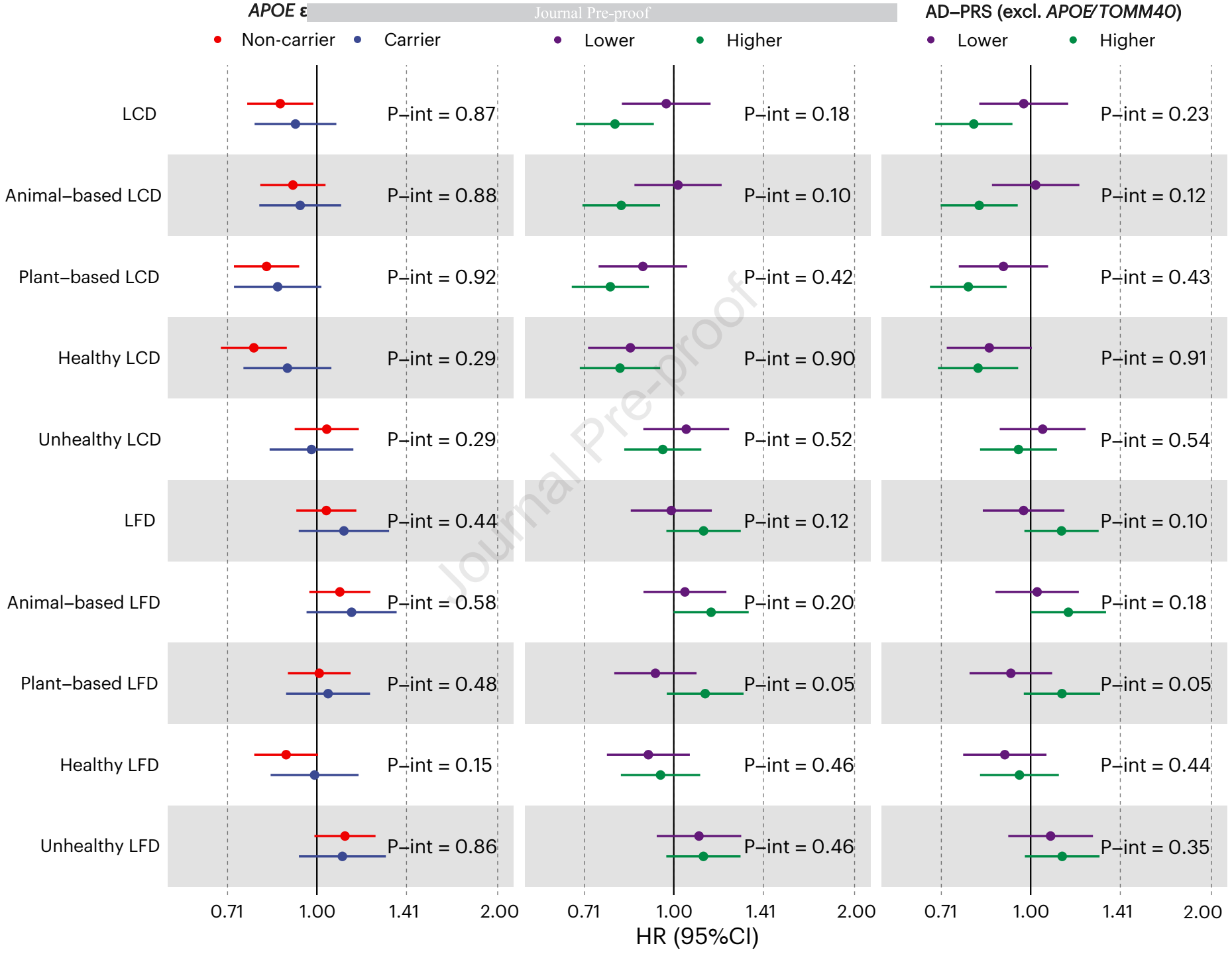
This figure shows the hazard ratios (HRs) per standard deviation (SD) increment in low-fat and low-carbohydrate diet scores. The HRs were adjusted for age at baseline, sex, total energy intake, race, education level, smoking status, alcohol drinking status, frequency of exercise, BMI category, Center for Epidemiologic Studies-Depression (CES-D) score, type 2 diabetes, hypertension, and heart disease. P-interactions were calculated using the likelihood ratio tests.

