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Special Article

Income, diet, and cognitive function: observational analyses and candidate metabolomic pathways identified by Mendelian randomization

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ABSTRACT

Background: Household income has been shown to have impact on cognitive function, with dietary patterns and gut microbiota–related metabolic pathways potentially acting as mediating pathways. Our study integrates observational analyses and Mendelian randomization (MR) to explore these associations.

Methods: The observational analysis included 13,457 participants from the UK Biobank who experienced cognitive transitions. A multistate Markov model was applied to assess the effect of income level on cognitive trajectory, while mediation analysis and quantile regression were performed using baseline data. We applied a two-sample, two-step MR approach utilizing genetic instruments from the IEU Open genome-wide association studies (GWAS) project to determine the causal effects of income on cognition, and further estimate the mediating roles of dietary patterns and 1400 gut metabolites linking income with cognitive performance.

Results: Over a median follow-up of 8.96 years, a total of 14,040 cognitive transitions were recorded (7429 deterioration events and 6801 improvements), with higher income associated with a lower risk of cognitive deterioration. MR analyses confirmed a causal relationship between income and cognitive performance (OR: 2.140, 95% CI: 1.923–2.381; $P < 0.001$). Notably, cheese and coffee intake demonstrated significant mediation effects in both observational and two-way, two-step MR. The protective effect of cheese appeared to be mediated by gut metabolites, particularly via tryptophan/tyrosine and carnitine/ergothioneine.

Conclusions: Our findings indicate a significant link between income and cognitive performance, cheese and dried fruit may mediate this protective effect through amino acid and carnitine metabolism pathways. Interventions targeting dietary patterns have the potential to prevent cognitive decline attributable to low income.

1. Introduction

Dementia, including Alzheimer's disease (AD), is one of the primary causes of disability and death among the older people, and represents a serious public health issue [1]. With the global population aging rapidly, dementia has become a major economic burden for older adults and their families, posing increasing challenges to healthcare systems and social services in both high- and low-middle-income countries [2].

Previous studies have associated dementia risk with socioeconomic status (SES), a comprehensive concept that measured a person's position from income, education and occupation [3,4]. Evidence suggests that SES may influence cognitive function through multiple mediating

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pathways, including lifestyle behaviors, depressive symptoms, and vascular risk factors [5–8], highlighting potential targets for interventions to reduce the burden of dementia. In our study, we focused specifically on household income as the primary indicator of SES, because it represents a direct and widely used measure of material resources and is strongly linked to daily living conditions and health-related behaviors [9,10].

Income level has been revealed association with daily dietary choices. Diet quality generally improved with income [11], while low-income families tend to purchase unhealthy food products rather than intake of enough types and frequency of healthy foods including vegetables and fruits, neglecting the nutritional quality of foods [12]. A large body of epidemiological studies have shown that adherence to healthy dietary patterns, including the Mediterranean diet (MeDi), the DASH diet, and the MIND diet [13,14], may help reduce cognitive decline and dementia risk. The protective effects of these diets may be partly mediated by their food components and derived gut metabolites, including amino acids, lipids and organic acids which can exert anti-inflammatory and antioxidant effects; such mechanisms have been validated in MeDi [15,16]. Recent animal studies further suggest that high-salt diets may impair memory by altering the gut microbiota and reducing butyrate production. However, it remains discordance among the correlation between food consumption and the risk of dementia and unknown causal relationship, and incomplete verification of the role of gut metabolites in this link.

A critical yet often overlooked issue in cognitive research is the dynamic nature of cognitive decline. Cognitive impairment does not always follow a linear or irreversible course; rather, individuals may transition bidirectionally between cognitive states [17]. This pattern is especially relevant when assessing cognitive trajectories in middle-aged and older populations. Traditional cross-sectional studies are insufficient to capture such complexity. To address this, we applied a multistate Markov model to analyze the dynamic transitions in cognitive function over time [18].

Therefore, in this study, we adopted a hierarchical framework to examine the associations of income and cognition trajectory. We further assessed the mediating roles of dietary habits by analyzing their key constituent food items and downstream gut metabolites by two-way, two-step Mendelian randomization.

2. Methods

2.1. Study design and population

This study adopted a mixed research design that integrated observational cohort analysis and Mendelian randomization (MR), in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization (STROBE-MR) guideline [19].

The UK Biobank is a large-scale prospective cohort study that recruited over 500,000 participants aged 37–73 years across the United Kingdom between 2006 and 2010, with multiple follow-up assessments conducted thereafter [20]. Participants completed a comprehensive touchscreen questionnaire covering sociodemographic characteristics, physical and mental health, and a series of brief cognitive tests, and also provided biological samples. Detailed information regarding the study design, implementation, and data collection is available at https://www.ukbiobank.ac.uk. All participants provided written informed consent.

This study utilized data from three waves of UK Biobank (2006–2010, 2014, and 2019) (**Table S1**). For the primary analysis, participants were included if they completed cognitive assessments in at least two waves and had valid data for at least three cognitive tasks, resulting in a final analytic sample of 13,457 participants for the cognitive change analysis.

Additionally, for the mediation analysis and quantile regression, we included participants who possessed complete data on dietary questionnaires and the four cognitive tests at baseline**(Figure S1)**.

In the MR analysis, three core instrumental variables assumptions were established as follows: relevance that the selected SNPs must be associated with the exposure, independence that the selected SNPs must be independent of confounding factors that could affect the exposure or outcome, exclusion restriction that the selected SNPs must affect the outcome solely through their effect on the exposure and have no direct effect on the outcome. We employed a two-step MR approach based on genetic instruments derived from the IEU Open Genome-Wide Association Study (GWAS) project to perform mediation analyses. We aimed to test a hypothesized mediating pathway whereby income causally affects cognitive traits through altering dietary patterns and then changing the conditions of gut metabolites. First, we explored the potential causal relationship between income and cognitive traits (pathway 1), income and dietary patterns (pathway 2), dietary patterns and cognitive traits (pathway 3), while considering the influence of confounding factors within this pathway, and established an "income-dietary pattern-cognitive traits" framework. Second, we identified gut metabolites that are causally associated with dietary patterns (Pathway 4) and validated whether these metabolites have a causal relationship with cognitive traits (Pathway 5). Fig. 1A illustrates our proposed causal chain.

2.2. Sources of GWAS data

Table S2 summarizes our GWAS data sources

2.3. Data sources of income

For the observational study, income was assessed using the average total household income before tax from the UK Biobank touchscreen questionnaire. Participants were classified into six categories: less than £18 000, £18 000–30 999, £31 000–51 999, £52 000–100 000, more than £100 000, and do not know (excluded from the study). For the MR analysis, We selected the average total household income before tax as the measurement of income. GWAS statistics for income (ID: ukb-b-7408) were obtained from the IEU Open GWAS project (https://gwas.mrcieu.ac.uk/) with a total sample of 397,751 covering 9851,867 SNPs.

2.4. Data sources for dietary patterns and gut metabolites

Dietary information was obtained from the UK Biobank touchscreen food frequency questionnaire (FFQ), which includes 29 questions on food and 18 on alcohol [21]. We specifically selected 17 quantifiable dietary factors that provided clear intake frequency suitable for analysis: cereal, bread, cooked vegetables, salad/raw vegetables, fresh fruit, dried fruit, oily fish, non-oily fish, processed meat, poultry, beef, lamb, pork, cheese, tea, water, and coffee. For more detailed information about these questions and possible answers, please refer to the **Table S3**. GWAS data for mediators were divided into two parts. The first part consisted of dietary patterns data, which included the intake of 20 types of food from the IEU Open GWAS project. The second part included gut metabolites data, encompassing 1400 metabolites, sourced from the GWAS Catalog summary statistics repository.

