International Journal of Epidemiology, 2025, **54(6)**, dyaf182
https://doi.org/10.1093/ije/dyaf182
Original article

Original article

Glycemic index, glycemic load, and risk of dementia: a prospective analysis within the UK Biobank cohort

Nil Novau-Ferré[1,2,3], Javier Mateu-Fabregat[1,2,3], Christos K. Papagiannopoulos[4], Christos V. Chalitsios[4], Laura Panisello[1,2,3], Georgios Markozannes[4,5], Konstantinos K. Tsilidis[4,5], Mònica Bulló[1,2,3,6,*,‡], Christopher Papandreou[2,7,‡]

[1]Nutrition and Metabolic Health Research Group, Department of Biochemistry and Biotechnology, Rovira i Virgili University (URV), Reus, Spain
[2]Institute of Health Pere Virgili (IISPV), Reus, Spain
[3]Center of Environmental, Food and Toxicological Technology (TecnATox), Rovira i Virgili University, Reus, Spain
[4]Department of Hygiene and Epidemiology, School of Medicine, University of Ioannina, Ioannina, Greece
[5]Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, United Kingdom
[6]CIBER Physiology of Obesity and Nutrition (CIBEROBN), Carlos III Health Institute, Madrid, Spain
[7]Department of Nutrition and Dietetics Sciences, School of Health Sciences, Hellenic Mediterranean University (HMU), Siteia, Greece

*Corresponding author. Department of Biochemistry and Biotechnology, Rovira i Virgili University, Reus, Spain. E-mail: monica.bullo@urv.cat

‡Joint last authors.

Abstract

Background: Dementia risk is influenced by metabolic and lifestyle factors, including hyperinsulinemia, chronic inflammation, and type 2 diabetes. Glycemic index (GI) and glycemic load (GL) reflect the quality and quantity of dietary carbohydrates and their impact on glucose metabolism and systemic health. However, their associations with the risk of dementia subtypes remain unclear. This study examined the associations between dietary GI and GL and the risk of all-cause and different dementia subtypes, such as Alzheimer's disease (AD), vascular dementia (VD), and frontotemporal dementia.

Methods: A prospective analysis was conducted by using data from 202 302 dementia-free participants in the UK Biobank cohort. Dietary GI and GL were estimated by using the Oxford WebQ 24-hour web-based dietary questionnaire. Cox proportional hazards regressions with restricted cubic splines were used to evaluate nonlinear relationships. Two-piece Cox models were used to identify inflection points, which served as reference values to estimate hazard ratios (HRs).

Results: Dementia incidence was 0.89 per 1000 person-years. GI (mean±SD: 48.71 ± 7.68) showed an inverse J-shaped association with dementia risk, while GL (121.49 ± 39.00) showed a J-shaped pattern, with inflection points at 49.30 and 111.01, respectively. After adjusting for potential confounders, GI values of <49.30 were inversely associated with dementia risk [HR, 0.838; 95% confidence interval (CI), 0.758–0.926], while GL values of >111.01 were associated with higher dementia risk (HR, 1.145; 95% CI, 1.048–1.251). Similar findings were observed for AD and VD.

Conclusion: Low-GI diets may offer protective effects against all-cause dementia, AD, and VD, whereas high-GL diets may increase the risk. These findings underscore the importance of considering both carbohydrate quality and quantity in dementia prevention and management strategies.

Keywords: glycemic index; glycemic load; all-cause dementia; Alzheimer's disease; vascular dementia; UK Biobank.

Key Messages

- We aimed to examine the associations between dietary glycemic index (GI) and glycemic load (GL) and the risk of all-cause and different dementia subtypes, including Alzheimer's disease (AD), vascular dementia (VD), and frontotemporal dementia in the UK Biobank cohort.
- Individuals consuming low-GI diets exhibited a 16% reduced risk of all-cause dementia, AD, and VD, whereas those consuming high-GL diets had a 15% increased risk.
- Refining dietary recommendations, with a specific focus on carbohydrate quality and quantity, holds promise for dementia prevention and management, regardless of conventional risk factors such as age, sex, *APOE* ε4 status, or type 2 diabetes.

Received: 18 March 2025; **Accepted:** 23 September 2025

Introduction

Dementia is a progressive and incurable neurological disorder that includes Alzheimer's disease (AD), vascular dementia (VD), frontotemporal dementia (FTD), and dementia with Lewy bodies. In the UK, the prevalence of dementia is expected to increase by 55%, from ∼885 000 cases in 2019 to 1.6 million by 2040 [1].

Although the exact biological mechanisms underlying dementia are not fully understood, growing evidence suggest that both genetic predisposition and lifestyle factors contribute to the development of AD and other forms of dementia. This reflects the multifactorial nature of dementia, involving metabolic dysfunction, neuroinflammation, and vascular pathology [2]. Avoiding tobacco, engaging in regular physical activity, limiting alcohol consumption, and maintaining a healthy diet may help reduce the risk of dementia [3]. In mouse models of AD, high-sugar [4] and high-fat diets [5] have been shown to aggravate metabolic disorders, such as glucose intolerance, insulin resistance (IR), and hypercholesterolemia, which, in turn, exacerbate AD pathology by inducing memory impairment and increasing amyloid-beta (Aβ) deposition. In humans, recent meta-analyses provide evidence that type 2 diabetes (T2D) and hyperinsulinemia are associated with an increased risk of AD and other types of dementia [6]. As these metabolic conditions are expected to rise globally [7], optimizing blood glucose and insulin responses through targeted nutritional interventions could play a crucial role in preventing cognitive decline.

Carbohydrates have the most significant impact on blood glucose and insulin regulation, making both their quality and quantity critical to metabolic and cognitive health. The glycemic index (GI) and glycemic load (GL) are two widely recognized dietary metrics used to assess the impact of carbohydrate consumption on postprandial blood glucose and insulin levels [8]. GI reflects the rise in blood glucose after consuming a specific type of carbohydrate, whereas GL accounts for both the type and the quantity of carbohydrates consumed. While robust evidence links high-GI and high-GL diets to an increased risk of several metabolic diseases, including obesity, T2D, and cardiovascular diseases [9], emerging studies have also associated high-GL diets with greater Aβ deposition [10]—all of them are recognized as early hallmarks of AD onset. However, only a limited number of longitudinal studies have evidenced the association of GL with cognitive decline [11, 12], highlighting the need for further large-scale prospective studies to better understand the role of carbohydrate quality and quantity in dementia risk.

