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Author reply – Letter to the Editor "elevated C-reactive protein and IL-6 signalling are not the only determinants of sleep quality and duration"

We thank Dr. Finsterer for the interest in our recent work on the involvement of C-reactive protein (CRP) in the regulation of sleep duration (Iakunchykova et al., 2024) and wish to use this opportunity to provide additional clarification.

We agree that sleep quality and regulation of sleep duration are complex and a poorly understood phenomena which most likely involve many mechanisms. Dr. Finsterer lists many of the diseases and conditions that are known to influence sleep quality, as well as exogenous factors. However, little is known on sleep regulation, in particular establishment of individuals sleep duration, in so called physiological norm. One of immune system's function is to support homeostasis, so it is reasonable to hypothesize that it is involved in sleep regulation (Salvador et al., 2021). In our study we illuminate the regulatory role of soluble immune proteins on sleep duration rather than immune responses to acute stimuli. We conducted a study on homeostatic aspects of immune system by employing methods of genetic analysis: uni-/multi-variable Mendelian Randomization (MR) and polygenic risk score (PGS) analysis. They allow to estimate the association free from biases due to confounding by other factors influencing sleep duration. Application of MR and PGS analysis also answers the concern of Dr. Finsterer regarding CRP being non-specific biomarker associated with range of environmental insults as well as pathological processes. In our study we employed genetically determined differences in CRP blood levels as exposure variables, therefore the results are less likely to be biased due to confounding by other factors influencing both CRP and sleep.

We agree with Dr. Finsterer that self-reported sleep duration is not necessarily in agreement with objective measures of sleep duration. In the Supplemental Material of the published paper (Iakunchykova et al., 2024), we indeed find that accelerometry measured sleep duration was not significantly associated with CRP in MR analyses. Further studies are required to understand the causes for the disagreements between subjective and objective measurements of sleep duration, as we believe, they are crucial for understanding sleep and its dysregulation.

We would prefer the formulation that higher genetically determined baseline levels of CRP are contributing to regulation of subjectively measured sleep duration, as this is our actual finding. Although CRP is widely used as a marker of acute inflammation, CRP at baseline concentrations also has homeostatic functions, like wound healing, tissue repair, and clearance of damaged cells (Del Giudice and Gangestad, 2018), and sleep quality is a more complex parameter than sleep duration.

Our analysis and results provide a starting point for further genetic studies that aim to understand the homeostatic role of immune system in regulation of habitual sleep duration. As more proteomic and genotyping data covering a whole range of immune pathways comprising of a network of hundreds of proteins become available (Zhao et al., 2023), we are looking forward to develop methodological approaches that would allow to integrate these data for analysis of mechanisms of sleep regulation, in addition to the impact of known exogenous and endogenous factors.

CRediT authorship contribution statement

Olena Iakunchykova: Conceptualization, Writing – original draft, Writing – review & editing. **Michael E. Benros:** Validation, Writing – review & editing. **Yunpeng Wang:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

There are no conflict o interest among all authors.

Data availability

No data was used for the research described in the article.

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