2.5. Cognitive function tests

Cognitive assessments in the UK Biobank study were conducted using a fully automated touchscreen questionnaire. In this study, we focused on four core cognitive domains: reaction time (RT), numeric memory (NM), fluid intelligence (FI), and pairs matching memory (PMM) [22]. These tasks respectively assess processing speed, short-term working memory, verbal and numerical reasoning, and verbal declarative memory [23]. Due to skewed distributions, RT and PMM values were log-transformed using log(x) and log(x+1), respectively [24].

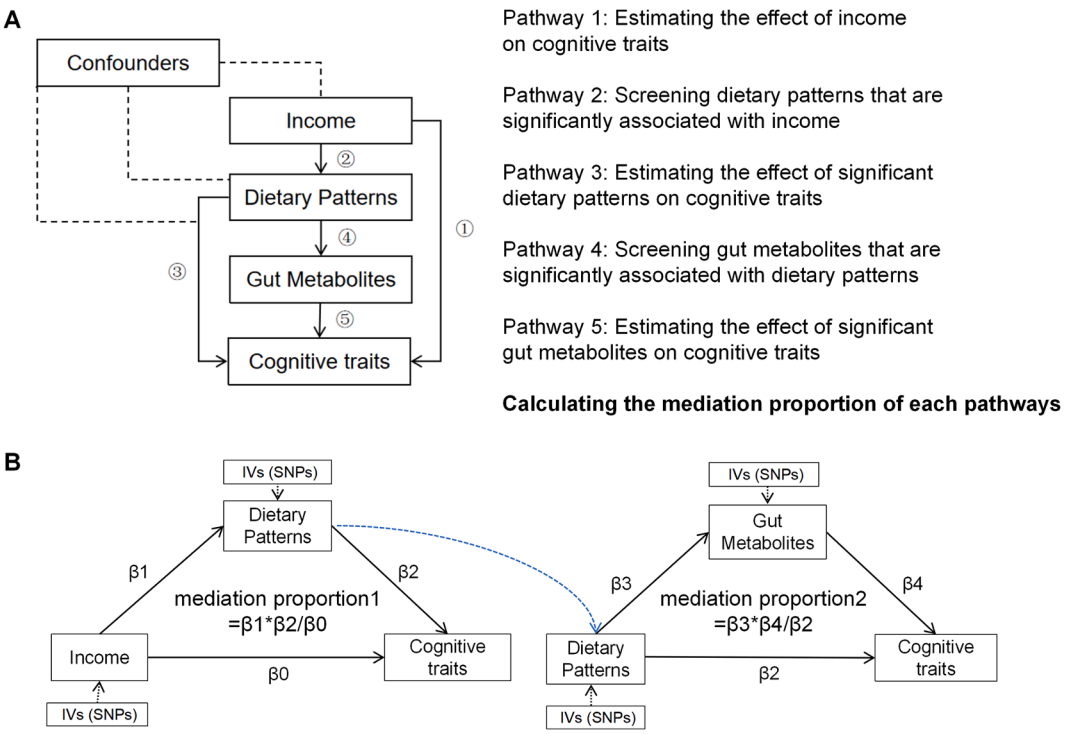

Fig. 1. Overview of the study design. IVs = instrumental variables, SNPs = single nucleotide polymorphisms.

2.6. Global cognitive score

To assess overall cognitive ability, we constructed a global cognitive score using principal component analysis (PCA) across the four cognitive tests [24,25]. Participants were included if they completed at least two of the three assessment waves and had data on at least three cognitive tasks. Missing test scores were imputed using a two-step approach: first, nearest-neighbor interpolation was conducted based on the same test scores from adjacent waves; then, multiple imputation by chained equations (MICE) was applied using baseline age, sex, ethnicity, income, and educational level as covariates [26]. All cognitive scores were standardized as z-scores. Since higher scores in RT and PMM indicate poorer cognitive performance, their z-scores were multiplied by -1 to ensure that higher values consistently represented better cognition [22]. PCA was conducted separately for each wave, and the first principal component (PC1) was extracted as the composite cognitive score. To maintain directional consistency, PC1 scores in waves i0 and i2 were multiplied by -1 to match the loading direction of wave i3. The final PC1 explained 35.4 %, 37.4 %, and 38.4 % of the total variance in waves i0, i2, and i3, respectively (**Table S4**).

For downstream analysis, we divided the overall sample into quartiles based on the PC1 distribution to define four levels of cognitive performance: Q1 (lowest quartile) indicating the poorest cognition, Q4 (highest quartile) indicating the best, and Q2–Q3 representing intermediate cognitive levels.

In the MR analysis, we obtained the GWAS statistics related to the cognitive traits from the IEU Open GWAS project, including Alzheimer's disease (ID:ieu-a-297), Dementia (ID:finn-b-F5_DEMENTIA), and Cognitive performance (ID:ebi-a-GCST006572).

2.7. Assessment of covariates

Baseline covariates were collected through the UK Biobank touchscreen questionnaire, including age, sex, ethnicity (White or non-White), employment status (yes or no), educational attainment (high or low), family history of dementia (yes or no), smoking status (never, previous or current), alcohol consumption (never, previous or current), and physical activity level (low, moderate, or high). Obesity was defined as a body mass index (BMI) greater than 30 kg/m^2. Hypertension and diabetes status were recorded as binary variables (yes or no). The Townsend Deprivation Index (TDI) was used as an indicator of material deprivation within the population, with lower (more negative) values indicating less deprivation. Participants were categorized into quartiles based on the TDI distribution.

In the MR analysis, we selected body mass index, alcohol use, ever smoked, educational attainment, physical activity, low density lipoprotein cholesterol levels, high density lipoprotein cholesterol levels, direct low density lipoprotein levels and diastolic blood pressure as confounders for bias control. All GWAS data for confounders were sourced from the IEU Open GWAS project.

2.8. Statistical analysis

Participant characteristics were summarized as mean ± standard deviation or number (percentage), depending on the distribution. Baseline characteristics were compared between individuals with and without changes in cognitive status using Welch's *t*-test for continuous variables and the chi-square test for categorical variables.

We employed a multistate Markov model to investigate the effect of income level on transitions in cognitive status, using the msm package in R for multistate modeling. The model was based on the Markov assumption, which posits that future transitions depend only on the current cognitive state, not on the historical trajectory [27]. A clock-forward modeling strategy was used, taking the baseline time as the starting point to examine the influence of income on transitions across cognitive quartiles (Q1–Q4).

Hazard ratios (HRs) and 95 % confidence intervals (CIs) for each transition pathway were estimated within a Cox regression framework [28]. The model was adjusted for covariates including age, sex, ethnicity, employment status, education level, family history of dementia, smoking status, alcohol consumption, physical activity, hypertension, diabetes, obesity status, and Townsend Deprivation Index (TDI). Missing values for covariates were imputed using the multiple imputation by chained equations (MICE) method.

We used quantile regression to examine the heterogeneous effects of income on baseline cognitive performance. Mediation analyses were conducted for 17 dietary factors, with eight ordinal variables analyzed using ordinal logistic and linear regression, and nine continuous variables using linear regression. Mediation effects were estimated by the product-of-coefficients method and tested via bootstrap. All models were adjusted for the covariates described above.