This study investigates the association between dietary GI and GL and the risk of developing all-cause dementia in UK Biobank (UKB)—a large population-based cohort. Furthermore, the relationship between GI and GL with dementia subtypes is examined. This research seeks to deepen our understanding of the role that carbohydrate quality and quantity play in neurodegenerative processes and inform the development of effective prevention strategies.

Methods

Data sources and study population

Data were obtained from UKB [13], which comprises >500 000 men and women aged 37–73 years, recruited between 2006 and 2010. However, as the sampling is volunteer-based, it did not fully represent the UK population [14]. Detailed information covering demographic data, lifestyle factors, and dietary habits was obtained via a self-completed touch-screen questionnaire and a brief verbal interview. Biological samples were obtained and trained staff undertook physical measurements. Further details on the study's design and methods are available elsewhere [13]. The UKB study received approval from the North West Multicentre Research Ethics Committee and all participants agreed to their inclusion and provided written informed consent at the time of enrolment [13].

Between 2009 and 2012, a total of 210 850 participants completed at least one 24-hour dietary-recall questionnaire. In the current study, we excluded participants with dementia diagnosis at baseline, implausible energy intakes (<800 or >4200 kcal/day in men; <500 or >3500 kcal/day in women) [15], and those with atypical dietary reports (dietary GI = 0). To assess the potential modifying effect of genetics, only participants with available genetic data were included.

Outcome assessment

The primary outcome was incident all-cause dementia. Algorithmically defined all-cause dementia, together with three subtypes of dementia (AD, VD, and FTD), was obtained from the UKB database (https://www.ukbiobank.ac.uk, data field: 42 018). These validated algorithmically defined outcomes by the UK Biobank Outcomes Adjudication Group were derived from a combination of coded information in the UKB baseline assessment, hospital admission records, and death registries (https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/alg_outcome_dementia.pdf). The positive predictive values ranged from 33% to 100% for all-cause dementia, 57% to 100% for AD, and 19% to 91% for VD [16]. The follow-up time was defined as being from the date of enrolment to the date of first dementia diagnosis, death, loss to follow-up, or censoring, whichever occurred first. Analyses were censored at the latest available date for hospital admission data (31 October 2022 for England/Wales and 9 November 2022 for Scotland), depending on the participant's origin.

Twenty-four-hour dietary assessment

The WebQ—a 24-hour web-based dietary questionnaire validated in large-scale cohort studies—was established as an effective method for capturing habitual dietary intake [17]. From February 2011 to April 2012, ∼320 000 participants, with randomly selected subsets of participants in each round, were invited via e-mail at intervals of 3–4 months, on specific days of the week, to complete up to five repeated dietary questionnaires (total $N = 210\,850$ in the follow-up). The WebQ captured the consumption of standard portions of 206 foods and 32 drinks over the preceding 24-hour period.

Estimation of GI and GL

The GI of carbohydrate-containing foods and beverages was determined by using a glucose-based scale ranging from 0 to 100, with glucose serving as the reference standard, following a step-based methodology [18]. GI values were obtained from international GI tables complemented with data from alternative sources or similar food items when necessary [19–21]. Portion sizes for foods and beverages were estimated by using the Food Portion Sizes guide published by the Food Standards Agency (2002) [22], as well as product labels. Carbohydrate content, expressed as grams per 100 grams of

food or per 100 mL of beverage, was obtained from McCance and Widdowson's Composition of Foods 2021 edition [23].

The dietary GL was calculated by multiplying the GI of each food item by the available carbohydrate content (in grams) per serving and dividing by 100. The daily GI was then obtained by dividing the total GL by the total carbohydrate intake and multiplying by 100. The daily GI and GL values were averaged across all available time points (minimum 1, maximum 5) for each participant.

Statistical analyses

The baseline characteristics of the participants were summarized as mean (SD) for continuous variables and frequencies (%) for categorical variables. The distributions of mean dietary GI and GL are shown in Supplementary Fig. S1. Fully adjusted Cox proportional hazard models (details provided below) with restricted cubic splines with two degrees of freedom [10th, 50th (reference), and 90th percentiles] were used to explore the nonlinear association between the variables and the risk of incident all-cause dementia, AD, VD, and FTD [24]. The significance of the nonlinear terms was evaluated by using likelihood-ratio tests. To address nonlinearity and to assess the association between the exposure and the all-cause dementia, threshold analysis with a two-piecewise Cox regression model using a smoothing function was used. To determine the inflection point, a rigorous analytical framework using likelihood-ratio tests and bootstrap resampling methods ($n = 1000$) were employed. Fully adjusted models (details provided below) were fitted with potential breakpoints incrementally set between the 20th and 80th percentiles of GI or GL, at 0.5%ile intervals. The breakpoint that maximized the log-likelihood was selected, indicating the most significant threshold effect.

Minimally adjusted models controlled for age, sex, and energy intake (kcal/d). Fully adjusted models further accounted for smoking status, body mass index (BMI), education level, physical activity [international physical activity questionnaire (IPAQ) group], sleep duration, diabetes, socioeconomic status (Townsend Deprivation Index), and *APOEε4* carriers. Detailed categorization and coding of covariates can be found in the Supplementary files and Supplementary Table S1, respectively. Those potential confounders were selected a priori based on previous studies and conceptualized by using a directed acyclic graph (Supplementary Fig. S2). The average missingness (min, max) for covariates was 4.24% (0.00, 17.51%) (Supplementary Fig. S3). Multiple imputation was performed in the entire dataset, prior to variable categorization, by using the MissForest algorithm [25] with several iterations to refine the imputed values. The variables distribution was assessed for significant differences compared with the original data, both visually and statistically. Density plots and the Kolmogorov–Smirnov test or bar plots and the chi-square test were used for continuous and categorical variables, respectively (Supplementary Fig. S4), suggesting a good performance of the method. The proportional hazards assumptions for the Cox model were assessed by using both statistical tests and graphical diagnostics examining Schoenfeld residuals, with results presented for the full-model analyses (Supplementary Fig. S5). R version 4.2.2 (http://www.R-project.org) was used for all analyses.

To evaluate the robustness of our findings, a series of sensitivity and subgroup analyses were conducted, with the methods detailed in the Supplementary files.

