Interaction Between Occupational Exposures and Antioxidant Genes on Chronic Obstructive Pulmonary Disease in UK Biobank

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BACKGROUND AND AIM

Occupational exposure to vapours, gases, dusts, and fumes (VGDF) has been associated with lower lung function[1] and a higher risk of chronic obstructive pulmonary disease (COPD).[2] The proportion of COPD attributable to occupational exposures has been estimated at 14%.[3] A proposed mechanism underlying the effect of VGDF on COPD is through oxidative stress. A reduced antioxidant capacity has been found in COPD patients[4] and higher levels of oxidative stress biomarkers have been associated with exposure to VGDF.[5] The effect of VGDF on the lung might be apparent (or might be substantial) only in the presence of genetic variation (e.g., single nucleotide polymorphisms [SNP]) in antioxidant genes, indicating a gene–environment interaction. The study aimed to identify interactions between variants in well-known antioxidant genes and VGDF exposure on COPD risk.

METHODS

To assess antioxidant gene–VGDF interactions, the authors included 199,607 working individuals from the large UK Biobank (UKB; aged 39–71; 49% male; 44% never-smoker). Of these, 16,389 individuals had COPD spirometrically defined as forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC)< lower limit of normal (GLI-2012) and 34% were exposed to VGDF estimated using the airborne chemical (ACE) job exposure matrix.[6] All independent SNP within 15 antioxidant genes selected based on a recent review were analysed.[7] Gene–VGDF interactions were invested using a case-only approach using BOLT-LMM adjusted for sex, age, height, smoking status, genotyping batch, and centre, and accounting for population stratification/relatedness. Analyses were stratified according to smoking status. For significant interacting SNP, the authors assessed effects on gene-expression and DNA methylation levels using the online tool PhenoScanner.[8]

RESULTS

Overall, subjects exposed to VGDF had a 7% increased risk of COPD (Table 1a). However, this increase in risk was only seen in ever-smokers and was significantly different to never-smokers (interaction $p=8.79x10^{-5}$).

In the SNP–VGDF interaction analyses, the authors identified nine nominally significant interactions ($p<0.05$) for the antioxidant genes *CAT* (two SNP), *GC* (two SNP), *GSTP1*, *GSTT1*, *NOS1*, *SOD1,* and *SOD2*. Except for a SNP in *GC*, none of the SNP had a marginal effect on COPD and would therefore not be found if ignoring the effect modification by VGDF. Of the nine SNP, only two rare SNP with minor allele frequencies <3% in *GSTP1* (rs8191445) and *NOS1* (rs145671209) survived correction for multiple testing (false discovery rate <5%). Subjects exposed to VGDF and carrying a copy of the minor allele of the *GSTP1* and *NOS1* SNP had a respective 19% and

30% higher risk of COPD compared to subject not exposed to VGDF and not carrying a copy of the minor allele (Table 1b). Although the interactions were only significant in never-smokers, the three-way SNP–VGDF–smoking interactions were not significant (p=0.338 for *GSTP1* and p=0.460 for *NOS1*). The *GSTP1* SNP was associated with expression of two nearby genes (*DOC2GP/NDUFS8*) in whole blood. No association was found with DNA methylation for either SNP.

CONCLUSION

These results suggest that VGDF exposure is associated with a higher risk of COPD, but that this risk may be confined to smokers. Those with rare variations in the antioxidant genes *GSTP1* and *NOS1* may be more susceptible to the effects of VGDF on COPD, and this effect might be more apparent in never-smokers. Further work is needed to replicate these results in independent samples and to investigate the possibility of three-way SNP–VGDF–smoking interactions.

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Table 1: Results of the association analysis of A) VGDF with COPD (marginal effect of VGDF); and B) of the SNP-VGDF interaction analyses for both the *GSTP1* and the *NOS1* SNP, stratified by smoking.

	All (N=199,607)			Never-smokers (n=112,476)			Ever-smokers (n=87,180)		
	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
a) Marginal effect of VGDF									
VGDF	1.07	1.03–1.11	**$2.59x10^{-4}$**	1.01	0.95–1.06	0.851	1.12	1.07–1.18	**$1.45x10^{-6}$**
b) Results from the interaction analysis									
VGDF	1.06	1.02–1.10	**$3.20x10^{-3}$**	0.99	0.94–1.04	0.695	1.12	1.06–1.17	**$1.32x10^{-5}$**
GSTP1 (rs8191445)	0.90	0.82–0.98	**0.020**	0.90	0.79–1.03	0.121	0.89	0.78–1.01	0.074
VGDF**GSTP1*	1.19	1.03–1.37	**0.019**	1.27	1.03–1.57	**0.024**	1.13	0.93–1.38	0.212
VGDF	1.06	1.02–1.10	**$1.44x10^{-3}$**	0.99	0.94–1.05	0.846	1.12	1.07–1.17	**$5.73x10^{-6}$**
NOS1 (rs145671209)	0.89	0.78–1.01	0.069	0.86	0.71–1.03	0.094	0.93	0.77–1.11	0.408
VGDF**NOS1*	1.30	1.07–1.59	**0.010**	1.42	1.05–1.91	**0.021**	1.21	0.92–1.60	0.171

Significant results are presented in bold.

CI: confidence interval; COPD: chronic obstructive pulmonary disease; OR: odds ratio; SNP: single nucleotide polymorphism; VGDF: vapours, gases, dusts, and fumes.