We selected SNPs significantly ($P<5*10–8$) associated with income, mediators and cognition as instrumental variables (IVs). We then removed linkage disequilibrium through setting the correlation coefficient threshold for two SNPs at r2 = 0.001 within a region range set to 10,000 kb. We also aligned the effect alleles of the IVs associated with income and cognition.

We conducted a two-sample MR to assess the causal relationship of each pathway mentioned above. Three popular MR methods were used for features containing multiple IVs: inverse-variance weighted (IVW) test, MR-Egger regression, weighted median. And we used IVW as our main approach to estimate the effect when heterogeneity or horizontal pleiotropy was acceptable. MVMR was utilized for confounders control, ensuring the reliability of causal inference between income, mediators and cognition.

We applied False Discovery Rate (FDR) adjustments for multiple comparisons in the targeted MR analyses. For the high-dimensional MR analyses, Benjamini–Hochberg FDR correction was applied within method-specific hypothesis families (e.g., IVW, MR-Egger, weighted median), treating each method as an independent hypothesis space.

The total effect of income gained in previous MR analysis can be split into direct and indirect effects. The indirect effect was estimated using the product of coefficient method, and the proportion mediated was calculated by dividing the indirect effect by the total effect. (Fig. 1**B**)

To ensure the robustness of our findings across different analytical frameworks, we performed a series of sensitivity analyses for both the observational and MR models.

For the observational analyses, we applied a linear mixed model (LMM) to the continuous global cognitive score to mitigate the impact of practice effects and separate within-person cognitive change from between-person baseline differences. The LMM incorporated random intercepts and random slopes for time. Additionally, to account for informative censoring and survival bias caused by non-random attrition and mortality, we performed an inverse probability of censoring weighting (IPCW) analysis. Stabilized weights, calculated using baseline covariates including baseline cognitive scores, were applied to the multistate Markov models to adjust for potential bias in our transition estimates.

For the MR analyses, sensitivity analyses included assessments of sample heterogeneity using funnel plot and Cochran's Q test, horizontal pleiotropy checks through MR-Egger intercept analysis, leave-one-out approach by sequentially removing each SNP to observe whether the results significantly change.

All statistical analyses were performed using the R packages: mice, mstate, ipw, lme4, two-sample MR, MR-PRESSO and MVMR.

3. Results

3.1. Participant characteristics

Table 1 presents the baseline characteristics of the study participants. Among the 25,012 individuals included, 13,457 (53.8 %) experienced changes in cognitive status during follow-up. Overall, the mean age was 54.5 years (SD = 7.54), with 49.6 % being male and 95.9 % identifying as white. A total of 76.2 % had received higher education, and 95.4 % were employed at baseline. Regarding lifestyle factors, 60.8 % were never smokers, and 95.4 % reported current alcohol consumption. The proportions of participants with high, moderate, and low physical activity levels were 41.3 %, 41.6 %, and 17.1 %, respectively. The prevalence of hypertension, diabetes, and obesity was 19.3 %, 2.7

Table 1
Baseline characteristics of study population according to cognitive status change.

Characteristic	Total N=25,012	Cognition changed		p-value
		Changed N = 13,457	Unchanged N = 11,555	
Age, Mean ± SD	54.5 ± 7.54	54.49 ± 7.46	54.5 ± 7.63	0.922[1]
Sex, n (%)				0.014[2]
Female	12,596 (50.4 %)	6874 (51.1 %)	5722 (49.5 %)	
Male	12,416 (49.6 %)	6583 (48.9 %)	5833 (50.5 %)	
Race, n (%)				<0.001[2]
Non-white	1035 (4.1 %)	449 (3.3 %)	586 (5.1 %)	
White	23,977 (95.9 %)	13,008 (96.7 %)	10,969 (94.9 %)	
Education, n (%)				0.082[2]
Low	5943 (23.8 %)	3141 (23.4 %)	2802 (24.3 %)	
High	19,041 (76.2 %)	10,309 (76.6 %)	8732 (75.7 %)	
TDI_q, n (%)				<0.001[2]
Q1 (least deprived)	6786 (27.2 %)	3755 (27.9 %)	3031 (26.3 %)	
Q2	6809 (27.3 %)	3712 (27.6 %)	3097 (26.9 %)	
Q3	6542 (26.2 %)	3511 (26.1 %)	3031 (26.3 %)	
Q4 (most deprived)	4834 (19.4 %)	2459 (18.3 %)	2375 (20.6 %)	
Smoke, n (%)				0.363[2]
Current	1516 (6.1 %)	795 (5.9 %)	721 (6.3 %)	
Never	15,185 (60.8 %)	8153 (60.7 %)	7032 (61.0 %)	
Previous	8269 (33.1 %)	4490 (33.4 %)	3779 (32.8 %)	
Physical activity, n (%)				0.107[2]
high	8959 (41.3 %)	4757 (40.6 %)	4202 (42.0 %)	
moderate	9039 (41.6 %)	4940 (42.2 %)	4099 (41.0 %)	
low	3718 (17.1 %)	2013 (17.2 %)	1705 (17.0 %)	
Hypertension, n (%)				0.377[2]
No	20,186 (80.7 %)	10,888 (80.9 %)	9298 (80.5 %)	
Yes	4826 (19.3 %)	2569 (19.1 %)	2257 (19.5 %)	
Diabetes, n (%)				0.997[2]
No	24,305 (97.3 %)	13,078 (97.3 %)	11,227 (97.3 %)	
Yes	671 (2.7 %)	361 (2.7 %)	310 (2.7 %)	
Family dementia history, n (%)				0.021[2]
No	21,402 (85.6 %)	11,451 (85.1 %)	9951 (86.1 %)	
Yes	3610 (14.4 %)	2006 (14.9 %)	1604 (13.9 %)	
Employment status, n (%)				0.609[2]
Employed	21,793 (95.4 %)	562 (4.6 %)	498 (4.7 %)	
Unemployed	1060 (4.6 %)	11,729 (95.4 %)	10,064 (95.3 %)	
Obesity, n (%)				0.576[2]
No	20,313 (81.4 %)	10,910 (81.2 %)	9403 (81.5 %)	
Yes	4649 (18.6 %)	2518 (18.8 %)	2131 (18.5 %)	
Alcohol, n (%)				0.022[2]
Current	23,862 (95.4 %)	12,882 (95.7 %)	10,980 (95.1 %)	
Never	580 (2.3 %)	281 (2.1 %)	299 (2.6 %)	
Previous	560 (2.2 %)	292 (2.2 %)	268 (2.3 %)	

[1] Welch Two Sample *t*-test
[2] Pearson's Chi-squared test

%, and 18.6 %, respectively. Additionally, 14.4 % of participants reported a family history of dementia. Compared with participants whose cognitive status remained stable, those who experienced cognitive transitions were more likely to be female and White, have higher socioeconomic status, report a family history of dementia, and consume alcohol more frequently ($P < 0.05$).

3.2. Effect of income on cognitive transitions

Fig. 2**A** illustrates the observed cognitive state transition patterns during follow-up. The analysis included four cognitive states, where Q1 represents the poorest cognitive performance and Q4 indicates the highest level of cognitive functioning [24]. Among 13,457 participants who experienced at least one cognitive transition, a total of 14,050 state changes were recorded over a median follow-up of 8.96 years (IQR: 5.93–12.32). Of these, 7429 transitions (51.6 %) represented cognitive deterioration, while 6801 (48.4 %) reflected cognitive improvement. The proportion of deterioration was slightly lower among participants in the highest income group compared to those in the lowest. Among deteriorative transitions, the most frequent was from cognitive state Q4 to Q3, followed by Q2 to Q1. For improvement transitions, Q2 to Q3 was the most common, followed by Q3 to Q4.