Results

Cohort characteristics

Out of 502 536 participants, 210 850 completed at least one 24-hour dietary-recall questionnaire and 202 302 (112 171 females and 90 131 males) participants with available genetic data were included in the analysis (Supplementary Fig. S6). No differences in baseline characteristics were found compared with the total population, except for T2D diagnosis, which showed a negligible effect size (Cramer's $V = 0.013$) (Supplementary Table S2). Over a median of 13.25 years of follow-up (range 0.1–15.87 years) (Supplementary Table S3), a total of 2362 dementia cases were diagnosed, comprising 1094 (46.3%) females and 1268 (53.7%) males (Table 1). Participants who developed dementia were older at recruitment (63.81 ± 4.84 vs 56.03 ± 7.92 years), were more likely to be former smokers, had a lower educational level, and had a 2-fold higher prevalence of T2D compared with those who remained cognitively healthy.

Association between glycemic measures and all-cause dementia

The mean dietary GI was 48.72 ± 7.68 among participants who developed dementia and 48.09 ± 7.55 among those who did not [Cohen's $d = 0.081$; 95% confidence interval (CI), 0.041–0.122]. Similarly, the mean dietary GL was 123.22 ± 40.49 for participants who developed dementia and 121.47 ± 38.98 for those who remained cognitively healthy (Cohen's d=–0.045; 95% CI, –0.086 to –0.004). Three major food categories—bread/pasta/rice, followed by fruit/vegetables and soup/snacks/pastries—contributed >45% of the total dietary GI (Supplementary Fig. S7). The detailed GI contribution for specific foods is provided in Supplementary Table S4.

An inversed J-shape association was observed for dietary GI (P for nonlinearity < .013) (Fig. 1). When threshold effects were examined, the risk of all-cause dementia decreased with the increment of dietary GI for GI diets of <49.30 [hazard ratio $(HR)_{per\ 10\text{-}unit\ increment}$, 0.838; 95% CI, 0.758–0.926] (Supplementary Table S5).

The association between dietary GL and the risk of all-cause dementia followed a J-shape (P for nonlinearity = .021) (Fig. 2). In the threshold effect analysis, diets with a GL of >111.01 were associated with an increased risk of dementia in the fully adjusted model ($HR_{per\ 50\text{-}unit\ increment}$, 1.145; 95% CI, 1.048–1.251) (Supplementary Table S5). No association was found between GL levels of <111.01 and incident dementia.

Finally, the percentage of energy intake from carbohydrates followed a J-shape (P for nonlinearity < .001), with the risk of incident dementia increasing at higher carbohydrate intake levels, particularly >50% of the total energy intake (Supplementary Fig. S8).

Association between glycemic measures and dementia subtypes

We further conducted threshold effect analyses to explore the potential nonlinear associations between glycemic measures and dementia subtypes (AD, VD, and FTD). A dietary GL of >111.01 was associated with an increased risk of AD. For

Table 1. Baseline characteristics of the analytic sample of UKB participants stratified by incident dementia.

Characteristics	Participants ($N = 202\,302$)	Nondementia ($N = 199\,940$)	All-cause dementia ($N = 2362$)
Age at recruitment (years)	56.12 (7.93)	56.03 (7.92)	63.81 (4.84)
Sex			
Female	112 171 (55.5%)	111 077 (55.6%)	1094 (46.3%)
Male	90 131 (44.6%)	88 863 (44.4%)	1268 (53.7%)
BMI (kg/m^2)	26.93 (4.63)	26.92 (4.63)	27.28 (4.67)
Smoking status			
Never	114 564 (56.6%)	113 439 (56.7%)	1125 (47.6%)
Previous smoker	71 987 (35.6%)	70 915 (35.5%)	1072 (45.4%)
Current smoker	15 751 (7.8%)	15 586 (7.8%)	165 (7.0%)
Education			
Higher	119 869 (59.3%)	118 706 (59.4%)	1163 (49.2%)
Vocational	23 701 (11.7%)	23 444 (11.7)	257 (10.9%)
Upper secondary	12 256 (6.1%)	12 107 (6.1%)	149 (6.3)
Lower secondary	29 470 (14.6%)	29 115 (14.6%)	355 (15.0)
Other	17 006 (8.4%)	16 568 (8.3%)	438 (18.5%)
Townsend Deprivation Index (quintiles)			
1 (least deprived)	40 461 (20.0%)	39 966 (20.0%)	495 (21.0%)
2–4	121 381 (60.0%)	119 986 (60.0%)	1395 (59.1%)
5 (most deprived)	40 460 (20.0%)	39 988 (20.0%)	472 (20.0%)
Sleep duration (hours/day)	7.16 (1.01)	7.16 (1.00)	7.25 (1.21)
Physical activity levels[a]			
Low (least active)	40 125 (19.8%)	39 692 (19.9%)	433 (18.3%)
Moderate	81 913 (40.0%)	79 982 (40.0%)	931 (39.4%)
High (most active)	81 264 (40.2%)	80 266 (40.2%)	998 (42.3%)
Prevalent type 2 diabetes			
Yes	13 862 (6.9%)	13 472 (6.7%)	390 (16.5%)
No	188 440 (93.2%)	186 468 (93.3%)	1972 (83.5%)
APOE ε4 carriers			
Yes	56 839 (28.1%)	55 577 (27.8%)	1262 (53.4%)
No	145 463 (71.9%)	144 363 (72.2%)	1100 (46.6%)
Dietary energy intake (kcal/d)	2016.46 (500.45)	2016.29 (500.19)	2030.04 (522.33)
Glycemic index	48.71 (7.68)	48.72 (7.68)	48.09 (7.55)
Glycemic load	121.49 (39.00)	121.47 (38.98)	123.22 (40.49)
Follow-up (years)	13.16 (1.68)	13.19 (1.63)	10.13 (2.79)

Continuous variables are presented as mean (standard deviation); categorical variables are presented as frequencies (percentage).
[a] Self-reported physical activity levels according to the IPAQ.

