

The synergistic impact of homocysteine and docosahexaenoic acid (DHA) on cognitive functioning and impairment: insights from The Maastricht Study

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Background

- 45% of all dementia cases could potentially be delayed or prevented through the modification of fourteen risk factors. Nutritional factors are not yet fully recognized as such due to suggestive but inconclusive evidence.¹
- However, elevated plasma homocysteine, reflecting low B-vitamin status, and lower plasma docosahexaenoic acid (DHA) levels have been associated with poorer cognition.
- Moreover, emerging evidence suggests a potential synergistic interaction between B-vitamins and DHA.
- The **ERA4Health Boomerang project** was initiated to investigate this potential interaction across different European cohorts.

Aim of this study

To assess the interaction between plasma homocysteine and plasma DHA in relation to cognitive functioning and impairment in the Dutch population-based cohort The Maastricht Study.

Methods

- This study used cross-sectional data from the population-based cohort The Maastricht Study (n = 1,092, 59.8 ± 7.9 years, 50.0% women). The Maastricht Study is enriched with type 2 diabetes mellitus participants.²
- Multiple linear regression analysis was used to assess the association of homocysteine and DHA with cognitive functioning.
- Binary logistic regression analysis was used to assess the association of homocysteine and DHA with prevalent cognitive impairment (23.26% cognitively impaired).
- All statistical analyses were adjusted for demographic, somatic and lifestyle factors.

References

- Livingston G, Huntley J, Liu KY, et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. Lancet. 2024;404(10452):572-628.
- Schram MT, Sep SJS, van der Kallen CJ, Dagnelie PC, Koster A, Schaper N, et al. The Maastricht Study: an extensive phenotyping study on determinants of type 2 diabetes, its complications and its comorbidities. European Journal of Epidemiology. 2014;29(6):439-51.

Measurements

-  Plasma homocysteine levels were measured by liquid chromatography (LC) tandem mass spectrometry (MS) (LC/MS-MS).
-  Plasma DHA levels were measured by nuclear magnetic resonance (NMR) spectroscopy.
-  Cognitive functioning was tested across three domains: verbal memory, information processing speed, and executive functioning and attention.
-  Cognitive impairment was defined as 1.5 SD below the norm for age, sex and education in any cognitive domain.

Results

- There was a significant interaction between homocysteine and DHA in their relation to cognitive functioning ($p_{\text{interaction}} = 0.019$), indicating that **at lower homocysteine concentrations, higher DHA was related to better cognitive functioning** (Figure 1).
- Analyses stratified on homocysteine tertiles were consistent with this interaction: the positive association between DHA and cognitive functioning was most pronounced in the lowest and middle tertile and not present in the higher tertile (Table 1).
- A similar interaction was observed for cognitive impairment ($p_{\text{interaction}} = 0.050$), with a comparable pattern of associations across homocysteine tertiles.
- Individually, neither homocysteine nor DHA showed significant independent associations with cognitive functioning or cognitive impairment.

