

APOE Genotype Modifies Within-Person Associations of the Carbohydrate-to-Fat Ratio with Cognition

Jakob Norgren¹, Adrián Carballo-Casla^{2, 3}, Giulia Grande^{2, 4}, Anne Börjesson-Hanson^{1, 4}, Hong Xu¹, Maria Eriksdotter^{1, 6}, *Erika J Laukka^{2, 4}, *Sara Garcia-Ptacek^{1, 6}.

¹Division of Clinical Geriatrics, Center for Alzheimer Research, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden. ² Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet & Stockholm University, Stockholm, Sweden. ³ Center for Networked Biomedical Research in Epidemiology and Public Health (CIBERESP), Madrid, Spain. ⁴ Stockholm Gerontology Research Center, Stockholm, Sweden. ⁵ Clinical Trial Unit, Department of Geriatrics, Karolinska University Hospital, Stockholm, Sweden. ⁶ Theme Inflammation and Aging, Karolinska University Hospital, Stockholm, Sweden. * Shared senior-authorship

In *APOE* $\epsilon 3/\epsilon 4$ and $\epsilon 4/\epsilon 4$ carriers, Global Cognition was better when their diet included less Carbohydrates and more Fat.

Background: The *APOE* $\epsilon 4$ allele increases Alzheimer's risk and modifies responses to dietary factors. We aimed to replicate our previous findings from the FINGER cohort (Figure 1) that a lower dietary carbohydrate-to-fat ratio was more favorably associated with global cognition among individuals with *APOE* genotypes $\epsilon 3/\epsilon 4$ and $\epsilon 4/\epsilon 4$ (*APOE*34/44) than among non-*APOE*34/44.

Method: We analyzed data from the Swedish National study on Aging and Care in Kungsholmen (SNAC-K), including participants aged ≥ 60 years with dietary and cognitive assessments at baseline and at least one follow-up at year 3 or 6 (mean age 70 ± 9 years; 62% female; 26% *APOE*34/44). Among 1,537 individuals who were cognitively intact at baseline (MMSE ≥ 27 and no dementia within 9 years), 781 met the criterion for meaningful within-individual exposure contrast (defined by median-split). Diet was assessed using validated food frequency questionnaires. The primary exposure of interest was the carbohydrate-to-fat ratio (log, z). Fiber was additionally analyzed. Fixed-effects regression models estimated within-person associations between time-varying exposure and outcome values, adjusting for time and time-varying confounders. Within-person analyses of longitudinal data eliminate confounding by time-invariant factors such as pre-study habits, personality traits, and genetics.

Results: The association between carbohydrate-to-fat ratio and global cognition was negative among *APOE*34/44 and positive among non-*APOE*34/44 (Figure 2). Interaction by *APOE* genotype was statistically significant for both the carbohydrate-to-fat ratio and fiber ($P \leq 0.03$).

Conclusion: The findings support our hypothesis that a lower carbohydrate-to-fat ratio than proposed by official dietary guidelines may benefit cognitive health among individuals with *APOE* genotypes $\epsilon 3/\epsilon 4$ and $\epsilon 4/\epsilon 4$.

Reference: ¹ Norgren J, Sindi S, Matton A, Kivipelto M, K  reholt I. APOE-genotype and Insulin Modulate Estimated Effect of Dietary Macronutrients on Cognitive Performance: Panel Analyses in Non-Diabetic Older Adults at Risk for Dementia. The Journal of nutrition 2023. DOI: 10.1016/j.tjnut.2023.09.016.