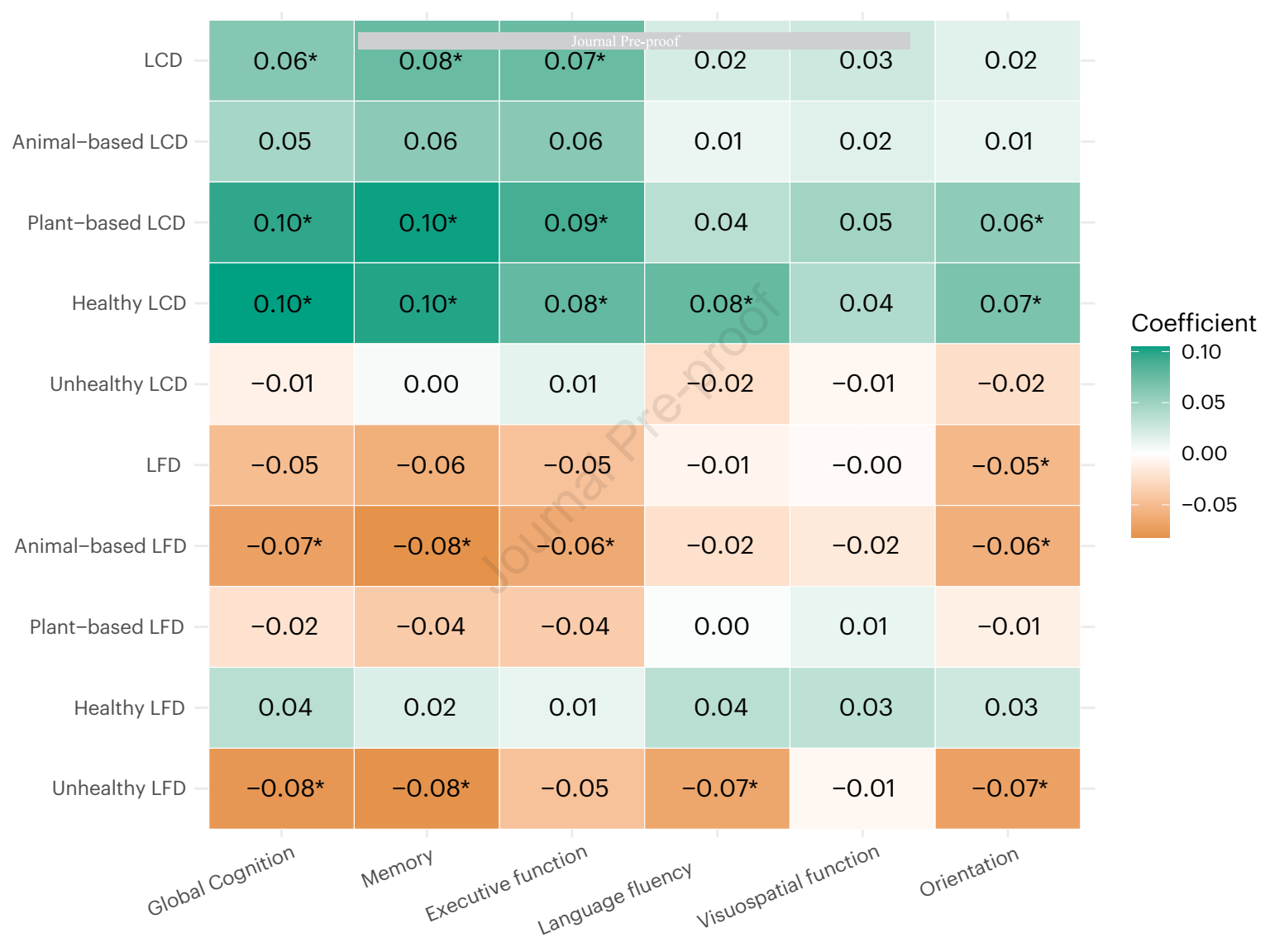
Figure 3. Associations of low-fat and low-carbohydrate diet scores with global and domain-specific cognitive function (N=1321)

The beta coefficients represent the differences in global and domain-specific cognitive z-scores per standard deviation (SD) increment in the dietary scores, adjusted for age at baseline, sex, total energy intake, race, education level, smoking status, alcohol drinking status, frequency of exercise, BMI category, Center for Epidemiologic Studies-Depression (CES-D) score, type 2 diabetes, hypertension, and heart disease. The associations with P-value <0.05 after false discovery rate adjustment were marked with an asterisk.





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