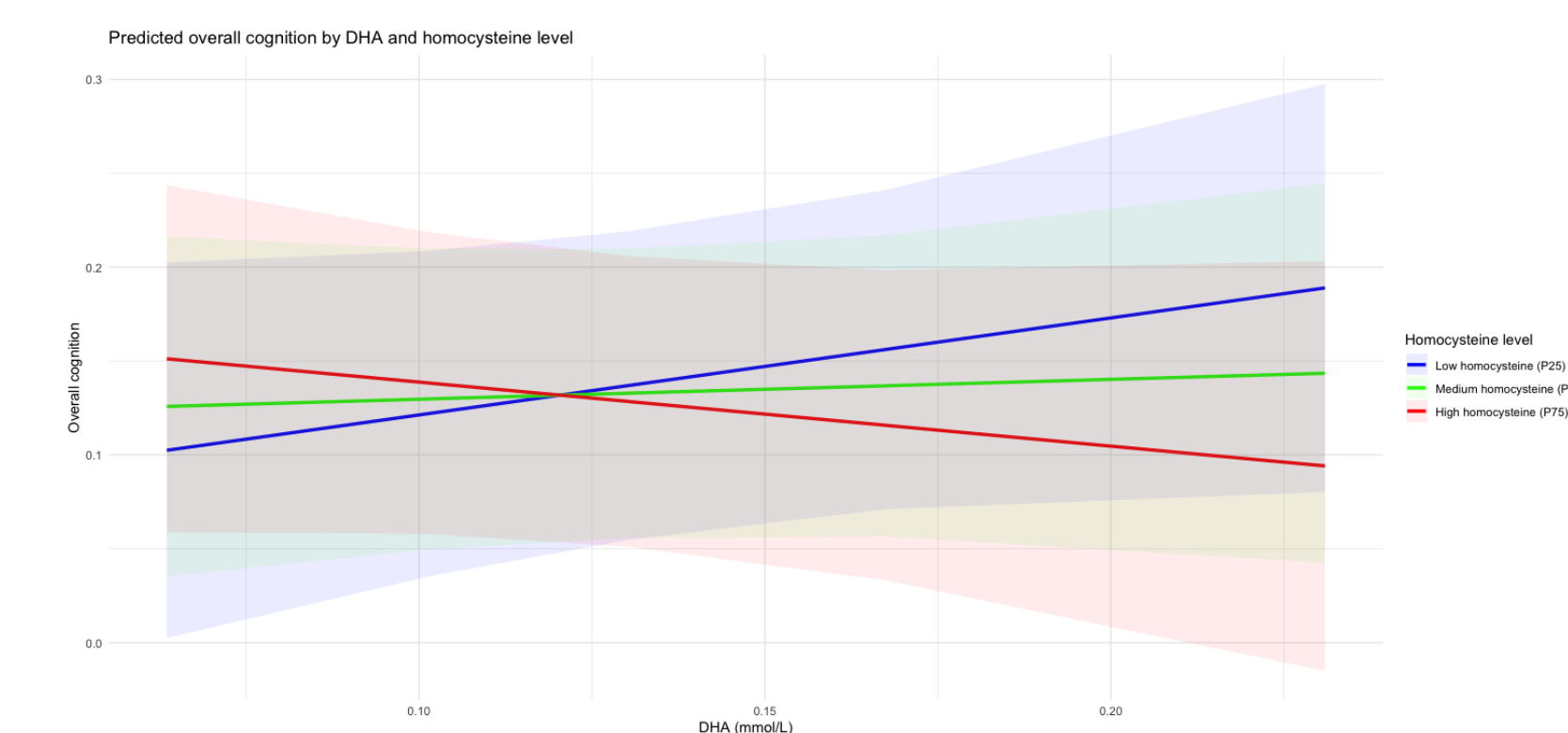


Figure 1. Predicted overall cognition score by the interaction between DHA and homocysteine levels

	Low homocysteine			Middle homocysteine			High homocysteine		
	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value
Model 1	-0.739	-2.001 – 0.523	0.250	-0.136	-1.433 – 1.160	0.836	-0.715	-1.987 – 0.557	0.270
Model 2	0.058	-0.988 – 1.104	0.913	0.403	-0.694 – 1.499	0.470	-0.384	-1.448 – 0.681	0.479
Model 3*	0.112	-1.048 – 1.272	0.850	0.648	-0.581 – 1.877	0.301	-0.348	-1.535 – 0.838	0.564
Model 4	0.361	-0.917 – 1.639	0.579	0.039	-1.224 – 1.302	0.951	-0.919	-2.216 – 0.377	0.164

B = regression coefficient; CI = confidence interval

Model 1: Crude

Model 2: Model 1 + adjusted for age, sex, education, T2DM

Model 3*: Model 2 + adjusted for hypertension, history of cardiovascular disease, depression, antidepressants, cholesterol, lipid-modifying medication, Body Mass Index, estimated Glomerular Filtration Rate, triglycerides

Model 4: Model 3 + adjusted for smoking status, physical activity, energy intake, alcohol consumption

* Main model

Table 1. Association between DHA and cognitive function stratified by homocysteine levels

Conclusion

- These preliminary findings in The Maastricht Study suggest that **DHA may indeed be beneficial for cognition, but only when homocysteine is low**.
- Given that nutritional factors such as B-vitamins and DHA are modifiable, these may represent potential new targets for dementia risk reduction.