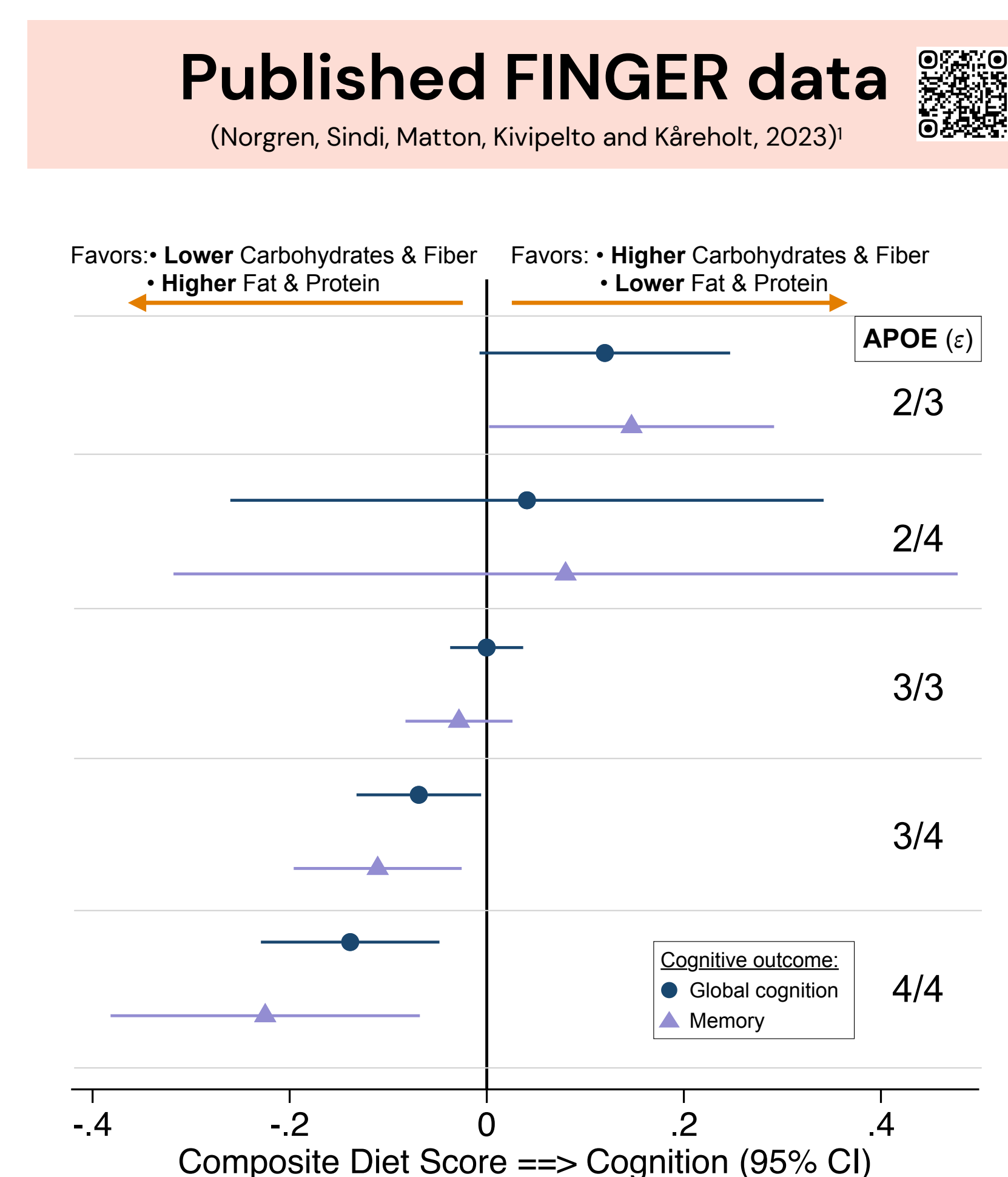
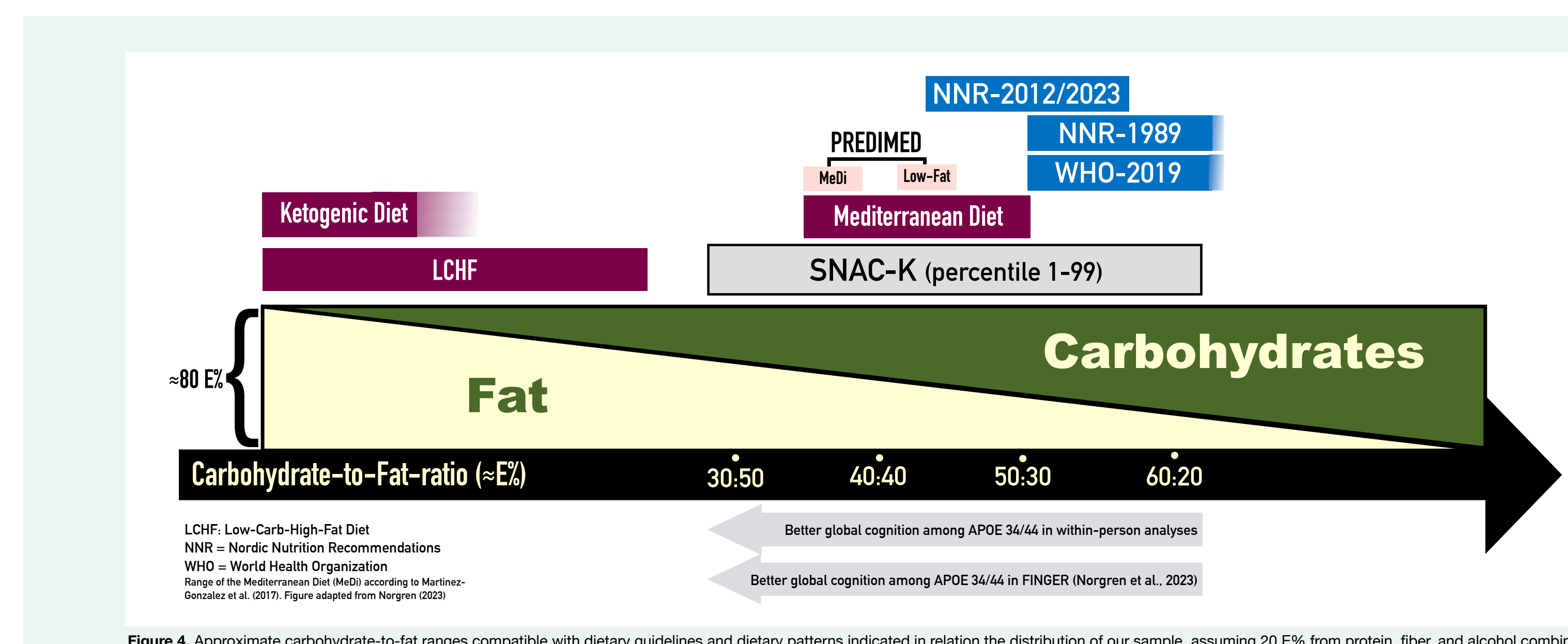
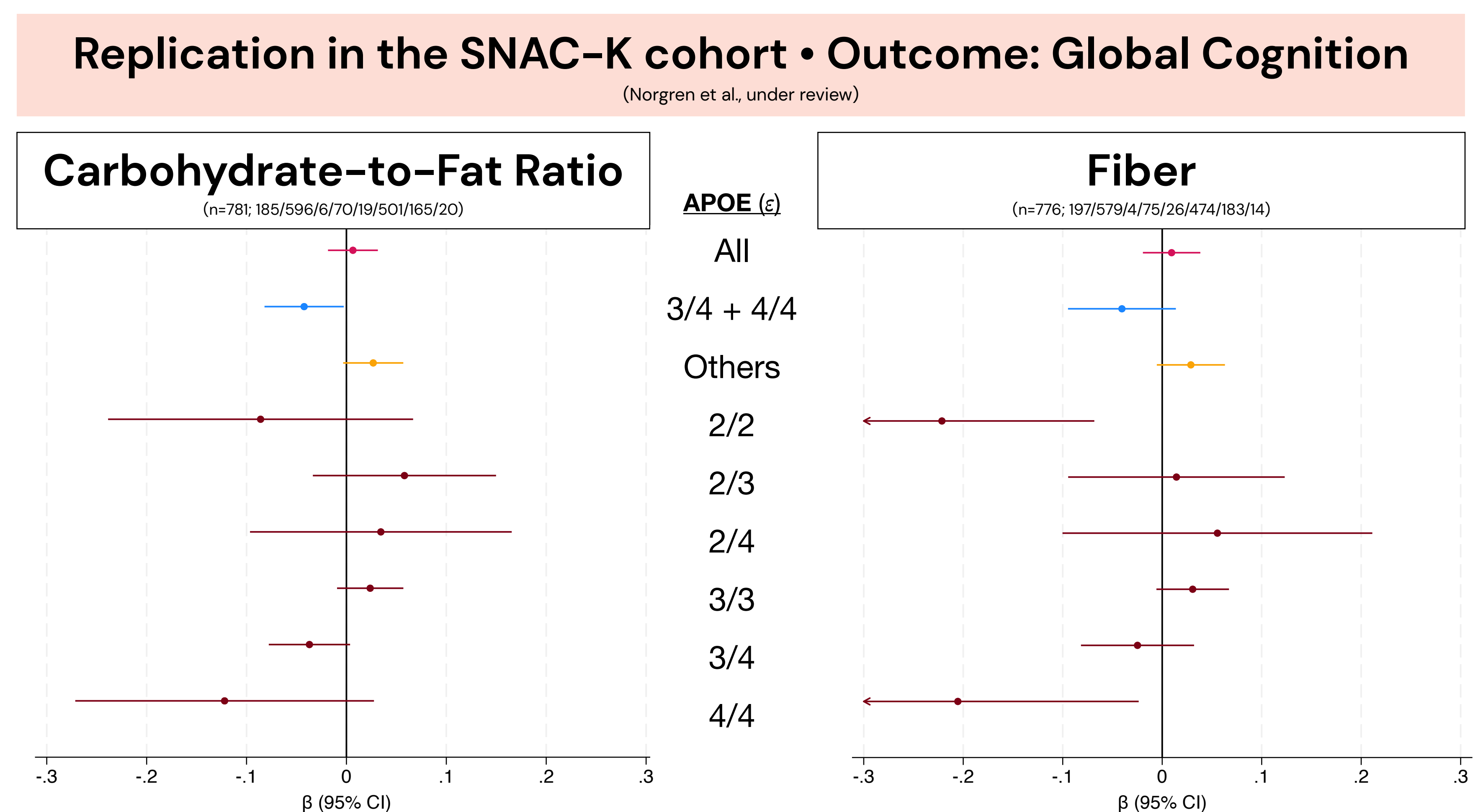


Figure 1. Within-person associations between a Lower-carbohydrate-fiber-Higher-fat-protein composite score and cognitive outcomes, as indicated. FINGER data (n=676) published 2023. APOE2/2 excluded due to n=1.



Contact:
Jakob Norgren, PhD, Postdoc
jakob.norgren@ki.se
+4670-678 22 87
Karolinska Institutet
Stockholm, Sweden.

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Our recent paper from SNAC-K:
"Meat Consumption and Cognitive Health by APOE Genotype" (Norgren et al., 2026)