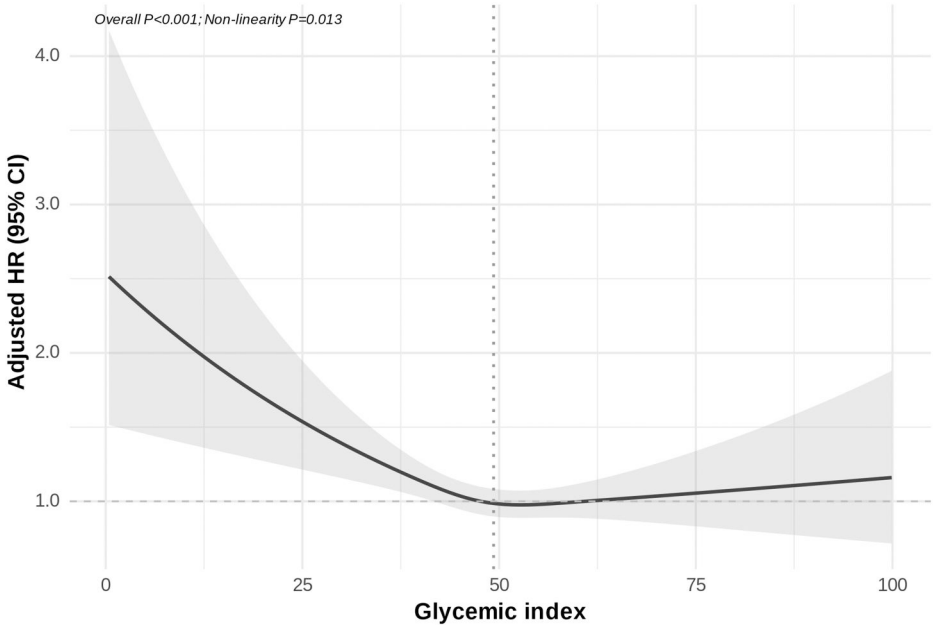

Figure 1. Association of dietary GI with risk of incident dementia. A fully adjusted Cox proportional hazard model with restricted cubic splines with two degrees of freedom was used, adjusted for age, sex, smoking status, BMI, education level, physical activity, sleep duration, diabetes, socioeconomic status, *APOE*ε4, and total energy intake. HR, hazard ratio; CI, confidence interval.

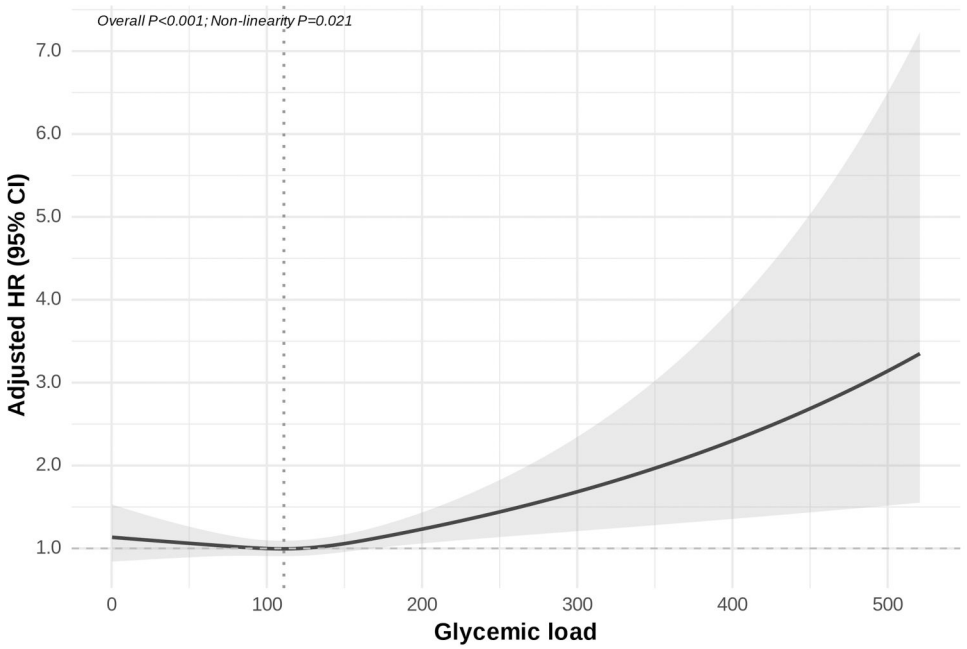

Figure 2. Association of dietary GL with risk of incident dementia. A fully adjusted Cox proportional hazard model with restricted cubic splines with two degrees of freedom was used, adjusted for age, sex, smoking status, BMI, education level, physical activity, sleep duration, diabetes, socioeconomic status, *APOE*ε4, and total energy intake.

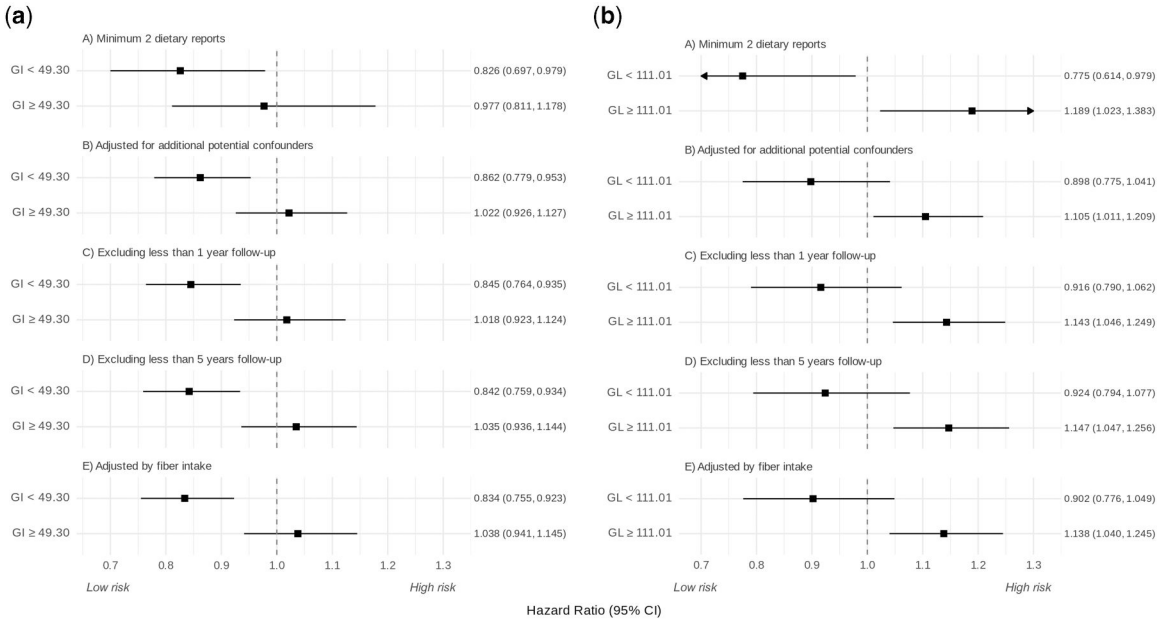

Figure 3. Association between (a) GI and (b) GL and risk of dementia in sensitivity analyses considering the threshold effect at 49.30 and 111.01, respectively. Results are expressed for changes of 10 and 50 units for GI and GL, respectively, adjusted for age, sex, smoking status, BMI, education level, physical activity, sleep duration, diabetes, socioeconomic status, *APOE*ε4, and total energy intake. Analyses (a) including participants with a minimum of two dietary reports ($N = 120\,327$, including 1189 dementia cases); (b) adjusting for additional potential confounders, including history of depression, CVD, ethnicity, alcohol status, or use of dementia medication; (c) excluding participants with <1 year ($N = 202\,187$, including 2353 dementia cases) of follow-up; (d) excluding participants with <5 years ($N = 199\,994$, including 2231 dementia cases) of follow-up; (e) further adjusting for dietary fiber intake.

