Supplemental Material

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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Figure S2. Prediction of irreversible or long-lasting health effects in soldiers exposed to airborne nerve agent above the U.S. Environmental Protection Agency’s Acute Exposure Guideline Level 2 (AEGL-2) but below the detection threshold of the widely deployed U.S. M8A1 nerve agent alarm device. On the basis of current science, the AEGL levels define the airborne concentration-time thresholds (expressed as mg/m\(^3\) per min) of a chemical as the level above which the general population, especially genetically susceptible individuals, could be expected to experience the following adverse effects: above AEGL-1 = notable discomfort, irritation, or certain asymptomatic nonsensory effects that are not disabling and are transient and reversible upon cessation of exposure; above AEGL-2 = irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape; above AEGL-3 = life threatening health effects or death. As tens of thousands of M8A1 detection alarms sounded repeatedly following U.S. and Coalition bombing of Iraqi chemical weapon storage sites throughout the conflict period, most soldiers donned mission oriented protective posture (MOPP) impervious suits, masks and gloves. Since, however, the AEGL-2 threshold (0.087 mg/m\(^3\) for 10 min, 0.05 mg/m\(^3\) for 30 min, etc.) was substantially below the M8A1 detection threshold (0.11 mg/m\(^3\)), there were undoubtedly periods of time before and after alarms sounded when solders were unprotected and exposed to AEGL-2 concentrations of nerve agent over the short times sufficient to cause irreversible or serious, long-lasting health effects, particularly for more genetically susceptible individuals. Thus, the detection threshold of the M8A1 detector would have prevented incapacitating or fatal nerve agent exposures (above AEGL-3) if they had occurred, but not AEGL-2 exposures, which did occur but in 1991 were not yet known to have long-lasting effects. The greater sensitivity of the Czech GSP-11 (0.05 mg/m\(^3\)) and the French AP2C/APACC (0.01 mg/m\(^3\)) detection devices explains the repeated Czech and French detections not detected by the ubiquitous U.S. M8A1 detectors. Figure reproduced from *Neuroepidemiology* 2013; 40: 160-177 by permission of S. Karger AG, Basel.

References
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| Method for calculating correct asymmetric 95% confidence intervals | SAS macro source | RERI | 95% Confidence interval |
|---------------------------------------------------------------------|------------------|------|-------------------------|
| Likelihood-based asymmetric CI calculated directly from a linear odds ratio model | Richardson and Kaufman 2009<sup>2</sup> | 5.0423 | 1.6722 – 10.8654 |
| Method of variance estimates recovery (MOVER) for asymmetric CI calculated from logistic regression parameters | Zou 2008<sup>3</sup> | 5.0422 | 1.6757 – 10.8579 |

Abbreviation: RERI, relative excess risk due to interaction; CI, confidence interval
**Table S3.** Definition of the method used in our SAS macro to perform the sensitivity analysis to estimate the effect of misclassification of veterans’ recall of having heard nerve gas alarms on our estimate of the strength of the GxE interaction.

4x2 table from cross-table analysis of the original data

|        | G 0 | G 1 | Total |
|--------|-----|-----|-------|
| E      |     |     |       |
| Yes    | a₀  | a₁  | Ncases₀ |
| No     | b₀  | b₁  | Ncases₁ |
| Cases  |     |     |       |
| Controls | c₀  | c₁  | Ncontrols₀ |
|        | d₀  | d₁  | Ncontrols₁ |

4x2 table corrected for misclassification in E by the formulas below

|        | G 0 | G 1 | Total |
|--------|-----|-----|-------|
| E      |     |     |       |
| Yes    | A₀  | A₁  |       |
| No     | B₀  | B₁  |       |
| Cases  |     |     |       |
| Controls | C₀  | C₁  |       |
|        | D₀  | D₁  |       |

\[
\begin{align*}
A₀ &= \frac{a₀ - Ncases₀ (1 - Sp₀)}{Se₀ - (1 - Sp₀)} \\
B₀ &= Ncases₀ - A₀ \\
C₀ &= \frac{c₀ - Ncontrols₀ (1 - Sp₀)}{Se₀ - (1 - Sp₀)} \\
D₀ &= Ncontrols₀ - C₀ \\
A₁ &= \frac{a₁ - Ncases₁ (1 - Sp₁)}{Se₁ - (1 - Sp₁)} \\
B₁ &= Ncases₁ - A₁ \\
C₁ &= \frac{c₁ - Ncontrols₁ (1 - Sp₁)}{Se₁ - (1 - Sp₁)} \\
D₁ &= Ncontrols₁ - C₁
\end{align*}
\]

Abbreviations: G, has the risk genotype; E, exposed to the environmental risk; N, number of cases or controls with (1) or without (0) G; POR, prevalence odds ratio; Se and Sp, sensitivity and specificity of recall of E in case or control groups stipulated to model levels of recall bias; subscripted numbers indicate having the risk genotype (1) or not (0).

