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Response to "Comment on 'Evaluation of a Gene–Environment Interaction of *PON1* and Low-Level Nerve Agent Exposure with Gulf War Illness: A Prevalence Case–Control Study Drawn from the U.S. Military Health Survey's National Population Sample'"

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In his letter Curtis[1] raises an important consideration: Because the *paraoxonase-1* (*PON1*) Q192R genotype has long been known to vary across racial/ethnic groups,[2] the gene–environment (G × E) interaction we reported could have been biased if ancestry was associated with both exposure (hearing nerve agent alarms) and outcome (Gulf War illness cases vs. controls).

In the 1,016 veterans in our case–control sample,[3] the distribution of race/ethnicity was as follows: non-Hispanic White 72%, Black 21%, Hispanic 4%, Native American 1%, Asian 1%, and unknown 1%. As predicted, *PON1* 192R allele frequency was higher in the Black (68%) and Hispanic (41%) groups than in the non-Hispanic White group (29%) but could not be evaluated in the other groups owing to the small sample sizes. Because Black, Hispanic, Native American, and Asian populations are all known to have elevated *PON1* 192R allele frequencies,[2,4] we combined these groups into "other," an indicator of minority status for analysis. All of our multivariable logistic regression analyses were adjusted for seven confounding variables: soldiers' age, sex, military rank, active duty vs. Guard/Reserve status, military service branch, special strata, and intensity of combat exposure.[3]

In an adjusted logistic regression model of exposure in the 508 controls,[5] minority status was weakly associated with hearing nerve agent alarms (adjusted odds ratio = 2.18; 95% confidence interval: 1.29, 3.66). In the final adjusted model of the disease assessing the G × E interaction, however, adding minority status had virtually no effect on the estimate of the G × E interaction on either the multiplicative or the additive scale, and it had no discernible effect on the strength of classification of the model reflected by the model *C*-statistic (Table 1). In stratified analyses we conducted in response to Curtis's letter,[1] the G × E interaction was supported in both the non-Hispanic White and the other groups despite increased sampling variability (Table 2).

The sensitivity analysis for unmeasured confounders in our paper demonstrated that the estimated G × E interaction was sufficiently strong that the association between an unmeasured confounder and both the environmental exposure and the disease would have to be extremely strong to explain away the finding.[3]

Table 1. The effect of adding minority status on the G × E interaction of *PON1* Q192R RR vs. QQ genotypes and hearing nerve agent alarms measured on the multiplicative and additive scales, by confounder-adjusted multivariable models.

	Multiplicative scale[a]		Additive scale[b]
Minority status included	POR from the G × E interaction term (95% CI)	Model *C*-statistic[c]	Synergy index (95% CI)
No	3.41 (1.20, 9.72)	0.885	4.71 (1.82, 12.19)
Yes	3.49 (1.21, 10.00)	0.885	4.22 (1.50, 11.82)

Note: CI, confidence interval; G × E, gene–environment; POR, prevalence odds ratio.
[a]From logistic regression.
[b]Calculated with Zou's SAS macro.[3]
[c]Area under the receiver–operator characteristic curve.

Table 2. Stratification of the analyses of G × E interaction of *PON1* Q192R RR vs. QQ genotypes and hearing nerve agent alarms by race/ethnicity.

	Multiplicative scale[a]		Additive scale[b]
Race/ethnicity	POR from the G × E interaction term (95% CI)	Model *C*-statistic[c]	Synergy index (95% CI)
Minority[d]	3.42 (0.58, 20.20)	0.740	6.75 (0.28, 163.03)
Non-Hispanic White	5.56 (1.00, 30.90)	0.873	4.11 (1.12, 15.10)

Note: CI, confidence interval; G × E, gene–environment; POR, prevalence odds ratio.
[a]From logistic regression.
[b]Calculated with Zou's SAS macro.[3]
[c]Area under the receiver–operator characteristic curve.
[d]Because of limited sample size, the minority analyses could be adjusted for only two of the seven confounders (age and active duty status), whereas the analysis in the non-Hispanic White group was adjusted for all seven confounders.

In the initial draft of our manuscript, we included Black vs. other in our multivariable models to show that race/ethnicity had no significant effect on the G × E interaction. Given that it contributed virtually nothing to the model, after the initial journal review we removed it to avoid contributing needlessly to implicit racial bias, a growing concern in science,[6] particularly among geneticists.[7]

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