

Plasma metabolomic signatures of nut consumption and their associations with cognitive function



Mengjia Zhao, MPH^{1#}, Siya Shan, BM^{1#}, Tongtong Li, PhD¹, Gulisiya Hailili, PhD¹, Yuhui Li, BM¹, Hangrui Zhang, BM¹, Yimin Zhu, BM¹, Minyu Wu, PhD¹ and Changzheng Yuan, ScD^{1,2*}

¹ School of Public Health, the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China.

² Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA.

✉ Mengjia Zhao, Email: zhmj2521@zju.edu.cn



KEY TAKE AWAYS

Our study identified replicable plasma metabolomic signatures of nut consumption and showed that these signatures partially mediated the positive association between nut intake and cognitive function.

BACKGROUND

Evidence is limited on the associations between nut consumption, their plasma metabolomic signatures and cognitive function.

METHODS

Design and participants: We used data from two prospective cohorts of adults aged ≥ 45 years: UK Biobank (UKB, N = 10,306) and Whitehall II (WHII, N = 5,877).

Metabolite identification: Plasma metabolites associated with nut consumption (consumer vs. non-consumer) were independently identified in each cohort.

Score construction: Cohort-specific metabolite scores for nut intake were constructed using elastic-net regression.

Mediation analysis: The potential mediating role of these metabolite scores in the nut consumption–cognition association was evaluated using causal mediation analysis.

CONCLUSION

Our study supports the positive association between nut consumption and cognitive function and identifies replicable plasma metabolomic signatures of nut intake. These signatures offer objective biomarkers to complement dietary assessment and open new avenues for understanding the nuts-cognition.

RESULTS

Figure1. Heatmap of plasma metabolites associated with nut consumption in the UK Biobank and Whitehall II

