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Letter to the Editor

Response to Comment on 'A Mendelian Randomization Study About Causal Associations Between Tofu Consumption and Stroke As Well As Related Subtypes'

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We thank authors for their letter regarding our study "A Mendelian Randomization Study about Causal Associations between Tofu Consumption and Stroke as well as Related Subtypes". We welcome the chance to respond to their comments, and we believe there are interesting points raised that are worthy of discussion and clarification.

The first issue related to tofu heterogeneity and soybean sources. Mendelian randomization (MR) inherently depends on aggregated genome-wide association study (GWAS) phenotypes, rendering subtype resolution unattainable with current datasets — a limitation analogous to the constraints identified in the PLOS ONE coffee study [1]. Although unmeasured heterogeneity may exist, our study furnished the first genetic evidence linking tofu consumption to intracerebral hemorrhage, thereby redirecting critical attention to the potential cerebrovascular risks associated with soy products. Sensitivity analyses robustly validated the association's stability, aligning with the methodological standards outlined in the MR Guidelines [2]. Future research should prioritize GWAS focused on tofu subtypes and mechanistic investigations, emulating how coffee research drove estrogen-receptor (ER)-stratified analyses and single nucleotide polymorphism (SNP) refinement. Although exploratory in nature, our work established an essential causal inference framework for subsequent investigations.

The second query related to tofu consumption measurement. Current methods mainly rely on self-reported dietary instruments (food frequency questionnaires, FFQs), which are susceptible to recall bias and cultural misclassification — challenges analogous to those documented in East Asian populations where tofu is a dietary staple [3]. Standard FFQs often fail to discriminate between tofu subtypes or cooking modalities, potentially conflating subtype-specific associations. Regional terminology variations further introduce measurement error, as evidenced in cross-cultural dietary studies [4]. In the context of MR, such measurement imprecision may induce attenuation bias, where weak genetic instruments interacting with mismeasured exposures could obscure true causal effects. This aligns with the emphasis of MR Guidelines on mitigating exposure misclassification [2]. Future research should prioritize standardized assessment protocols integrating tofu-subtype coding and subtype-specific instrumental variables developed via GWAS-based exposure modeling. By addressing these gaps, studies can more accurately dissect causal relationships, paralleling coffee research that was advanced through brewing-method-stratified analyses [1]. Such advancements would enhance the precision of cerebrovascular risk assessments associated with tofu consumption.

The third query related to the subtype of stroke. Our article's introduction and analysis comprehensively addressed stroke subtypes, including intracerebral hemorrhage (ICH), ischemic stroke, and subarachnoid hemorrhage (SAH). SAH was explicitly included in both data analysis and discussion sections. We recommend reviewing the "Results" and "Discussion" segments for detailed subtype-specific findings.

The final comment related to industry sponsorship and future directions. We have carefully reviewed the studies in question to assess potential vested interests with the tofu industry, including checks on funding sources, author affiliations, and conflict-of-interest disclosures. After thorough scrutiny, no evidence of industry ties was identified. To supplement the discussion on the positive significance of tofu for stroke, we have reviewed relevant literature to support our arguments [5–8]. A meta-analysis [9] showed that high soybean intake can reduce the incidence of type 2 diabetes, cardiovascular disease, and stroke in women–specifically, the incidence of these three conditions in women. This beneficial effect may be largely attributed to the role of isoflavones. Women under the age of 65 who consume significantly less tofu than the lowest intake quartile are more likely to suffer from ICH, as shown by a case-control study (adjusted hazard ratios = 0.26, 95% CI: 0.08–0.85) [7]. Based on existing evidence, future investigations could focus on elucidating the regulatory mechanisms of tofu components on cerebrovascular inflammation, oxidative stress, and platelet aggregation to identify specific targets, conducting prospective cohort studies across diverse

ethnicities, genders, and comorbidities to validate the generalizability of tofu's stroke-preventive effects.

Author Contributions

YW wrote the reply with input from all authors who agreed to account for the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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