Fig. 2**B** illustrates the associations between income levels and the risk of cognitive state transitions. After adjusting for covariates, individuals with higher income levels exhibited a lower risk of cognitive deterioration compared to those in the lowest income group (Income Level 1). Specifically, for the transition from cognitive state Q3 to Q1, the hazard ratios (HRs) were:Level 3: HR = 0.749 (95 % CI: 0.586–0.956),Level 4: HR = 0.721 (95 % CI: 0.559–0.930) and Level 5: HR = 0.677 (95 % CI: 0.484–0.947), corresponding to relative risk reductions of 25.1 %, 27.9 %, and 32.3 %, respectively. Higher income levels appeared to be associated with a progressively lower risk of deterioration, with the most pronounced risk reduction observed in the highest income group. In addition, Income Level 2 was significantly associated with a reduced risk of transitioning from Q4 to Q1 (HR = 0.531; 95 % CI: 0.307–0.916).

However, in the direction of cognitive improvement, participants in higher income groups were also less likely to experience upward transitions. Specifically, compared to Level 1,Income Level 4 showed a significantly lower likelihood of transitioning from Q3 to Q4 (HR = 0.806; 95 % CI: 0.653–0.996), Income Level 5 showed a further reduced probability (HR = 0.721; 95 % CI: 0.569–0.913), and for the transition from Q1 to Q2, Income Level 5 also had a significantly reduced risk (HR = 0.708; 95 % CI: 0.557–0.901).

A

State transitions	Overall (N=13457)	Income levels 1 (N=1379)	2 (N=2880)	3 (N=4326)	4 (N=4207)	5 (N=1258)
Q4 Q3 Q2 Q1						
Worsening	7249(51.6)	736(53.4)	1513(52.5)	2226(51.5)	2116(50.3)	658(52.3)
	1850(25.5)	122 (8.8)	313 (10.9)	541 (12.5)	631 (15.0)	243 (19.3)
	764(10.5)	55 (4.0)	167 (5.8)	236 (5.5)	222 (5.3)	84 (6.7)
	195(2.7)	29 (2.1)	41 (1.4)	56 (1.3)	51 (1.2)	18 (1.4)
	1797(24.8)	181(13.1)	317 (11.0)	561 (13.0)	583 (13.9)	155 (12.3)
	817(11.3)	103 (7.5)	176 (6.1)	263 (6.1)	212 (5.0)	63 (5.0)
	1826(25.2)	246(17.8)	499(17.3)	569(13.2)	417(9.9)	95(7.6)
Improving	6801(48.4)	643(46.6)	1367(47.5)	2100(48.5)	2091(49.7)	600(47.7)
	1818(26.7)	246(17.8)	499(17.3)	569(13.2)	417(9.9)	95(7.6)
	728(10.7)	58(4.2)	131(4.5)	223(5.2)	242(5.8)	74(5.9)
	140(2.1)	9(0.7)	31(1.1)	49(1.1)	38(0.9)	13(1)
	1844(27.1)	157(11.4)	383(13.3)	573(13.2)	577(13.7)	154(12.2)
	620(9.1)	78(5.7)	141(4.9)	195(4.5)	163(3.9)	43(3.4)
	1651(24.3)	224(16.2)	380(13.2)	508(11.7)	431(10.2)	108(8.6)

B

State transitions	Income levels 1 (N=1379)	2 (N=2880)	3 (N=4326)	4 (N=4207)	5 (N=1258)
Q4 Q3 Q2 Q1					
Worsening					
		0.984 (0.763-1.179)	0.880 (0.714-1.083)	0.818 (0.663-1.010)	0.914 (0.725-1.154)
		1.225 (0.893-1.681)	1.067 (0.786-1.447)	0.975 (0.715-1.327)	0.964 (0.676-1.375)
	Ref	**0.531 (0.307-0.916)**	0.637 (0.390-1.040)	0.963 (0.577-1.608)	0.851 (0.451-1.605)
		1.024 (0.849-1.235)	1.051 (0.881-1.254)	1.030 (0.862-1.232)	0.950 (0.758-1.190)
		0.812 (0.631-1.044)	**0.749 (0.586-0.956)**	**0.721 (0.559-0.930)**	**0.677 (0.484-0.947)**
		1.032 (0.883-1.208)	0.981 (0.840-1.146)	0.972 (0.823-1.148)	0.947 (0.742-1.209)
Improving					
		0.938 (0.753-1.168)	0.890 (0.721-1.097)	**0.806 (0.653-0.996)**	**0.721 (0.569-0.913)**
		1.059 (0.761-1.472)	1.026 (0.750-1.404)	0.899 (0.654-1.236)	0.732 (0.503-1.066)
	Ref	-	-	-	-
		1.162 (0.962-1.404)	1.132 (0.944-1.356)	1.052 (0.875-1.266)	0.991 (0.787-1.248)
		1.171 (0.879-1.559)	1.145 (0.867-1.511)	1.044 (0.780-1.397)	0.892 (0.603-1.321)
		1.023 (0.863-1.212)	0.884 (0.750-1.042)	0.967 (0.814-1.148)	**0.708 (0.557-0.901)**

Fig. 2. (A) Number (%) of participants transitioning between cognitive quartiles (Q1–Q4) during follow-up. (B) Adjusted hazard ratios (95 % CI) for income-related cognitive transitions. Income levels: 1 = <£18,000; 2 = £18,000-£30,999; 3 = £31,000-£51,999; 4 = £52,000-£100,000, 5 = >£100,000 of average total household income before tax. Model adjusted for sex, age, ethnicity, education level, employment status, TDI, smoking status, physical activity, hypertension, diabetes, family history of dementia, obesity, and alcohol consumption. Arrows indicate transition direction. Bold indicate significant transitions (P < 0.05).

These findings suggest that while higher income is associated with protection against severe cognitive decline, the reduced likelihood of upward transitions may largely reflect baseline stability and ceiling effects rather than a true reduction in improvement potential. High-income participants typically present with higher initial cognitive status, which statistically limits the probability of observing further transitions to improved states.

3.3. Quantile regression analysis

Results from the quantile regression models demonstrated a consistent and significant positive association between income level and cognitive performance across all quantiles (all $P < 0.001$). Specifically, the coefficients represent the difference in cognitive z-scores between each income group and the lowest income group at a given percentile of the cognitive distribution. We observed that the positive impact of income was strongest among individuals with lower cognitive performance; for instance, at the 10th quantile (Q=0.10), the highest income group scored 0.832 standard deviations higher than the lowest income group, whereas this difference attenuated to 0.661 at the 90th quantile (Q=0.90) (Table 2).

Notably, a consistent positive association was observed, with higher income levels linked to better cognitive scores across income categories throughout the cognitive score distribution.

3.4. Mediation analysis in the observational study

Mediation analysis was conducted to investigate whether dietary patterns mediated the association between income and cognitive performance. Among the seventeen dietary factors assessed, ten showed significant mediation effects(**Table S5**). Cheese intake exhibited the strongest beneficial mediating role, accounting for 3.6 % of the total effect of income on cognition, followed by tea (2.1 %) and coffee (0.6 %). In contrast, bread consumption showed a detrimental mediating role, with a mediated proportion of –2.1 %.

