Author response to Comment on: Exploring the association between weight loss-inducing medications and multiple sclerosis: insights from the FDA adverse event reporting system database

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We thank Dr Khouri et al. for their interest in our article titled "*Exploring the association between weight loss-inducing medications and multiple sclerosis: insights from the FDA adverse event reporting system database*"[1] and for sharing their considered perspectives. We appreciate the opportunity to address some of the points raised in their commentary.

First and foremost, we would like to clarify that we did not use the term "inverse causality" in our article. We used the term "inverse association," fully recognizing that association does not imply causation. Our terminology was chosen to highlight potential relationships that merit further investigation and to generate hypotheses rather than to suggest any direct protective effects. The term inverse signal or inverse association has also been used in previously published studies employing a similar methodology.[2–5]

We do agree that there are notable limitations inherent in using voluntary reporting databases such as the US Food and Drug Administration Adverse Event Reporting System (FAERS) database, and we have highlighted several of those limitations in our article. We used OpenVigil 2.1 MedDRA-v24[6] (rather than raw FAERS data) which employs data cleaning and pre-processing methods on FAERS data. Yet, we acknowledge that the possibility of duplicates cannot be fully eliminated. Regarding the use of controls, we indeed included non-diabetic medications known for their weight loss effects, whether as a potential side effect or primary indication (such as orlistat, phentermine, bupropion, topiramate, zonisamide, amphetamine, and naltrexone). We, however, agree that incorporating additional sensitivity analyses and controls would enhance the robustness of our findings.

Finally, we concur that complementing pharmacovigilance data with other methodological approaches, such as omics approaches and in vitro or in silico testing, can yield more comprehensive insights. However, this integration was beyond the scope of our current report. Our primary objective was to generate hypotheses based on observed potential associations that could be validated through more rigorous methodologies in future studies.

Declarations

Ethics approval and consent to participate

Not applicable since our original study was based on publicly available anonymous data from the FDA Adverse Event Reporting System database.

Consent for publication

Not applicable.

Author contributions

Afsaneh Shirani: Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Anne H. Cross: Conceptualization; Investigation; Writing – review & editing.

Olaf Stuve: Conceptualization; Investigation; Writing – review & editing.

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Competing interests
A.S. serves on the editorial board of the *Journal of Central Nervous System Disease* and *Brain Sciences*. She is also an editor for the *Multiple Sclerosis* section of *Current Treatment Options in Neurology* and an associate editor for *Frontiers in Neurology* and *Frontiers in Immunology*. She has received an honorarium for serving on the advisory medical board for TG therapeutics. A.H.C. has received honoraria for consulting for Biogen, Bristol Myers Squibb, EMD Serono, Genentech, Horizon, Janssen, Novartis, Octave, and TG Therapeutics and serves as President of the Board of Governors of the Consortium of MS Centers. A.H.C. was supported in part by Manny & Rosalyn Rosenthal – Dr John L. Trotter MS Center Chair in *Neuroimmunology*. O.S. serves on the editorial boards of *Therapeutic Advances in Neurological Disorders*, *Expert Review of Clinical Immunology*, and he is a section editor for *Current Treatment Options in Neurology*, has served on data monitoring committees for Genentech-Roche, and Novartis without monetary compensation, has advised EMD Serono, Novartis, and Octave Bioscience, receives grant support from EMD Serono, is a 2021 recipient of a Grant for Multiple Sclerosis Innovation (GMSI), Merck KGaA, is funded by a Merit Review grant (federal award document number (FAIN) BX005664-01) from the United States (U.S.) Department of Veterans Affairs, Biomedical Laboratory Research and Development, is funded by RFA-2203-39314 (PI) and RFA-2203-39305 (co-PI) grants from the National Multiple Sclerosis Society (NMSS). O.S. is an Associate Editor of *Therapeutic Advances in Neurological Disorders*, therefore, the peer review process was managed by alternative members of the Board and the submitting Editor was not involved in the decision-making process.

Availability of data and materials
None

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