VD, a high dietary GL showed an association with increased risk only in the minimally adjusted model. Conversely, below the threshold, the risk of both AD and VD consistently decreased as the GI increased (Supplementary Table S6).

Sensitivity analyses

The nonlinear associations between dietary GI and GL and the risk of all-cause dementia remained robust across various sensitivity analyses (Fig. 3 and Supplementary Table S7).

When the analysis was restricted to participants who completed at least two dietary assessments, a direct association between high dietary GI and increased dementia risk ($HR_{per\ 10\text{-unit increment}}$, 1.189, 95% CI, 1.023–1.383) was observed, as well as an inverse association between low dietary GL with dementia incidence ($HR_{per\ 50\text{-unit increment}}$, 0.775, 95% CI, 0.614–0.979). Conversely, a higher dietary GL was associated with a higher dementia risk ($HR_{per\ 50\text{-unit increment}}$, 1.189, 95% CI, 1.023–1.383).

Adjustment for additional potential confounders and assessment of the risk for reverse causality confirmed the robustness and consistency of the association between dietary GI and GL and the risk of all-cause dementia. The associations between dietary GI and GL and dementia risk remained consistent after the consideration of fiber intake.

No association was found between GL and dementia risk among *APOEε4* noncarriers (Fig. 4 and Supplementary Table S8). Finally, with stratification by the T2D status prior to dementia, the negative association of the GI was strengthened, whereas the statistical significance of the GL was lost in people with T2D.

The results from the Fine and Gray model were consistent with those of the primary Cox regression analysis. Low-GI diets remained significantly associated with a reduced risk of all-cause dementia (sHR, 0.837; 95% CI, 0.755–0.926; $P < .001$), while high-GL diets were associated with increased risk (sHR, 1.144; 95% CI, 1.049–1.249; $P = .002$).

Discussion

Using data from >200 000 UKB participants, we identified nonlinear associations between dietary glycemic measures and the risk of all-cause dementia. Specifically, low-GI diets were associated with a reduced risk of all-cause dementia, while high-GL diets were associated with an increased risk of all-cause dementia after a median follow-up of >13 years.

Although glucose is the primary energy source for brain metabolism, elevated circulating glucose levels may impair brain metabolism, potentially compromising cognitive function, increasing the risk of dementia [26–28]. A meta-analysis of 144 prospective studies reported that individuals with T2D have a 1.91-fold higher risk of developing dementia compared with those without diabetes [29]. Evidence further suggests that the association between diabetes and dementia strengthens over time [30], with even newly diagnosed diabetes increasing the dementia risk by 16%, as shown in a large Canadian cohort of nearly 900 000 people [31]. Consistently, analyses within UKB have associated IR with poorer verbal and numerical reasoning ability and slower processing speed [32]. Similarly, our group reported that IR, diabetes status and duration, poor glycemic control, and insulin treatment were associated with a greater cognitive decline over 2-year changes [32]. Mechanistically, hyperglycemia and IR disrupt glucose homeostasis, leading to central nervous system microvascular damage, increased Aβ production and tau phosphorylation, impaired clearance of these neurotoxic proteins, and elevated inflammation and oxidative stress [33–35]. Specifically, insulin dysregulation in AD contributes directly to pathology by increasing brain atrophy and worsening cognitive decline [36], while, in VD, IR leads to vasoconstriction and reduced cerebral perfusion, resulting in insufficient oxygen supply and increasing apoptosis [30, 31, 37]. These findings underscore the importance of early metabolic control, including nutritional interventions based on low-GI and low-GL diets to help prevent cognitive decline.

In 2019, the International Carbohydrate Quality Consortium highlighted the importance of regulating GI nutrition content across Europe [38], reporting that low-GI and low-GL diets improve glucose and insulin metabolism, contributing to the prevention and management of diabetes. Low-GI foods have been associated with improved insulin sensitivity, lower postprandial glycemic levels, a decreased incidence of diabetes [39], reduced blood pressure [40], enhanced satiety [41], and reduced obesity [42]. Given the established link between metabolic dysregulation and dementia, these metabolic benefits may contribute to cognitive protection. A meta-analysis in adults reported that low-GL breakfasts were associated with modest improvements in immediate episodic memory and trends toward enhanced delayed memory, which is particularly relevant, as subtle

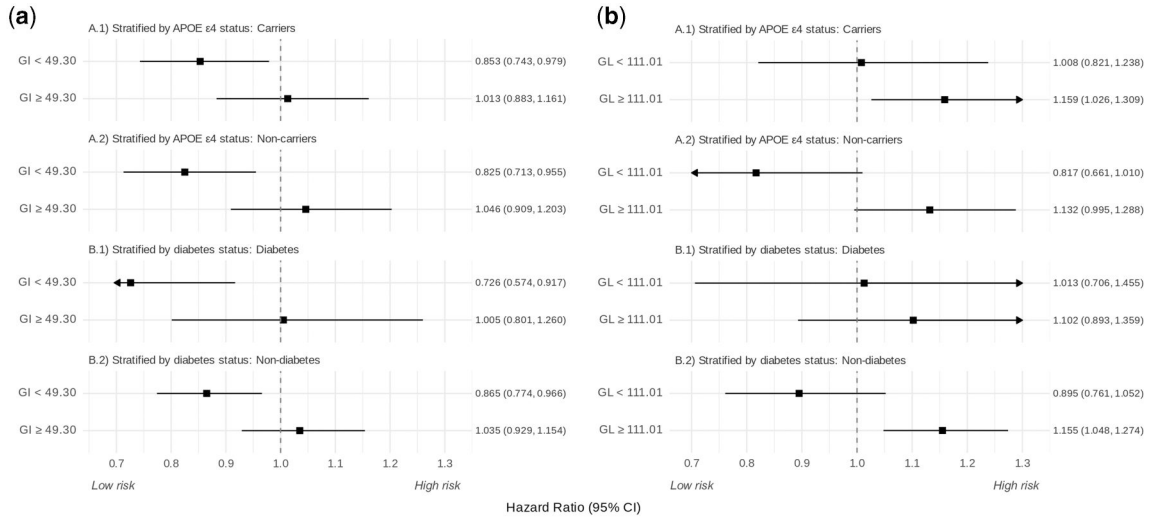

Figure 4. Subgroup analyses considering the threshold effect at 49.30 and 111.01, respectively, for the association between (a) GI and (b) GL and risk of dementia. Results are expressed for changes of 10 and 50 units for GI and GL, respectively. Analyses include those stratified (a) into *APOEε4* carriers and noncarriers, and (b) into previously diagnosed and nondiagnosed with diabetes. Adjusted, if not stratified, by age, sex, smoking status, BMI, education level, physical activity, sleep duration, diabetes, socioeconomic status, *APOEε4*, and total energy intake.