3.5. Effects of income on cognitive traits

To further validate the associations observed in the observational analyses, we performed a two-sample MR analysis to assess the causal effect of income on cognitive traits. The MR results confirmed that higher income causally improved cognitive performance (OR = 2.140; 95 % CI: 1.923–2.381; P < 0.001; Fig. 3, **Table S6**), consistent with findings from the observational data. In addition, higher income significantly reduced the risk of AD (OR = 0.721; 95 % CI: 0.536–0.971; P = 0.031; Fig. 3), further supporting the observed protective role of income in cognitive function.

Table 2
Quantile regression analysis of the association between income levels and global cognitive scores.

Global cognitive score	Income levels			
	Income 18,000£ to 30,999£	Income 31,000£ to 51,999£	Income 52,000£ to 100,000£	Income Greater than 100,000£
Q=0.10	0.310 (0.254–0.366)	0.520 (0.462–0.577)	0.685 (0.620–0.750)	0.832 (0.743–0.922)
Q=0.25	0.248 (0.201–0.296)	0.451 (0.401–0.500)	0.635 (0.582–0.687)	0.794 (0.705–0.884)
Q=0.5	0.205 (0.164–0.245)	0.402 (0.361–0.444)	0.568 (0.523–0.613)	0.744 (0.667–0.820)
Q=0.75	0.189 (0.146–0.233)	0.372 (0.326–0.418)	0.522 (0.472–0.573)	0.717 (0.636–0.798)
Q=0.9	0.194 (0.137–0.251)	0.398 (0.340–0.457)	0.498 (0.431–0.564)	0.661 (0.561–0.760)

Reference category: income < 18,000£. Model adjusted for sex, age, ethnicity, education level, employment status, TDI, smoking status, physical activity, hypertension, diabetes, family history of dementia, obesity, and alcohol consumption. Q=0.10, 0.25, 0.50, 0.75, 0.90 represent the 10th, 25th, 50th, 75th, and 90th quantiles of cognitive score distribution, respectively. All associations were statistically significant ($P < 0.001$).

3.6. Dietary mediation pathways between income and cognitive traits

Next, we explored the mediating mechanisms by which income affects cognitive traits, and how income impacts various cognitive traits by altering dietary patterns. The first step involved using MR analysis to examine how income influences 20 dietary patterns (**Figure S4, Table S7**). Income was causally positively associated with the intake of cereal (OR = 1.111; 95 % CI: 1.052, 1.173; $P < 0.001$), cheese (OR = 1.348; 95 % CI: 1.256, 1.447; $P < 0.001$), dried fruit (OR = 1.206; 95 % CI: 1.144, 1.271; $P < 0.001$), coffee (OR = 1.086; 95 % CI: 1.037, 1.138; $P < 0.001$), fresh fruit (OR = 1.091; 95 % CI: 1.046, 1.149; $P < 0.001$), lamb/mutton (OR = 1.106; 95 % CI: 1.065, 1.149; $P < 0.001$), oily fish (OR = 1.204; 95 % CI: 1.122, 1.291; $P < 0.001$), salad/raw vegetables (OR = 1.081; 95 % CI: 1.034, 1.129; $P = 0.001$), and water (OR = 1.100; 95 % CI: 1.030, 1.174; $P = 0.004$). Conversely, income was found to be causally negatively associated with the intake of mixed vegetables (OR = 0.820; 95 % CI: 0.747, 0.899; $P < 0.001$) and processed meat (OR = 0.908; 95 % CI: 0.853, 0.967; $P = 0.003$).

The second step involved using MR analysis to examine how dietary patterns associated with income affect cognitive traits (**Table S8–9**). The results indicated that genetically predicted higher intake of cereal (OR = 1.244; 95 % CI: 1.049, 1.473; P = 0.012), cheese (OR = 1.554; 95 % CI: 1.354, 1.783; P < 0.001), dried fruit (OR = 1.540; 95 % CI: 1.172, 2.022; P = 0.002), and coffee (OR = 1.228; 95 % CI: 1.005, 1.499; P = 0.044) led to better cognitive performance.

We then observed an indirect effect of income on cognitive performance (Fig. 4**A**), mediated through specific dietary components: cereal accounted for 3.0 % of the total effect, cheese for 10.0 %, dried fruit for 10.6 %, and coffee for 2.2 %. There was no evidence of heterogeneity or horizontal pleiotropy in these associations (**Table S10–13**), indicating the validity of the instruments. Notably, the MR results partially differed from those of the observational analysis. Among the nine dietary factors identified as significant mediators in the observational study, only cheese and coffee were validated as mediators with causal effects in the MR analysis. Importantly, cheese showed the strongest beneficial mediation effect in both observational and MR frameworks.

For the above MR results, we introduced confounding factors and conducted MVMR analysis, revealing four mediating pathways from income to cognitive performance: higher income may improve cognitive performance by increasing the intake of cheese, coffee, cereal, and dried fruit. There was no mediating pathway between income and AD.

3.7. Effects of dietary patterns on gut metabolites and cognitive performance

To further elucidate the biological mechanisms through which diet influences cognition, we incorporated 1400 gut metabolites and matched them with dietary patterns to characterize the biological changes associated with different dietary habits. We specifically focused on cheese and coffee intake, which demonstrated significant mediation effects in both observational and MR analyses.

We estimated the effects of significant dietary patterns on 1400 gut metabolites and found that 162, 206, 105, and 210 metabolites were significantly associated with the intake of cheese, coffee, cereal, and dried fruit, respectively (**Table S14**). We further evaluated the effects of metabolites significantly associated with dietary patterns on cognitive performance (**Table S15,16**). The results showed that cheese and coffee intake were significantly associated with cognitive performance through 7 and 9 metabolites, respectively, while cereal and dried fruit were linked through 5 and 8 metabolites, respectively. Importantly, we identified two key metabolite ratio pathways mediating the protective

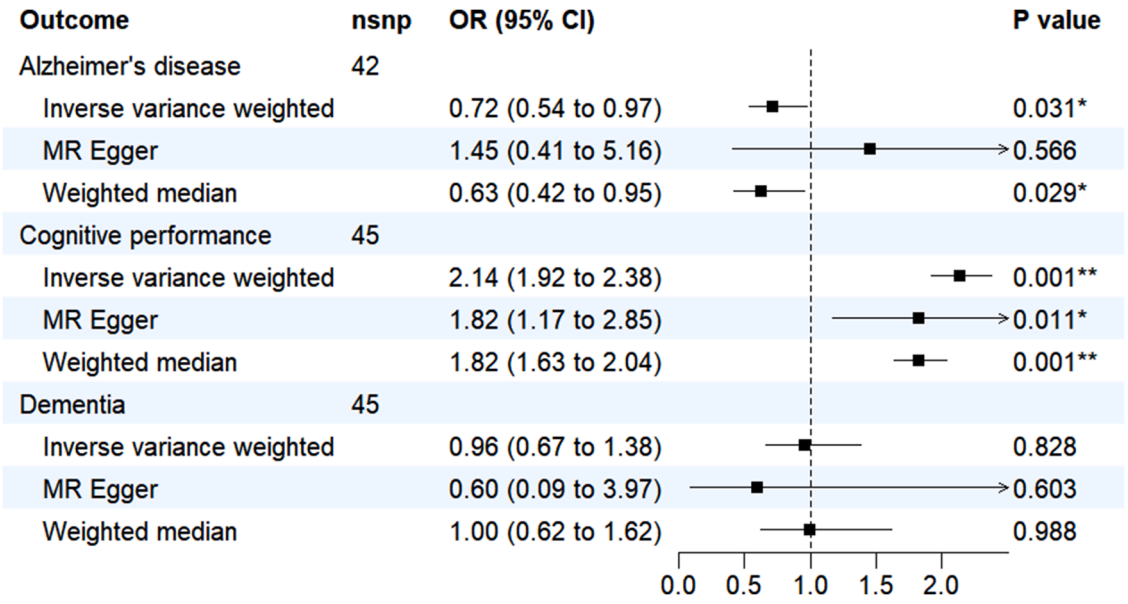

Fig. 3. Mendelian randomization analysis of causal effects between income and cognitive traits. OR = odds ratio, CI = confidence interval.

