Dear Editor,

We would like to thank the authors of this letter for their comments on our study published in 2019\(^1\). The authors made two points in their commentary based on our paper. The first (1) was about accounting for the matching variables in the statistical analysis, the second (2) was about the potential impact of differential follow up between the refractory myasthenia gravis (MG) patient compared with the non-MG controls. For both of these points we have provided our responses below.

Regarding the first point (1), the letter’s authors pointed towards two references that discuss these issues in greater detail\(^2,3\). The main conclusions for the Sjölandera et al. paper are as follows\(^3\):

We have shown how ignoring the matching variables in a cohort study with matching of the unexposed to the exposed yields the effect of exposure on the exposed population, in the absence of additional confounders or other bias sources. We have further shown, however, that ignoring the matching variables in a cohort study can leave bias if there are additional confounders, even with adjustment for the additional confounders. This bias can be avoided by adjusting for the matching variables.

While we adjusted for additional confounders in our logistic and negative binomial models, we thought it was still necessary to adjust for the patient-related matching variables (age and gender) in our analysis, which we did, and therefore do not agree with the letter’s authors.

Regarding the second point (2), we acknowledge that there was a discrepancy in the length of follow up period between the refractory MG patients and non-MG controls, although not statistically significant (median (IQR) 63.19 (28.57–97.73) vs. 74.28 (43.45–111.81) months, \(p=0.0704\)), as described in our article. However, we do not agree with the authors that this is an issue for the following reasons.

Firstly, the refractory MG patients and non-MG controls were compared for rates of GP visits, hospitalisations, emergency and outpatient visits. In this analysis the differences in the length of follow-up period was controlled for either (1) through presenting the results per person-years of follow up (rates) or (2) through including follow-up as an offset variable in the logistic or binomial models. In the context of a long-term chronic disease such as MG, there is a scientific interest at describing the healthcare resource use over long period of times, and we had no reason to think that the rates of HCRU would vary over the person-years of follow-up.

Secondly, the shorter follow up period in the non-MG controls, compared with the refractory MG patients, shows that the design of the study has likely selected for controls that are sicker than the general English population. The reason for this is likely because it was a requirement for controls to be active in their GP practice at the same age that MG patients had their first diagnosis (late 50s). This would of course favourably select for controls in their 50s that are having more frequent visits with their GP and therefore are more likely to have a chronic condition. Therefore, if anything we are comparing HCRU rates to a slightly sicker control population and therefore, if anything we are underestimating the difference in HCRU rate between refractory MG patients compared with controls. This further emphasises our point that MG patients have many health care interactions throughout their lifetime.

Again, we would like to thank the authors for their interesting comments on our study. We hope that there are many future studies that continue to emphasise the unmet need for individuals with refractory MG.

Transparency

Declaration of funding

The original research for this project was funded by Alexion Pharmaceuticals.

Declaration of financial/other relationships

AE is an employee of Genentech, Inc., and shareholder of F. Hoffmann-La Roche Ltd. This work was conducted while AE was a consultant to Alexion, prior to joining Genentech.

SM is employed by Evidera, but other than that I have no conflicts of interest.

LH is currently working at Biohaven Inc., New Haven Ct and was a former employee of Alexion. she has no stocks/shares Alexion.

SJ has served as an international advisory board member for Alexion, ArgenX, Regeneron, Immunovant and UCB pharmaceuticals, is currently an expert panel member of Myasthenia Gravis consortium for Argenx pharmaceuticals and has received speaker fees from Terumo BCT.

Acknowledgements

None stated
References

[1] Harris L, Graham S, MacLachlan S, et al. Healthcare resource utilization by patients with treatment-refractory myasthenia gravis in England. J Med Econ. 2019;22(7):691–697.

[2] Jewell NP. Statistics for epidemiology. Boca Raton (FL): CRC Press; 2003.

[3] Sjolander A, Greenland S. Ignoring the matching variables in cohort studies - when is it valid and why? Stat Med. 2013;32(27):4696–4708.

Linda Harris
Biohaven Pharmaceuticals, New Haven, CT, USA
lindah3031@gmail.com

Sophie Graham and Sharon MacLachlan
Evidera, Hammersmith, UK

Alex Exuzides
Genentech, San Francisco, NC, USA

Saiju Jacob
University Hospitals Birmingham, Birmingham, UK

Received 16 June 2021; accepted 24 June 2021

© 2021 Evidera Ltd. Published by Informa UK Limited, trading as Taylor & Francis Group.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.