

Meta-analysis of blood serum Cu, Fe, and Zn stable isotope compositions from healthy controls using individual participant and aggregate data

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In the last twenty years, studies on the use of Cu, Fe, and Zn isotope ratios in blood serum as diagnostic and prognostic markers of disease have become increasingly prevalent [1]. These studies typically include up to several tens of samples from a diseased population [2] and a similar number of presumed-healthy subjects (or cited the control group of another study [3]). Sample preparation for isotopic analysis is labour-intensive and limits the number of measurements that can reasonably be performed. When considered in the broader context of clinical research, these investigations are small and can contain biases that make statistical analysis and data interpretation challenging. Initial investigations sought to establish whether factors, such as age, sex, diet, and menopausal status must be controlled for healthy subjects [4]. However, with only a limited number of healthy subjects assessed in each study, these questions remain unresolved. To that end, a meta-analysis using individual participant and aggregate data was conducted. This involved an extensive search for relevant articles in the databases of PubMed, EBSCOhost, and SCOPUS up to January 2022. Relevant articles were screened and validated by three independent reviewers. When necessary, additional information (sex, age, serum Cu, Fe, and Zn concentrations) was requested from corresponding authors. Serum Cu, Fe, and Zn isotope datasets were identified, spanning North America, Europe, and Asia, with 13 studies and one unpublished dataset for Cu (305 healthy subjects), six studies for Fe (173 healthy subjects), and six studies and one unpublished dataset for Zn (127 healthy subjects). Potential geographic differences and the causes of inter-study variability were also investigated, and reference ranges established in healthy subjects. Ultimately, this meta-analysis will ensure patient cohorts are compared against appropriately-matched control groups, thereby enhancing the ability of isotope metallomics researchers to develop metal isotope ratio-based markers of disease.

References

[1] Vanhaecke & Costas-Rodríguez, *View*, 2021, **2**, 20200094.

[2] Hastuti, Costas-Rodríguez, Matsunaga, Ichinose, Hagiwara, Shimura & Vanhaecke, *Scientific Reports*, 2020, **10**, 1–12.

[3] Van Campenhout, Hastuti, Lefere, Van Vlierbergh,