Title: Regarding: Nicotinic acetylcholine receptors α7 and α9 modifies tobacco smoke risk for multiple sclerosis

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Dear Editors,

We read with interest the study by Briggs\(^1\); in which 75 variants from 332 SNPs appeared to modify the effect of smoking on MS susceptibility at an uncorrected p value threshold of 0.05. Haplotype-based analyses, stratified analyses, and replication in a case-only cohort of another ~1000 individuals with MS supported the hypothesis that variants in CHRN7A and CHNR9A modify the effect of smoking on MS susceptibility.

We previously performed analogous analyses using the UK Biobank, a longitudinal cohort study comprising over 500,000 individuals recruited between 2006 and 2010\(^2\). MS cases were defined using ICD-10 coded diagnoses derived from hospital episode statistics (linked secondary healthcare records). Smoking status prior to age 20 was defined as a binary variable using self-reported smoking status and age of starting smoking. Individuals with high relatedness (one of each pair with Kinship coefficient >0.0844), high genotype missingness (>10%), non-European genetic ancestry, and those with missing data for either age at MS diagnosis or smoking initiation were excluded. MS cases diagnosed prior to age 20 were also excluded\(^3\). Code is available at https://github.com/benjacobs123456/CHRN_variants_GE/blob/master/CHRN_variants_GE.md.

After these exclusions, 1187 MS cases and 372558 unmatched controls remained. All SNPs within 50kb of CHRNA7/CHRNA9 (hg19 coordinates CHRNA7 chr15:32,322,691-32,464,722, CHRNA9 chr4:40,337,346-40,357,234) were extracted using genotype data imputed by UK Biobank. After application of standard SNP quality control\(^3\) we conducted GxE analysis using multivariable logistic regression in PLINK2 (version 2.0-20200328). Models included main and interaction effects, and controlled for age, sex, and the first ten genetic principal components as covariates.

254 SNPs and 158 SNPs passing QC in CHRN7A and CHRN9A respectively were identified. Ten SNPs (10/254) in CHRN7A and thirteen SNPs (13/158) in CHRN9A showed nominal evidence (p<0.05) of GxE interaction. LD clumping in PLINK (R\(^2\) cutoff of 0.5) identified 63 independent signals in CHRN7A and 27 independent signals in CHRN9A. We therefore applied a Bonferroni-adjusted p value threshold of 0.0006 (0.05/63+27). No SNPs showed evidence of GxE interaction surpassing the significance threshold.

Of the 82 SNPs for which effect estimates are reported by Briggs\(^1\), 27 passed QC in our dataset (21 in CHRN7A, 6 in CHRN9A). P values for all SNPs were of larger magnitude (i.e. less statistically significant) in our analyses, although they were highly correlated (r\(_{Pearson}\)=0.90). Similarly, beta coefficients for the SNP interaction term were between 4.13x and 9.25x smaller in UKB (median 5.16x), but again the effect estimates were highly correlated (r\(_{Pearson}\)=0.98).

Our results suggest that the observed interactions between SNPs in nicotinic receptor genes and smoking in determining MS susceptibility do not reach statistical significance in a large, independent, well-characterised UK-based cohort. Although GxE studies are notoriously underpowered, our results emphasise the need for independent replication and stringent correction for multiple comparisons to minimise the risk of type 1 errors. Further efforts are required to determine how genetic variants modulate the effect of smoking on MS risk.

References