Note: This approach extends to GxE interaction the standard method for correcting the strength of association of a risk factor from the stipulated Se and Sp of its measurement in cases and controls,¹ simplified by Pearce.⁴

¹ This table, corrected for misclassification, was analyzed by 2 approaches: first, our SAS macro called Zou’s SAS macro to estimate the strength of the GxE interaction on the additive scale with Rothman’s synergy index, and second, our macro estimated it on the multiplicative scale by exponentiating the coefficient of the interaction term from logistic regression to obtain the POR for the GxE interaction. When Se=Sp=1 is stipulated in the call statement for the macro, the analysis returns the baseline value of the GxE interaction uncorrected for misclassification in E; whereas, other values for Se and Sp correct it for misclassification. When the same values of Se and Sp are used for case and control groups, the model corrects for nondifferential misclassification; when different values are used, it corrects for differential misclassification. Since this approach is ecological, it cannot support subject-level covariate adjustment.
**Table S4.** Validation of our SAS macro for automating sensitivity testing to correct the odds ratio for misclassification of the environmental variable by reproducing Greenland and Lash’s published resins-lung cancer example.\(^1\)

| Cases | Controls |
|-------|----------|
|       | Se: 1.00 | 0.90 | 0.80 | 0.90 | 0.80 |
|       | Sp: 1.00 | 0.90 | 0.90 | 0.80 | 0.80 |

Greenland and Lash’s published results\(^a\)

|     |     |     |     |     |
|-----|-----|-----|-----|-----|
| 1.00| 0.90| 0.80| 0.90| 0.80|
| 2.83| 1.29| 1.57|     |     |

Results from our SAS macro\(^b\)

|     |     |     |     |     |
|-----|-----|-----|-----|-----|
| 1.00| 0.90| 0.80| 0.90| 0.80|
| 2.83| 1.29| 1.57|     |     |

Abbreviations: Se, sensitivity; Sp, specificity

\(^a\) Values in this panel are the odds ratio from logistic regression of the association of the binary environmental variable (occupational resins exposure) and the binary outcome variable (lung cancer) adjusted for the expected values of the sensitivity and specificity of measurement of the environmental variable in the cases and controls.

\(^b\) Inputs into each run of the SAS macro include SAS dataset name, the names of the outcome and environmental variables, and the 4 values of the expected sensitivity and specificity of measurement of the environmental variable in the cases and the controls based on background knowledge of possible reasons for misclassification.
Table S5. Numerical values for Figure 4. The association of GWI with measures of low-level nerve agent exposure and genetic predisposition.

| Characteristic | Cases (N = 508) | Controls (N=508) | POR (95% CI) |
|---------------|----------------|-----------------|-------------|
|               |                |                 |             |
| A. No. of nerve agent alarms <sup>a</sup> |                |                 |             |
| 0             | 111            | 287             | 1.00        |
| 1             | 80             | 62              | 2.45 (1.57-3.81) |
| 2-9           | 187            | 119             | 4.15 (3.01-5.72) |
| ≥10           | 130            | 40              | 8.57 (5.64-13.04) |
| B. In modeled Khamisiyah plume (days) |                |                 |             |
| 0             | 354            | 386             | 1.00        |
| 1             | 95             | 43              | 2.41 (1.63-3.55) |
| ≥2<sup>a</sup> | 25             | 13              | 2.10 (1.06-4.16) |
| Missing (unit location unavailable) | 34             | 66              |             |
| C. PON1 Q192R genotype |                |                 |             |
| QQ            | 172            | 234             | 1.00        |
| QR            | 227            | 216             | 1.43 (1.09-1.88) |
| RR            | 109            | 58              | 2.56 (1.76-3.72) |
| D. PON1 Q isoenzyme quartile |                |                 |             |
| Q1            | 174            | 92              | 2.81 (1.97-4.01) |
| Q2            | 113            | 127             | 1.32 (0.93-1.89) |
| Q3            | 118            | 136             | 1/29 (0.91-1.83) |
| Q4            | 103            | 153             | 1.00        |
| E. PON1 R isoenzyme quartile |                |                 |             |
| Q1            | 173            | 233             | 1.00        |
| Q2            | 52             | 52              | 1.35 (0.88-2.07) |
| Q3            | 140            | 116             | 1.63 (1.19-2.23) |
| Q4            | 143            | 107             | 1.80 (1.31-2.48) |
| F. BChE genotype |                |                 |             |
| UU            | 26             | 36              | 1.00        |
| UA            | 156            | 148             | 0.71 (0.42-1.21) |
| Rare          | 322            | 318             | 1.04 (0.79-1.37) |
| Missing       | 4              | 6               |             |
| G. BChE enzyme quartile |                |                 |             |
| Q1            | 142            | 119             | 1.00        |
| Q2            | 118            | 145             | 0.68 (0.48-0.96) |
| Q3            | 116            | 127             | 0.77 (9.54-1.09) |
| Q4            | 132            | 117             | 0.95 (0.67-1.34) |
| H. BChE dibucaine number quartile |                |                 |             |
| Q1            | 137            | 123             | 1.00        |
| Q2            | 137            | 121             | 1.016 (0.72-1.44) |
| Q3            | 111            | 126             | 0.79 (0.56-1.13) |
| Q4            | 122            | 138             | 0.79 (0.56-1.12) |
| Missing       | 1              | 0               |             |

