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

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