effect of cheese intake on cognitive performance: the tryptophan/tyrosine ratio, which mediated 4.3 % of the total effect, and the carnitine/ergothioneine ratio, which mediated 2.2 % of the total effect. Notably, dried fruit intake exhibited similar mediation pathways, with mediated proportions of 11.8 % and 3.1 %, respectively, through the same metabolite ratios(Fig. 4**B**).

There was no evidence of heterogeneity or horizontal pleiotropy among these associations(**Table S17–26**). In conclusion, we revealed that dietary patterns may influence cognitive performance through gut metabolites, with specific shared metabolites mediating the effects of cheese and dried fruit on cognitive performance.

3.8. Sensitivity analyses

Sensitivity analyses further confirmed the robustness of our observational results. The LMM analysis on the continuous cognitive score revealed substantial between-person baseline differences but consistent within-person decline rates($\beta = -0.007$ per year, $p < 0.001$). After adjusting for individual baseline differences, higher household income remained significantly associated with both a higher baseline cognitive score(income linear trend: $\beta = 0.417$, $p < 0.001$) and a slower rate of cognitive decline over time(income linear trend × time: $\beta = 0.006$, $p = 0.001$), aligning perfectly with our primary Markov model findings (**Table S27**). Furthermore, the IPCW analysis suggested the presence of informative censoring, as higher baseline cognitive impairment significantly increased the odds of dropout (**Table S28**). Applying the IPCW weights to the Markov transition models demonstrated that our primary estimates were highly robust. After adjusting for informative censoring, the protective effect of higher household income against cognitive deterioration remained strong, and additional significant protective pathways emerged, indicating that selective attrition of higher-risk individuals may have led to a modest underestimation of the protective effects of household income in the primary analysis (**Table S29**).

Similarly, we conducted several sensitivity analyses for our MR analysis of income on AD and cognitive performance. There was no heterogeneity or horizontal pleiotropy in the causal inference of income on AD and cognitive performance, meaning that the SNPs could only influence AD and cognitive performance through income (**Figure S2, Table S30**). Leave-one-out approach enhanced the robustness of our MR estimates, suggesting that there was no any omission of single SNP of income that significantly influenced the association relationship (Figure S3).

4. Discussion

This study integrates observational analyses based on UK Biobank data with MR analyses to systematically investigate the impact of SES, proxied by income, on cognitive performance and its potential mediating mechanisms. Our findings provide robust evidence for a causal relationship between higher income and both better cognitive performance and a lower risk of dementia. By adjusting for potential confounders, including education, one of the important indicators of SES, we further highlight the independent role of income in promoting cognitive function. This is in accordance with a previous longitudinal study of dementia incidence among the elderly in England [29]. Our findings are plausible because increasing income levels contribute to digital literacy improvement, manifested in richer resource acquisition and leisure modality [30], which subsequently facilitate the stimulation of cognition and enhancement of cognitive reserve [31]. Cognitive reserve is a concept of mismatch between cognitive performance and neurodegenerative pathology, and individuals with high cognitive reserve can mitigate the impact of AD pathological burden on brain function for a longer time [32]. Therefore, low-income individuals may be more susceptible to cognitive decline and develop AD, which is consistent with our findings.

Our observational cohort analysis further revealed a clear association between income levels and transitions across cognitive states. The relationship between income and cognitive transitions varied across the five income groups. Consistent with findings from the HRS and ELSA cohorts [5], we found that individuals with higher income levels were at lower risk of cognitive deterioration over time, particularly along the transition pathway from moderate cognitive function (Q3) to poor cognition (Q1).

Interestingly, our results also showed that individuals in higher income groups were less likely to experience cognitive improvement, either from poor cognition (Q1) to moderate (Q2), or from moderate (Q3) to high cognitive functioning (Q4). Data from the Chinese Longitudinal Healthy Longevity Survey (CLHLS) have shown that higher SES is associated with better baseline cognitive performance, but that this advantage diminishes over time [33], which may help explain our observations. Furthermore, our quantile regression results indicate that high-income individuals consistently exhibited superior baseline