memory deficits often precede dementia onset [43]. Similarly, a meta-analysis in children and adolescents found that low-GI breakfasts improved attention compared with high-GI meals [44] and previous cross-sectional studies in elderly people consistently reported positive associations between high-GL diets and poorer cognitive performance [45, 46]. Building on this evidence, our study links low-GI diets with a lower risk of both total and subtype-specific dementia. Conversely, participants who consumed high-GL diets were at an increased risk of all-cause dementia, particularly AD and VD. Mechanistically, high-GL diets contribute to adiposity and IR [47], with recent studies further linking them to increased Aβ deposition, particularly in metabolically active regions of the brain [10, 28, 35]. Supporting this, findings from the Nurses' Health Study reported that higher dietary GL further increased the risk of ischemic stroke [48]—a known precursor of VD—and, although still controversial, brain ischemia could induce cerebral Aβ deposition, as Aβ has been found to be elevated in the brains of patients with strokes [49].

Emerging evidence, although limited, indicates a potential interplay between genetic risk factors and carbohydrate intake, including quality and quantity [12]. Although we found no interaction between the *APOE* allele and GL/GI in our primary analyses, GL was not associated with all-cause dementia in *APOE*ε4 noncarriers, aligning with results from Gentreau and collaborators [12].

Our study has several strengths and limitations that should be considered. First, the large sample size of >200 000 participants, including 2362 cases of all-cause dementia, provides robust statistical power. Second, the prospective study design with >13 years of follow-up allows the evaluation of temporal relationships between dietary glycemic measures and dementia risk. Additionally, several sensitivity analyses were conducted to evaluate the robustness of the results, thereby enhancing their overall credibility. Furthermore, we observed consistent associations within specific dementia subtypes, including AD and VD. It is also important to acknowledge some potential limitations. Dietary intake was assessed by using web-based self-reported Oxford WebQ 24-hour dietary-recall questionnaires. While this tool has been validated, it may not fully capture the participants' usual dietary patterns and it may be subject to recall bias. Additionally, the GI of foods can vary significantly due to factors such as processing, cooking methods, ripeness, and storage time [50], which may have affected the accuracy of the GI values assigned to participants' diets. The UKB cohort predominantly consists of middle-aged and older British adults who tend to have healthier lifestyles and lower levels of socioeconomic deprivation, limiting the generalizability of the findings to more diverse populations [14]. Although the analyses accounted for genetic and lifestyle risk factors, with a primary focus on nutritional aspects, other key contributors to dementia risk, such as environmental exposures and comorbidity conditions, may not have been fully considered. Finally, despite the prospective design and sensitivity analyses excluding participants who developed dementia within the first 1 or 5 years of follow-up, the potential influence of cognitive decline on dietary habits remains a consideration, given the long preclinical phase of dementia.

Conclusion

In this study, we investigated the association between dietary GI and GL with all-cause and subtypes of dementia. Our findings suggest that low-GI diets may provide protective benefits against all-cause dementia, including AD and VD, while higher GL diets are associated with an increased risk. This underscores the importance of considering both the quantity and the quality of carbohydrates in formulating strategies for dementia prevention and management. Future research should focus on elucidating the biological mechanisms linking high-GL diets to dementia. Overall, our findings align with and expand the current literature, highlighting the critical role of metabolic health in the complex etiology of dementia.

Acknowledgements

This research has been conducted by using the UKB resource under application number 79696.

Author contributions

C. Papandreou: Conceptualization, Methodology, Data curation, Resources, Supervision, Formal analysis, Funding acquisition, Writing—review & editing. M Bulló: Conceptualization, Methodology, Resources, Supervision, Funding acquisition, Visualization, Writing—Original Draft. N Novau-Ferré: Data curation, Formal analysis, Methodology, Visualization, Writing original-draft. J Mateu-Fabregat, CK Papagiannopoulos, CV Chalitsios, L Panisello, G Markozannes, and KK. Tsilidis: Methodology, Visualization, Writing—Review & Editing. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Supplementary data

Supplementary data are available at *IJE* online.

Conflict of interest

The authors declare no conflict of interest.

Funding

This study has been funded by the Alzheimer's Association, through the projects AARG-NTF-22–924702 and AARG-NTF-23–1027318, the Instituto de Salud Carlos III (ISCIII), and the Spanish Ministry of Health, and co-funded by the European Union through the project PI19/00854 and PI22/001139. N.N.-F. received a fellowship from the Instituto de Salud Carlos III (ISCIII) Spanish Ministry of Health (grant number FI23/00268). J.M-F. received a pre-doctoral fellowship from the Generalitat de Catalunya's Agència de Gestió d'Ajuts Universitaris i de Recerca, Barcelona, Spain (grant number 2023 FISDU 00387). L.P. received a fellowship from the Rovira i Virgili University under the Programa Martí Franquès (grant number 2024PMF-PIPF-01). M.B. received the ICREA Academy 2022 Distinction from the Autonomous Government of Catalonia. The authors gratefully acknowledge the support of the Departament de Recerca i Universitats de la Generalitat de Catalunya to the Nutrition and Metabolic Health Research Group (2021 SGR 00213).

Data availability

The data used in this study were obtained from UKB under application number 79696 and are subject to the terms and conditions of the UKB access policy. The datasets analysed during the current study are not publicly available but may be accessible from the corresponding author upon reasonable request, in compliance with UKB's data-sharing policies, and for the purposes of future research collaborations.

Use of Artificial Intelligence (AI) tools

AI tools were not used for any part of this study or in writing the manuscript text.

