GENETICALLY PREDICTED EFFECTS OF DHA AND EPA ON COGNITIVE PERFORMANCE: EVIDENCE FROM TWO-SAMPLE MENDELIAN RANDOMIZATION

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Background: Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are biochemically distinct long-chain omega-3 polyunsaturated fatty acids with different brain distributions and metabolic roles. Despite their biological specificity, most intervention trials administer combined supplements, precluding fatty acid-specific causal conclusions. Whether individual circulating DHA and EPA levels exert independent effects on cognitive function remains unresolved.

Aim of the study: To estimate and formally compare the genetically predicted causal effects of circulating DHA and EPA on reaction time and general cognitive performance using a two-sample Mendelian randomization (MR) framework, with explicit assessment of FADS-cluster pleiotropy.

Materials and methods: Genome-wide significant SNPs were selected as instrumental variables for circulating DHA (N = 115,082; 45 independent instruments after LD clumping) and EPA (N = 7,367; 1 instrument), both from European-ancestry GWAS. Outcome GWAS included reaction time (N = 443,396; UK Biobank) and general cognitive performance (N = 257,828; Savage et al. 2018). LD clumping was performed locally using PLINK v1.90 and the 1000 Genomes Phase 3 European reference panel ($r^2 < 0.001$). Primary analysis used the inverse-variance weighted (IVW) method; sensitivity analyses included MR-Egger, weighted median, weighted mode, and MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) with outlier correction.

Results: Neither DHA nor EPA showed causal effects on reaction time across all analytical methods; null results were confirmed by MR-PRESSO outlier correction (distortion test p = 0.464). For cognitive performance, apparent negative DHA effects detected by pleiotropy-robust methods (weighted median: $\beta = -0.049$, $p = 5.2 \times 10^{-6}$; MR-Egger: $\beta = -0.064$, p = 0.011) did not survive MR-PRESSO outlier correction: removal of four fatty acid desaturase (FADS)-cluster instruments reversed the DHA estimate to non-significance ($\beta = +0.008$, p = 0.555; distortion test p = 0.002), indicating material violation of the exclusion restriction assumption. The single-instrument EPA estimate ($\beta = -0.395$, $p = 5.4 \times 10^{-6}$) cannot be assessed for pleiotropy and remains hypothesis-generating.

Conclusions: Genome-wide instrument selection for circulating DHA and EPA at the FADS locus does not support fatty acid-specific causal inference on cognitive outcomes. Apparent effects reflect FADS-cluster pleiotropy rather than direct neurobiological action of individual omega-3 fatty acids. Future MR studies on omega-3 cognition require larger EPA GWAS datasets with multiple independent instruments outside the FADS region.

Keywords: Mendelian randomization, omega-3 fatty acids, cognitive performance, FADS gene cluster, pleiotropy, causal inference

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