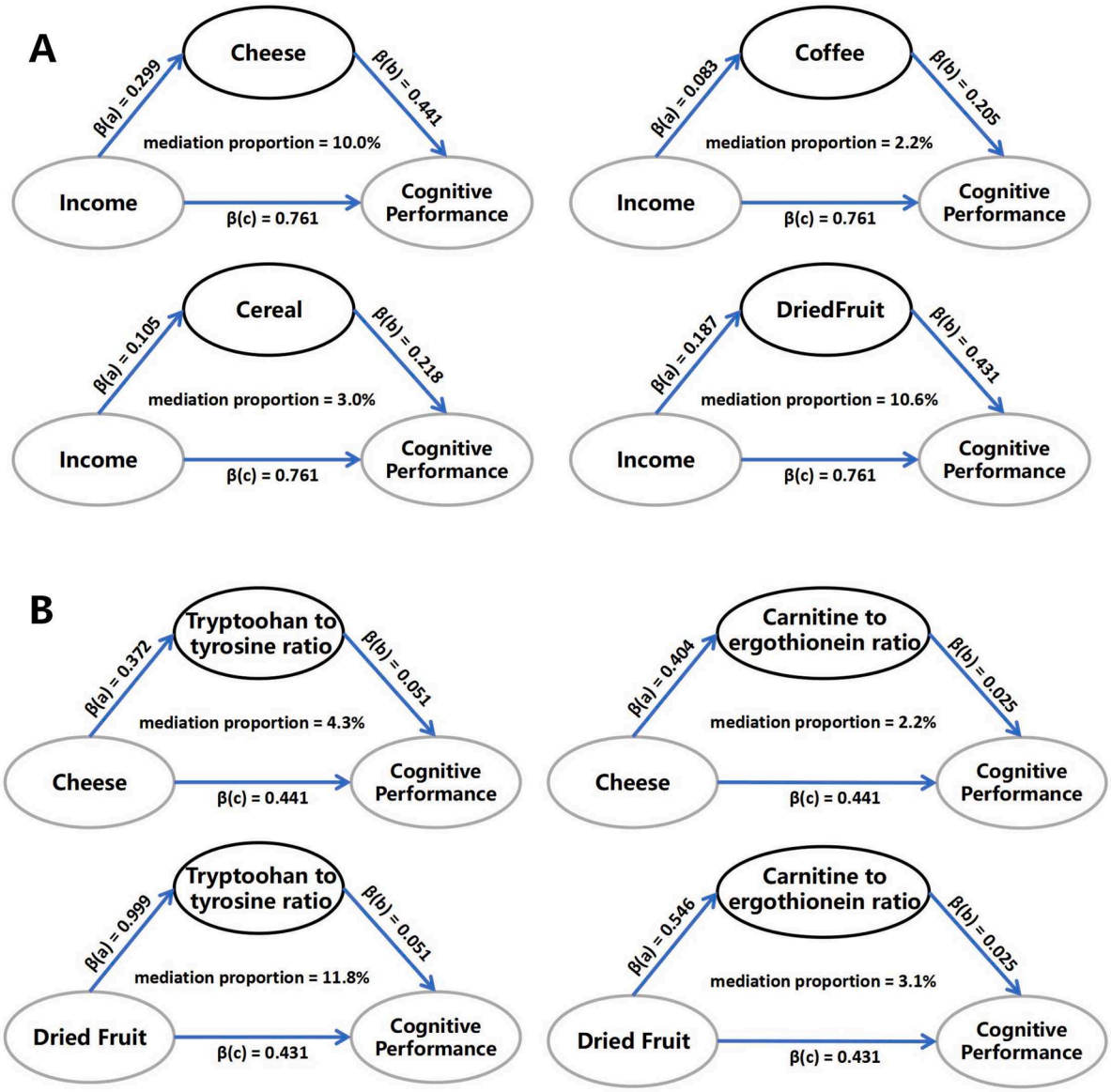

Fig. 4. (A) Mediation effects of cheese, coffee, cereal, and dried fruit on the association between income and cognitive performance in Mendelian randomization analysis. (B) The mediation effects of gut metabolites on the association between dietary patterns and cognitive performance (a. Cheese on cognitive performance through tryptophan to tyrosine ratio; b. Cheese on cognitive performance through carnitine to ergothionein ratio; c. Dried fruit on cognitive performance through tryptophan to tyrosine ratio; d. Dried fruit on cognitive performance through carnitine to ergothionein ratio).

cognitive function, limiting their potential for further upward transition. This phenomenon aligns with the "compensation effect" observed in cognitive intervention studies. For instance, a study on cognitive training for the elderly found that participants with higher education levels showed smaller improvements in cognitive scores compared to those with lower education [34]. Similarly, a meta-analysis of individual differences in training outcomes highlighted that "ceiling effects" often restrict high-performing individuals from demonstrating significant gains, whereas those with weaker initial abilities gain the most by mastering fundamental skills [35]. As noted by Shaw and Hosseini, this pattern is frequent in memory tasks where lower baseline ability predicts larger subsequent gains [36]. Therefore, the lower likelihood of improvement in the high-income group likely reflects their already optimized cognitive status, suggesting that the primary advantage of high income lies in the preservation of cognitive function rather than the likelihood of improving from a high baseline. Furthermore, it is critical to acknowledge that in the context of the natural history of aging, true cognitive improvement is relatively rare without targeted interventions.

The quantile regression model further revealed the complexity and heterogeneity in the association between income and cognitive performance. The results showed a significant positive association across all quantiles, with a clear dose–response relationship. Notably, the effect of income varied across the distribution of cognitive ability: the positive association between income and cognitive performance was stronger at the lower end of the cognitive spectrum(e.g., at the 0.10 quantile, the coefficient for the highest income level was 0.832), whereas the effect was relatively attenuated at the higher end (e.g., coefficient of 0.661 at the 0.90 quantile). These findings suggest that the association between income and cognitive performance is particularly pronounced in individuals with lower baseline cognitive abilities, highlighting the complex mechanisms through which socioeconomic status influences cognitive functioning. This also implies that tailored intervention strategies may be required for individuals with different baseline cognitive levels.

Dietary patterns play a pivotal role in cognitive health. For instance, pro-inflammatory diets can increase the risk of dementia through

systemic inflammation [37], whereas adequate dietary choline intake has been linked to better cognitive performance [38]. Diet is likely to serve as a mediating pathway between income and cognitive function. A recent U.S. cohort study found that older adults living in low-income urban communities with limited food access experienced a faster rate of cognitive decline [39]. Economic resources influence the quality of available food, and these dietary differences may affect brain health through mechanisms such as inflammation, oxidative stress, and nutrient availability [40]. Importantly, dietary interventions offer opportunities for prevention and can be translated into public health strategies. Therefore, we focused on exploring diet as a mediating mechanism in this study.

Mediation analysis in UK Biobank identified multiple dietary factors as mediators, including cognitive benefits of tea, coffee, and cheese, as well as detrimental impact of ultra-processed foods (bread), meat products (beef, poultry, processed meat), vegetables, and fish. However, only cheese and coffee showed consistent effects in subsequent MR analysis, suggesting that other observed associations may involve confounding factors or reverse causality rather than true causal relationships [41].

MR uses genetic variants as instrumental variables to assess potential associations between exposures and outcomes, thereby strengthening causal inference [42]. By leveraging genetic instruments fixed at conception, this framework also reduces confounding arising from environmental and behavioral factors, which is a key limitation of traditional observational mediation analyses.

Our two-step MR analysis, based on genetic evidence, further confirmed the benefit of income on cognitive performance, and identified a protective causal effect between income and the risk of AD. In addition, the use of multivariable MR allowed us to estimate the effect of dietary factors on cognition while adjusting for the shared genetic instruments of household income. This approach helps mitigate potential genetic pleiotropy between household income and dietary factors.

Through a comprehensive evaluation of different dietary preferences, we found that cereal, cheese, dried fruit, and coffee mediated the association between income and cognitive performance. It is crucial to interpret these specific food items not merely in isolation but as integral components of broader neuroprotective dietary patterns. For instance, cereals and dried fruits are foundational elements of the Mediterranean, DASH, and MIND diets, all of which have been consistently linked to reduced Alzheimer's disease risk. Consistent with this perspective, we interpret our results within a hierarchical framework: higher income likely facilitates the adoption of these holistic healthy dietary patterns, which are statistically captured here through specific marker foods.

Diet-derived gut metabolites are increasingly recognized as proximate mediators linking dietary patterns to brain health [43,44]. Higher Dietary Approaches to Stop Hypertension (DASH) scores and Beneficial-to-Gut-Microbiota Scores (BGMS) have been associated with better cognitive performance and a lower prevalence of psychometric mild cognitive impairment (p-MCI) [45]. Our subsequent analysis of 1400 gut metabolites revealed that the cognitive benefits of cheese and dried fruit intake were partially mediated through specific amino acid and carnitine-related metabolic pathways. These findings suggest that socioeconomic status may influence cognitive performance through multiple dietary patterns and their downstream gut metabolites, supported by both observational and genetic evidence. In the following sections, we interpret the key findings of our study from multiple perspectives, within the context of prior research.

Multiple common dietary patterns mediate the relationship between income and cognitive performance. Both observational studies and MR analysis demonstrated that higher income levels were associated with better cognitive performance, and that cheese and coffee intake showed significant positive mediating effects in both approaches, with cheese exhibiting the highest mediation proportion in both methods. However, the mediating foods identified by the two methods also showed partial inconsistencies. This may be because observational studies cannot adequately adjust for confounding factors, which can impact the results and lead to observed differences between observational and MR studies [46]. Observational studies are susceptible to these potential confounding or lifestyle factors, and certain associations may not represent true causality, whereas MR analysis inherently utilizes genetic data as a bridge to explore the causal relationship between income and cognition, effectively reducing the risk of reverse causality and minimizing the influence of confounding factors [47].