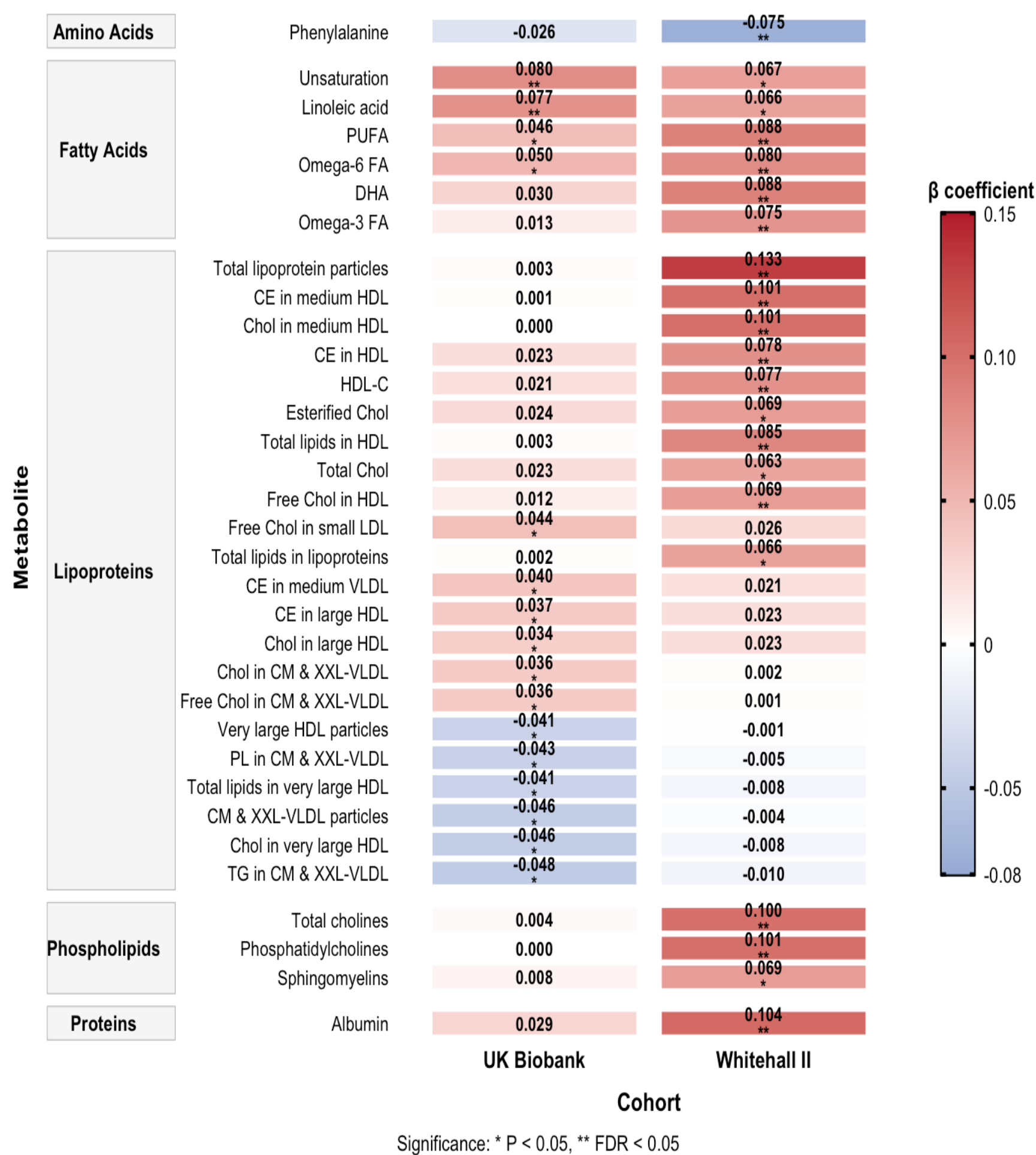


Table 1. Multivariable-adjusted associations between nut consumption and global cognitive function in the UK Biobank and Whitehall II

Variables	Non-consumers (0 g/day)	Consumers (>0 g/day)	P value
UK Biobank			
Nut consumption, median (Q1, Q3)	0	9.0 (3.0, 20.0)	/
Model 1, β (95% CI)	Reference	0.009 (0.006, 0.012)	<0.001
Model 2, β (95% CI)	Reference	0.009 (0.006, 0.012)	<0.001
Model 3, β (95% CI)	Reference	0.010 (0.007, 0.013)	<0.001
Whitehall II			
Nut consumption, median (Q1, Q3)	0	2.0 (2.0, 7.1)	/
Model 1, β (95% CI)	Reference	0.057 (0.023, 0.092)	0.001
Model 2, β (95% CI)	Reference	0.051 (0.016, 0.085)	0.004
Model 3, β (95% CI)	Reference	0.043 (0.008, 0.078)	0.011

Model 1 was adjusted for age, age square, sex, race, education level, married status (only in the WHII), income level, BMI, smoking status, and physical activity. Model 2 was adjusted for variables in Model 1 plus hypertension, diabetes, heart disease, stroke, depressive symptoms, cancer, and total energy intake. Model 3 was adjusted for variables in Model 2 plus the modified Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet score (excluding nut consumption).

Table 2. Causal mediation analysis of the nut-cognition association by the cohort-specific metabolite scores

Effect	β (95% CI)	P value
UK Biobank		
Total Effect	0.086 (0.026, 0.150)	0.006
Direct Effect	0.078 (0.017, 0.140)	0.012
Indirect Effect (ACME)	0.008 (0.000, 0.020)	0.030
Proportion Mediated, %	9.33 (0.40, 36.00)	0.036
Whitehall II		
Total Effect	0.052 (0.012, 0.091)	0.008
Direct Effect	0.039 (-0.001, 0.077)	0.058
Indirect Effect (ACME)	0.013 (0.008, 0.018)	<0.001
Proportion Mediated, %	24.84 (11.30, 96.90)	0.008

All models were adjusted for age, age square, sex, race, education level, income level, BMI, smoking status, physical activity, hypertension, diabetes, heart disease, stroke, depressive symptoms, cancer, total energy intake, and the modified Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet score (excluding nut consumption). The Whitehall II model was additionally adjusted for married status.

- Nut consumption was significantly associated with **better global cognitive function** in both cohorts: **UKB: $\beta = 0.010$, 95% CI: 0.007–0.013; WHII: $\beta = 0.043$, 95% CI: 0.008–0.078.**
- Several **nut-associated metabolites** were discovered and replicated across cohorts, including amino acids, fatty acids, lipoprotein subclasses, phospholipids, and proteins.
- The **cohort-specific metabolite scores** significantly mediated the association between nut consumption and global cognitive function, accounting for 9.3%–24.8% of the total effect: **UKB: 9.3%;WHII: 24.8%.**