Abbreviations: BChE, butyrylcholinesterase; CI, confidence interval; GWI, POR, prevalence. odds ratio. Statistics are unadjusted.

<sup>a</sup> No subject in our case-control sample was classified as in the computer-modeled nerve agent plume from Khamisiyah ammunition dump on all 3 days.
**Table S6.** Interaction on the additive and multiplicative scales of having been located in the Khamisiyah plume and *PON1 Q192R genotype* on GWI.

| PON1 Q192R genotype | QQ      | QR      | RR      | PORs for PON1 Q192R genotypes within strata of Khamisiyah plume exposure |
|----------------------|---------|---------|---------|--------------------------------------------------------------------------|
|                      | N cases/controls | N cases/controls | POR (95%CI) | N cases/controls | POR (95%CI) | QR vs QQ | RR vs QQ |
| Located in Khamisiyah plume |         |         |         |                                                          |         |         |         |
| No                   | 123/172 | 159/168 | 1.32 (0.96-1.82) | 72/46 | 2.19 (1.42-3.39) | 1.32 (0.96-1.82) | 2.19 (1.42-3.39) |
|                      | p=0.08  | p=0.08  | p<0.001 | p<0.001 | p<0.001 |
| Yes                  | 36/27   | 53/22   | 3.37 (1.95-5.83) | 31/7 | 6.19 (2.64-14.52) | 1.81 (0.89-3.65) | 3.32 (1.27-8.68) |
|                      | p=0.001 | p<0.001 | p<0.001 | p=0.10 | p=0.01 |

**POR (95%CI) for plume within strata of genotypes**

- Located in Khamisiyah plume: 1.86 (1.08-3.23) p=0.03
- Unadjusted: 1.0
- Adjusted for confounders: 1.0

**Additive scale: Synergy index (95%CI)**

- Unadjusted: 1.0
- Adjusted for confounders: 1.0 (Inestimable)

**Multiplicative scale: POR (95%CI) from LR interaction term**

- Unadjusted: 1.0
- Adjusted for confounders: 1.0

Note: The synergy index is a measure of interaction on the additive scale; it has the same distribution as the POR, viz., 0 to plus infinity with 1.0 as the equivalency point indicating no association. The ratio of the PORs, obtained from the interaction term in a logistic regression analysis, is a measure of interaction on the multiplicative scale. The potential confounders controlled for in the adjusted models include: age (years), sex (M, F), service branch (Army [referent], Navy, Air Force, Marines), rank (officer, enlisted), active duty vs Guard/Reserve, special strata (yes, no), Combat Exposure Scale (0=missing, 1=light [referent], 2=light to moderate, 3=moderate to heavy and heavy). One subject’s missing age was imputed to the mean age of the sample. Because of missing values on Khamisiyah plume exposure due to classified or missing unit location information for 34 cases and 66 controls, the analyses included 474 cases and 442 controls. Abbreviations: CI, confidence interval; PON1, paraoxonase-1; POR, prevalence odds ratio; RERI, relative excess risk due to interaction.

