Dear Editor,

Thank you very much for the opportunity to revise and resubmit our manuscript (NO: 87635). We sincerely appreciate the reviewers' comments and help. We have carefully revised the manuscript accordingly, which are marked with a red font. Our point-by-point responses are summarized below.

*Reviewer: 1*

**Point 1**

It is not clear how a validation was done on the a web-based questionnaires regarding diagnosis.

**Response 1**

Thanks for your important comment. We fully apologize for the mistake we made on the diagnosis of depression. Only in the cohort from UK Biobank, depression phenotype was based on self-reported responses to a web-based questionnaire. And in cohort from 23andMe_307k, the depression phenotype was determined based on self-reported information regarding clinical diagnosis or treatment for depression. In PGC_139k, the depression phenotype was clinically diagnosed. And there was a strong genetic correlation between each of these cohorts. The genetic correlation (rG) between PGC_139k and 23andMe_307k was 0.85 (se = 0.03). PGC_139k showed a rG of 0.87 (se = 0.04) with the UK Biobank. Similarly, the rG between the UK Biobank and 23andMe_307k was 0.85 (se = 0.03). In addition, the results could be replicated in an independent sample of 1,306,354 unrelated individuals from 23andMe. 97 of the 102 associated variants were nominally significant ($P < 0.05$), and 87 remained significant after Bonferroni correction ($P < 4.90 \times 10\text{-}4$). Hence, all these suggested that these variants represent robust associations with depression. And we have revised the definition of depression in the manuscript (Marked in yellow in MATERIALS AND METHODS).

*Reviewer: 2*

**Point 1**

Whether the UK Biobank data has any information of the number of individuals with

abnormal values is, however, not clear.

**Response 1**

Thanks for your important comment. UK Biobank used a broader phenotype relying on self-reported responses to a web-based questionnaire and a total of 127,552 cases and 233,763 controls were included in the original GWAS. We have added this information in the Table 1.

**Point 2**

ALM was measured by using bioelectrical impedance analysis (BIA) for fat-free mass at the arms and legs. The EWGSOP2 guidelines state that MRI and CT are considered to be gold standards for non-invasive assessment of muscle quantity/mass. According to the EWGSOP2, the estimation of muscle quantity or mass by BIA has certain disadvantages including the variations due to age and ethnicity of the population being studied and the necessity for further validation of prediction equations for specific populations. It would be useful if the authors could discuss whether these factors could have had some bearing on their results.

**Response 2**

Thanks for your important comment. We fully agree with your comment on the measurement for fat-free mass at the arms and legs. ALM was not directly measured by the BIA equipment but was estimated based on whole-body electrical conductivity. The estimates of BIA can be influenced by age, ethnicity, hydration status and other related discrepancies, which may subsequently influence the MR results. However, almost all studies utilized BIA to measure muscle mass, due to its affordability and portability, as well as the inclusion of studies involving healthy elderly individuals from the community [1]. We have added this information in the limitation part (Marked in yellow in DISCUSSION).

[1]. Li Z, Tong X, Ma Y, et al. Prevalence of depression in patients with sarcopenia and correlation between the two diseases: systematic review and meta-analysis. J Cachexia Sarcopenia Muscle. 2022 Feb;13(1):128-144. doi: 10.1002/jcsm.12908.

**Point 3**

Similarly, depression was defined by self-reported responses to a web-based questionnaire by individuals who had received a clinical diagnosis or treatment for depression. But the UK Biobank has used the Mental Health Questionnaire containing the Composite International Diagnostic Interview for a reliable diagnosis of depressive disorders. It is not clear what proportion of the participants included for this analysis had a CIDI diagnosis of depressive disorder.

**Response 3**

Thanks for your important comment. In the original GWAS, the authors reported that they used the broad definition of depression in the cohort of UK biobank. The exact proportion of the participants with a CIDI diagnosis of depressive disorder was unclear. Although previous studies reported that self-reported measures of depression were highly genetically correlated with those obtained from the clinically-diagnosed depression phenotype [1,2], there would be differences between "broad depression" and "clinically-diagnosed depression". We have added it in the limitation part (Marked in yellow in DISCUSSION).

[1]. Howard DM, Adams MJ, Shirali M, et al. Genome-wide association study of depression phenotypes in UK Biobank identifies variants in excitatory synaptic pathways. Nat Commun. 2018 Apr 16;9(1):1470. doi: 10.1038/s41467-018-03819-3.

[2]. Hyde CL, Nagle MW, Tian C, et al. Identification of 15 genetic loci associated with risk of major depression in individuals of European descent. Nat Genet. 2016 Sep;48(9):1031-6. doi: 10.1038/ng.3623.

**Point 4**

Another problem is that the term "depression" can be interpreted in many ways, from diagnosable depressive disorders to depressive symptoms elicited by questionnaires. It would be helpful if the authors could explicitly state the meaning of "depression" in their study.

**Response 4**

Thanks for your important comment. In the UK Biobank cohort, the depression phenotype, referred to as "broad depression", was determined based on self-reported responses to a web-based questionnaire. And in cohort from 23andMe_307k, the

depression phenotype was determined based on self-reported information regarding clinical diagnosis or treatment for depression. In PGC_139k, the depression phenotype was clinically diagnosed. We have rewritten the definition of depression in the manuscript (Marked in yellow in MATERIALS AND METHODS).

**Point 5**

Studies based on clinical assessments will still be needed to determine the association between the physical disorder of sarcopenia and depressive disorder in clinical populations.

**Response 5**

Thanks for your important comment. We have rewritten this part and added previous study to support our results in discussion (Marked in yellow in DISCUSSION).