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TITLE: Investigating heterogenous genetic effects contributing to smoking behavior using the UK Biobank

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ABSTRACT:
Tobacco smoking imposes a heterogenous burden within a population, disproportionally affecting certain groups of individuals while having contributed to millions of preventable deaths. Heterogenous tobacco usage is evident from longitudinal studies, which have suggested those with mood disorders such as anxiety and depression are more likely to later become nicotine-dependent smokers. Differing tobacco usage is furthermore seen between late-onset smokers compared to early-onset smokers, and between sexes. To partially explain these observations, family studies have implicated heterogenous genetic effects for numerous smoking behaviors, but little work using genetic marker data has been performed to support these findings. Here, we use the UK Biobank to infer heterogenous genetic effects for smoking heaviness using cigarettes per day (CPD) records, smoking initiation (SI), and smoking cessation (SC).We observed weak but suggestive evidence of disproportional SNP effects for CPD between MDD DSMV-like cases and controls ($\sqrt{\quad}$ 0.69, SE = 0.15, *p*-value = 0.047) and discover SNPs with MDD-dependent effects reaching genome-wide significance (GWS; *p*-value < $5x10^{-8}$) near *GYPA,* a gene previously implicated in COPD. We furthermore observed strong evidence for disproportional genetic effects for SI between sexes ($\sqrt{\quad}$ 0.82, SE =

0.02, *p*-value = 4.22×10^{-9}). Curiously, we observe no evidence for differing sex-specific SNP effects for SI at GWS but instead find 23 independent loci that reach GWS in one sex without reaching nominal significance (*p*-value < 0.05) in the opposite sex. This work suggests that the genetic determinants for smoking initiation are sex-dependent and discovers novel SI-associated loci using sex-stratified genome-wide association.

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