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RESPONSE TO LETTER TO THE EDITOR

Response by Hakala et al to Letter Regarding Article, "Cardiovascular Risk Factor Trajectories Since Childhood and Cognitive Performance in Midlife: The Cardiovascular Risk in Young Finns Study"

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In Response:

We thank Drs. Lai, Zhuang, and Liao for interest in our publication[1] indicating that longitudinal exposure to high systolic blood pressure, elevated serum total and low-density lipoprotein cholesterol, and obesity since childhood associates with poor cognitive performance in midlife. In addition, as more adverse risk factors were accumulated, worse cognitive performance was observed, which highlights the importance of cardiovascular risk factor monitoring from early age.

We understand the concern on the low feasibility of the trajectory modeling in clinical practice. Trajectory analyses identify homogenous and meaningful subpopulations within a large heterogeneous population. Although useful at population level, this is not applicable to individual-level data; for example, in clinical practice. Providing clinical perspective, we observed that the participants who belonged to the groups that were consistently within or close to ideal risk factor levels defined by the American Heart Association[2] had better cognitive performance in midlife. This finding is in line with our previous results indicating that exceeding age- and sex-specific cardiovascular risk factor guidelines in childhood/adolescence links with worse memory and learning in midlife[3]. Hence, if these associations were causal, preventive strategies for people exceeding guideline levels could offer an opportunity for primordial cognitive health promotion at an early age.

The authors also argued that our serum total cholesterol trajectory groups lack information on longitudinal variation. Generally, trajectory analyses offer a data-driven method to model natural history of longitudinally measured risk factors. This applies no a priori hypothesis for the groups, and assigns all participants, including those with fluctuating risk factor levels, into the trajectory group in which they have the highest probability of belonging. Therefore, the

criticism may be raised that the resulting groups do not exist or oversimplify the complex reality[4]. Therefore, we understand the authors' view on our serum total cholesterol trajectory groups. However, we carefully followed the diagnostic criteria related to trajectory modeling[4] and adjusted the subsequent analyses for an array of confounders. Hence, we consider that the trajectory modeling is conducted accurately.

The authors pointed out the lack of external validation of our trajectory models. The Young Finns Study was launched in 1980, when the participants were aged 3 to 18 years, and the cohort has been repeatedly followed until today. Because of the exceptional study design, we were able to conduct trajectory modeling from childhood to midlife. There are no other studies with identical data including repeatedly measured cardiovascular risk factors since childhood coupled with data on adulthood cognitive function, and therefore, external validation was impossible.

The authors suggested that our cardiovascular risk factor score was inaccurate because equal-sized risk points were given for groups with unequal effect estimates. We calculated the risk score to model the risk factor clustering, not to provide a clinically applicable tool for individual-level risk estimation. We agree that such a tool would be useful and that a sophisticated risk score may provide additional information for precise exposure levels. However, our results that suggest better cognitive health in midlife for those with lower number of adverse cardiovascular risk factors from childhood would remain, even using a more detailed risk factor score.

Conflicts of interest: none

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