References

1. Wittenberg R, Hu B, Araiza LB, Rehill A, *Projections of Older People with Dementia Care in the United Kingdom, 2019–2040; Care Policy and Evaluation Centre*. London, UK: London School of Economics, 2019.
2. Mangialasche F, Kivipelto M, Solomon A, Fratiglioni L. Dementia prevention: Current epidemiological evidence and future perspective. *Alzheimers Res Ther* 2012;**4**:6–8. https://alzres.biomedcentral.com/articles/10.1186/alzrt104
3. Lourida I, Hannon E, Littlejohns TJ *et al.* Association of lifestyle and genetic risk with incidence of dementia. *JAMA* 2019;**322**:430–7.
4. Cao D, Lu H, Lewis TL, Li N. Intake of sucrose-sweetened water induces insulin resistance and exacerbates memory deficits and amyloidosis in a transgenic mouse model of Alzheimer disease. *J Biol Chem* 2007;**282**:36275–82. https://pubmed.ncbi.nlm.nih.gov/17942401/
5. Rojas-Criollo M, Novau-Ferré N, Gutierrez-Tordera L *et al.* Effects of a high-fat diet on insulin-related miRNAs in plasma and brain tissue in APPSwe/PS1dE9 and Wild-Type C57BL/6J mice. *Nutrients* 2024;**16**:955. https://www.mdpi.com/2072-6643/16/7/955/htm
6. Cao F, Yang F, Li J *et al.* The relationship between diabetes and the dementia risk: a meta-analysis. *Diabetol Metab Syndr* 2024;**16**:101. https://pmc.ncbi.nlm.nih.gov/articles/PMC11092065/
7. Ong KL, Stafford LK, McLaughlin SA *et al.* Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *The Lancet* 2023;**402**:203–34. http://www.thelancet.com/article/S0140673623013016/fulltext
8. Jenkins DJ, Wolever TM, Taylor RH *et al.* Glycemic index of foods: a physiological basis for carbohydrate exchange. *Am J Clin Nutr* 1981;**34**:362–6.
9. Dwivedi AK, Dubey P, Reddy SY, Clegg DJ. Associations of glycemic index and glycemic load with cardiovascular disease: updated evidence from meta-analysis and cohort studies. *Curr Cardiol Rep* 2022;**24**:141–61. https://pubmed.ncbi.nlm.nih.gov/35119682/
10. Taylor MK, Sullivan DK, Swerdlow RH *et al.* A high-glycemic diet is associated with cerebral amyloid burden in cognitively normal older adults. *Am J Clin Nutr* 2017;**106**:1463–70. https://pubmed.ncbi.nlm.nih.gov/29070566/
11. Seetharaman S, Andel R, McEvoy C, Aslan AKD, Finkel D, Pedersen NL. Blood glucose, diet-based glycemic load and cognitive aging among dementia-free older adults. *J Gerontol A Biol Sci Med Sci* 2015;**70**:471–9. https://pubmed.ncbi.nlm.nih.gov/25149688/
12. Gentreau M, Raymond M, Chuy V *et al.* High glycemic load is associated with cognitive decline in apolipoprotein E ϵ4 allele carriers. *Nutrients* 2020;**12**:1–14. https://pubmed.ncbi.nlm.nih.gov/33255701/
13. Sudlow C, Gallacher J, Allen N *et al.* UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med* 2015;**12**:e1001779. https://pubmed.ncbi.nlm.nih.gov/25826379/
14. Fry A, Littlejohns TJ, Sudlow C *et al.* Comparison of sociodemographic and health-related characteristics of UK biobank participants with those of the general population. *Am J Epidemiol* 2017;**186**:1026–34. https://dx.doi.org/10.1093/aje/kwx246
15. Perez-Cornago A, Pollard Z, Young H *et al.* Description of the updated nutrition calculation of the Oxford WebQ questionnaire and comparison with the previous version among 207,144 participants in UK Biobank. *Eur J Nutr* 2021;**60**:4019–30. https://pubmed.ncbi.nlm.nih.gov/33956230/
16. Wilkinson T, Ly A, Schnier C; UK Biobank Neurodegenerative Outcomes Group and Dementias Platform UK *et al.* Identifying dementia cases with routinely collected health data: A systematic review. *Alzheimers Dement* 2018;**14**:1038–51. https://pubmed.ncbi.nlm.nih.gov/29621480/
17. Liu B, Young H, Crowe FL *et al.* Development and evaluation of the Oxford WebQ, a low-cost, web-based method for assessment of previous 24 h dietary intakes in large-scale prospective studies. *Public Health Nutr* 2011;**14**:1998–2005. https://pubmed.ncbi.nlm.nih.gov/21729481/
18. Louie JCY, Flood V, Turner N, Everingham C, Gwynn J. Methodology for adding glycemic index values to 24-hour recalls. *Nutrition* 2011;**27**:59–64.
19. Atkinson FS, Foster-Powell K, Brand-Miller JC. International tables of glycemic index and glycemic load values: 2008. *Diabetes Care* 2008;**31**:2281–3. https://pubmed.ncbi.nlm.nih.gov/18835944/
20. Foster-Powell K, Holt SHA, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. *Am J Clin Nutr* 2002;**76**:5–56. https://pubmed.ncbi.nlm.nih.gov/12081815/
21. GI Search—Glycemic Index. https://glycemicindex.com/gi-search/ (20 May 2024, date last accessed).
22. Food Standards Agency. *Food Portion Sizes*. 3rd ed. London: H.M. S.O, 2002. https://www.tsoshop.co.uk/product/9780112429616/Food-portion-sizes (25 May 2024, date last accessed).
23. Public Health England. Composition of Foods Integrated Dataset (CoFID). Available online: https://www.gov.uk/government/publications/composition-of-foods-integrated-dataset-cofid (17 February 2024, date last accessed).
24. Harrell FE. Regression Modeling Strategies. 2015. https://link.springer.com/10.1007/978-3-319-19425-7
25. Stekhoven DJ, Bühlmann P. MissForest—non-parametric missing value imputation for mixed-type data. *Bioinformatics* 2012;**28**:112–8. https://dx.doi.org/10.1093/bioinformatics/btr597
26. Crane PK, Walker R, Hubbard RA *et al.* Glucose levels and risk of dementia. *N Engl J Med* 2013;**369**:540–8. https://www.nejm.org/doi/full/10.1056/NEJMoa1215740
27. Burns CM, Chen K, Kaszniak AW *et al.* Higher serum glucose levels are associated with cerebral hypometabolism in Alzheimer regions. *Neurology* 2013;**80**:1557–64. https://pubmed.ncbi.nlm.nih.gov/23535495/
28. Morris JK, Vidoni ED, Wilkins HM *et al.* Impaired fasting glucose is associated with increased regional cerebral amyloid. *Neurobiol Aging* 2016;**44**:138–42. https://pubmed.ncbi.nlm.nih.gov/27318141/
29. Xue M, Xu W, Ou Y-N *et al.* Diabetes mellitus and risks of cognitive impairment and dementia: a systematic review and meta-analysis of 144 prospective studies. *Ageing Res Rev* 2019;**55**:100944. https://pubmed.ncbi.nlm.nih.gov/31430566/
30. Li F-R, Yang H-L, Zhou R *et al.* Influence of diabetes duration and glycemic control on dementia: a cohort study. *J Gerontol A Biol Sci Med Sci* 2021;**76**:2062–70. https://dx.doi.org/10.1093/gerona/glab221
31. Haroon NN, Austin PC, Shah BR, Wu J, Gill SS, Booth GL. Risk of dementia in seniors with newly diagnosed diabetes: a population-based study. *Diabetes Care* 2015;**38**:1868–75. https://dx.doi.org/10.2337/dc15-0491
32. Fanelli G, Mota NR, Salas-Salvadó J *et al.* The link between cognition and somatic conditions related to insulin resistance in the UK