Cheese, a fermented dairy product rich in protein and saturated fats [48], aligns with our findings, as multiple studies have reported that cheese consumption is associated with improved episodic memory and fluid intelligence [49], and with reduced risk of cognitive impairment and dementia. However, the saturated fat content of cheese may potentially increase the risk of cognitive decline. Therefore, it is important to stratify consumption by both cheese intake and fat content to explore their differential effects on cognitive function.

Coffee is important dietary sources of polyphenols and caffeine [50]. Polyphenols have been shown to exert protective effects on specific cognitive domains, most notably frontal executive functions, such as attention, processing speed, and memory encoding, consolidation, and retrieval [51]. Some studies suggest a J-shaped relationship between coffee consumption and the risk of cognitive impairment, such that drinking 1–2 cups per day is associated with the lowest risk, but excessive consumption of coffee or tea may increase the risk of Alzheimer's disease [52]. This adverse effect may be attributed to caffeine, which can cause sleep disturbances, anxiety, and impair fluid intelligence [53]. Taken together with our findings, we believe that moderate consumption of coffee should be supported.

Studies of gut metabolites downstream of the diet revealed the mediating role of the tryptophan/tyrosine ratio and carnitine/ergothionein ratio in the effects of cheese and dried fruit on cognitive performance. Tryptophan is the main amino acid contained in cheese, and indole, a product of tryptophan catabolism by gut microbiota, can penetrate the blood-brain barrier, inhibit astrocyte activation and reduce neuroinflammation [54]. Short-term oral administration of tryptophan-tyrosine-rich whey peptide improved episodic and spatial memory in mice, probably through activation of the dopamine system in the prefrontal cortex [55]. Serum acyl-carnitine levels show a continuous decrease in AD patients compared with normal individuals and mild cognitive impairment (MCI) patients [56]. L-carnitine may improve memory and cognition by regulating antioxidant status, preventing amyloid plaques deposition and neuronal death [57]. However, the specific role of metabolites and their sequence in AD progression as well as the upstream and downstream relationship are still unclear and need further study.

Our findings are supported by a study on income modulating dietary pattern adherence, which found that high-income participants were more likely to maintain the healthy constituents of the diet such as nuts, vegetables and cereals, and presented a slower decline of cognitive function and memory [58]. The price of food affects the dietary choices of low-income individuals, who do not tend to purchase foods that are relatively high in fiber and low in fat, salt, and sugar [59]. Moreover, in low-income countries, food systems may be more inclined to energy-dense and ultra-processed unhealthy foods, increasing the availability of unhealthy foods for low-income populations [60]. Therefore, efforts to reform food supply systems, control food prices, and shift in food consumption habits to healthier patterns among low-earning groups are necessary to bridge the wealth gap in dementia incidence.

Our study highlights the potential of dietary intervention as an important strategy to improve cognitive outcomes in low-income individuals. Specifically, we found that higher intake of cereal, cheese, dried fruit, and coffee mediated the association between income and cognitive performance, suggesting that promoting access to and consumption of these nutrient-rich foods may help mitigate income-related disparities in cognitive health. Previous studies have revealed that other

unhealthy tendencies in poor individuals, including physical inactivity, social isolation and sleep disorders, not only affect cognitive function but also are associated with pathological changes in AD such as brain amyloid deposition and altered glucose metabolism in the cerebral cortex [61,62].

The development of AD may be the long-term result of cognitive decline caused by changes in dietary habits and other lifestyle factors. Therefore, dietary choices should be considered as one potential target when developing strategies for the prevention of pre-dementia cognitive decline among low-income populations.

Strengths of our study include the first-ever integration of large-scale observational data from UK Biobank with MR analysis, combining real-world evidence with genetic causal inference to provide comprehensive and robust insights into dietary mediation of the income–cognition relationship. We leveraged large-scale GWAS summary data and genetically determined tools assigned at conception as instrumental variables for exposures and mediators—a random and natural process that reduces confounding and reverse causality bias, while offering a holistic profile of dietary patterns and downstream gut metabolites mediating the effect of income on cognitive performance. Sensitivity analyses further strengthen the validity of our findings.

This study also has several limitations. First, despite the use of multiple statistical methods to control for confounding factors, the observational cohort design remains susceptible to residual confounding, selection bias, and information bias. In particular, the UK Biobank may be affected by a healthy volunteer effect, whereby individuals with higher socioeconomic status and better health are overrepresented, potentially leading to an underestimation of socioeconomic inequalities and limiting the generalizability of our findings. Second, the cognitive tests used in the UK Biobank may exhibit ceiling effects among high-functioning individuals, which could affect the accurate assessment of cognitive improvement difficulties observed in the high-income group. In addition, the derived global cognitive score primarily reflects processing speed, memory, and reasoning domains, while other cognitive dimensions may not comprehensively assessed. Future studies should employ more sensitive cognitive assessment tools. Third, The Markov assumption implies that transition risks depend only on the current cognitive state. As cognitive decline may be influenced by long-term exposures such as chronic disease burden or psychological stress, our findings reflect state-conditional associations and may differ if prior history or cumulative effects were considered. Fourth, the potential limitation of utilizing income level as genetic data is that assortative mating, which means nonrandom mating based on income level, may therefore confound SNP-income associations and bias MR Estimates, genetic data within families (e.g., parent-offspring, siblings) may be a solution for further validation. Finally, the GWAS data used in this study were predominantly derived from white European populations in high-income countries, and thus, the generalizability of our findings to other ethnic groups or developing countries requires further investigation.

5. ConclusionThis study, by integrating observational analyses from the UK Biobank with MR, provides evidence for a causal association between income and cognitive performance. Cheese and coffee consistently exhibited beneficial mediating roles in both approaches, with cheese and dried fruits primarily exerting cognitive benefits through amino acid and antioxidant metabolic pathways, such as the tryptophan/tyrosine and carnitine/ergothioneine ratios. These findings highlight the potential of dietary interventions to mitigate income-related cognitive decline.

Abbreviations

SES	Socioeconomic Status
MR	Mendelian Randomization
GWAS	Genome-wide association studies
AD	Alzheimer's disease
RT	Reaction Time
NM	Numeric Memory
FI	Fluid Intelligence
PMM	Pairs Matching Memory
PCA	Principal Component analysis
MICE	Multiple Imputation by Chained Equations
LMM	linear mixed model
IPCW	inverse probability of censoring weighting
TDI	Townsend Deprivation Index

Author contributions: credit

Xingguang Zhao: Conceptualization, Data curation, Formal analysis, Writing – original draft. **Weijian Wu:** Data curation, Validation, Writing – original draft. **Qiaoxuan Zhang:** Methodology, Writing – review & editing. **Mengqian Ouyang:** Formal analysis, Writing – review & editing. **Haoyu Luo:** Validation. **Qun Yu:** Project administration. **Yingren Mai:** Data curation. **Zhiyu Cao:** Data curation. **Shaoqing Yang:** Writing – review & editing. **Mingsong Xu:** Project administration, Validation. **Jun Liu:** Project administration, Writing – review & editing, Funding acquisition. **Wang Liao:** Conceptualization, Project administration, Writing – review & editing.

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Data availability

The observational data underlying the results presented in this study are available from the UK Biobank upon successful application (https://www.ukbiobank.ac.uk/). The data used for the Mendelian randomization analyses can be obtained from the IEU Open GWAS project (https://gwas.mrcieu.ac.uk/), and Index of pub/databases/gwas/summary_statistics (https://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/).

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the authors used ChatGPT to improve the clarity and language of the manuscript. After using this tool, the authors carefully reviewed and edited the content as necessary and take full responsibility for the content of the published article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100582.

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