Biobank study cohort: a systematic review. *Neurosci Biobehav Rev* 2022;**143**:104927. https://pubmed.ncbi.nlm.nih.gov/36367493/
33. Strachan MWJ. R D Lawrence Lecture 2010^. The brain as a target organ in Type 2 diabetes: exploring the links with cognitive impairment and dementia. *Diabet Med* 2011;**28**:141–7. https://onlinelibrary.wiley.com/doi/full/10.1111/j.1464-5491.2010.03199.x
34. Fishel MA, Watson GS, Montine TJ *et al.* Hyperinsulinemia provokes synchronous increases in central inflammation and β-Amyloid in normal adults. *Arch Neurol* 2005;**62**:1539–44. https://jamanetwork.com/journals/jamaneurology/fullarticle/789658
35. Sato N, Morishita R. The roles of lipid and glucose metabolism in modulation of β-amyloid, tau, and neurodegeneration in the pathogenesis of Alzheimer disease. *Front Aging Neurosci* 2015;**7**:199. https://pubmed.ncbi.nlm.nih.gov/26557086/
36. Jack CR, Lowe VJ, Weigand SD *et al.*; Alzheimer's Disease Neuroimaging Initiative. Serial PIB and MRI in normal, mild cognitive impairment and Alzheimers disease: Implications for sequence of pathological events in Alzheimers disease. *Brain* 2009;**132**:1355–65. https://pubmed.ncbi.nlm.nih.gov/19339253/
37. Muniyappa R, Yavuz S. Metabolic actions of angiotensin II and insulin: A microvascular endothelial balancing act. *Mol Cell Endocrinol* 2013;**378**:59–69.
38. Barclay AW, Augustin LSA, Brighenti F, Delport E, Henry CJ, Sievenpiper JL *et al.* Dietary glycaemic index labelling: a global perspective. Antonia trichopoulou.10:10. https://doi.org/10.3390/nu13093244
39. Livesey G, Taylor R, Hulshof T, Howlett J. Glycemic response and health—a systematic review and meta-analysis: relations between dietary glycemic properties and health outcomes. *Am J Clin Nutr* 2008;**87**:258S–68S. https://pubmed.ncbi.nlm.nih.gov/18175766/
40. Evans CEL, Greenwood DC, Threapleton DE, Gale CP, Cleghorn CL, Burley VJ. Glycemic index, glycemic load, and blood pressure: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2017;**105**:1176–90. https://pubmed.ncbi.nlm.nih.gov/28404579/
41. Bornet FRJ, Jardy-Gennetier AE, Jacquet N, Stowell J. Glycaemic response to foods: Impact on satiety and long-term weight regulation. *Appetite* 2007;**49**:535–53.
42. Juanola-Falgarona M, Salas-Salvadó J, Ibarrola-Jurado N *et al.* Effect of the glycemic index of the diet on weight loss, modulation of satiety, inflammation, and other metabolic risk factors: a randomized controlled trial. *Am J Clin Nutr* 2014;**100**:27–35.
43. Gaylor CM, Benton D, Brennan A, Young HA. The impact of glycaemic load on cognitive performance: A meta-analysis and guiding principles for future research. *Neurosci Biobehav Rev* 2022;**141**:104824. https://www.sciencedirect.com/science/article/pii/S014976342200313X
44. Álvarez-Bueno C, Martínez-Vizcaíno V, López EJ, Visier-Alfonso ME, Redondo-Tébar A, Cavero-Redondo I. Comparative effect of low-glycemic index versus high-glycemic index breakfasts on cognitive function: A systematic review and meta-analysis. *Nutrients* 2019;**11**:1706. https://pubmed.ncbi.nlm.nih.gov/31344892/
45. Power SE, O'Connor EM, Ross RP *et al.* Dietary glycaemic load associated with cognitive performance in elderly subjects. *Eur J Nutr* 2015;**54**:557–68. https://pubmed.ncbi.nlm.nih.gov/25034880/
46. Garber A, Csizmadi I, Friedenreich CM *et al.* Association between glycemic load and cognitive function in community-dwelling older adults: results from the Brain in Motion study. *Clin Nutr* 2018;**37**:1690–9. https://pubmed.ncbi.nlm.nih.gov/28756038/
47. Ludwig DS, Ebbeling CB. The carbohydrate-insulin model of obesity: beyond "Calories In, Calories Out." *JAMA Intern Med* 2018;**178**:1098–103. https://pubmed.ncbi.nlm.nih.gov/29971406/
48. Yu E, Rimm E, Qi L *et al.* Diet, lifestyle, biomarkers, genetic factors, and risk of cardiovascular disease in the nurses' health studies. *Am J Public Health* 2016;**106**:1616–23. https://pubmed.ncbi.nlm.nih.gov/27459449/
49. Ouyang F, Jiang Z, Chen X *et al.* Is cerebral amyloid-β deposition related to post-stroke cognitive impairment? *Transl Stroke Res* 2021;**12**:946–57. https://pubmed.ncbi.nlm.nih.gov/34195928/
50. Venn BJ, Green TJ. Glycemic index and glycemic load: measurement issues and their effect on diet-disease relationships. *Eur J Clin Nutr*. 2007;**61 Suppl 1**:S122–31. https://pubmed.ncbi.nlm.nih.gov/17992183/

International Journal of Epidemiology, 2025, 54, 1–9
https://doi.org/10.1093/ije/dyaf182
Original article