* Adjusted RERI = 1.20 (95% CI -0.93 – 6.08)
Table S7. Interaction on the additive and multiplicative scales of having been located in the Khamisiyah plume and PON1 Q192R type Q isoenzyme activity level on GWI.

| PON1 Q192 type Q isoenzyme activity level | 4th quartile (lowest risk) | 3rd quartile (mid-low risk) | 2nd quartile (mid-high risk) | 1st quartile (highest risk) | POR (95% CI) for PON1 type Q activity quartiles within strata of alarms |
|------------------------------------------|---------------------------|----------------------------|----------------------------|---------------------------|---------------------------------------------------------------|
| N cases/controls                          | POR (95% CI)              | N cases/controls            | POR (95% CI)              | N cases/controls            | POR (95% CI) for 3rd vs 4th quartile | POR (95% CI) for 2nd vs 4th quartile | POR (95% CI) for 1st vs 4th quartile |
| Located in Khamisiyah plume               |                           |                            |                           |                           |                                           |                                           |                                           |
| No                                       | 79/115                    | 1.0                        | 84/102                    | 1.20 (0.80-1.80)           | p=0.38                                           | 1.20 (0.80-1.80)           | p=0.38                                           | 1.20 (0.80-1.80)           | p=0.38                                           | 1.20 (0.80-1.80)           | p=0.38                                           | 1.20 (0.80-1.80)           | p=0.38                                           |
| Yes                                      | 16/20                     | 1.17 (0.57-2.39)           | p=0.68                    | 3.93 (1.80-8.57)           | p<0.001                                           | 3.38 (1.27-8.98)           | p=0.01                                           | 2.86 (1.15-7.09)           | p=0.02                                           | 4.69 (1.88-11.71)          | p<0.001                                           | 2.41 (1.60-3.62)           | p<0.001                                           |
| PORs (95% CI) for alarms within strata of PON1 type Q activity | 1.17 (0.57-2.39)           | p=0.68                    | 3.28 (1.50-7.16)           | p=0.17                    | 3.08 (1.53-6.19)           | p=0.002                                           | 2.27 (1.13-4.57)           | p=0.02                                           |
| Additive scale: Synergy index (95% CI)    |                           |                            |                           |                           |                                           |                                           |                                           |                                           |
| Unadjusted                                | 1.0                       |                           |                           |                           |                                           |                                           |                                           |                                           |
| Adjusted for confounders                 | 1.0                       | (inestimable)             | (inestimable)             |                           |                                           |                                           |                                           |                                           |
| Multiplicative scale: POR (95% CI) from LR interaction term |                           |                            |                           |                           |                                           |                                           |                                           |                                           |
| Unadjusted                                | 1.0                       |                           |                           |                           |                                           |                                           |                                           |                                           |
| Adjusted for confounders                 | 1.0                       |                           |                           |                           |                                           |                                           |                                           |                                           |

Note: The synergy index is a measure of interaction on the additive scale; it has the same distribution as the OR, viz., 0 to plus infinity with 1.0 as the equivalency point indicating no association. The ratio of the PORs, obtained from the interaction term in a logistic regression analysis, is a measure of interaction on the multiplicative scale. The potential confounders controlled for in the adjusted models include: age (years), sex (M, F), service branch (Army [referent], Navy, Air Force, Marines), rank (officer, enlisted), active duty vs Guard/Reserve, special strata (yes, no), Combat Exposure Scale (0=missing, 1=light [referent], 2=light to moderate, 3=moderate to heavy and heavy). One subject’s missing age was imputed to the mean age of the sample. Because of missing values on Khamisiyah plume exposure due to classified or missing unit location information for 34 cases and 66 controls, the analyses included 474 cases and 442 controls. Abbreviations: CI, confidence interval; PON1, paraoxonase-1; POR, prevalence odds ratio; RERI, relative excess risk due to interaction.

\* Adjusted RERI = 1.65 (95% CI -0.44 – 5.88)
Table S8. Interaction on the additive and multiplicative scales of hearing nerve agent alarms and butyrylcholinesterase (BChE) genotype on GWI.

|                     | BChE genotype |                     |                     |                     |
|---------------------|---------------|---------------------|---------------------|---------------------|
|                     | UU            | UK                  | Rare genotypesa     | Pors for BChE genotypes within strata of alarms |
|                     | N cases/controls | N cases/controls | POR (95%CI)         | UK vs UU           |
|                     |               |                     |                     | Rare vs UU         |
| Heard nerve agent alarms |               |                     |                     |                     |
| No                  | 75/175        | 31/87               | 0.83 (0.51-1.36)    | 0.56 (0.20-1.53)   |
|                     |               |                     | p=0.46              | 0.26               |
| Yes                 | 247/143       | 125/61              | 4.78 (3.18-7.19)    | 3.27 (1.60-6.68)   |
|                     |               |                     | p=0.001             | p=0.001            |
| POR (95%CI) for plume within strata of genotypes | 4.03 (2.87-5.66) | 5.75 (3.45-9.59) | 5.88 (1.81-19.12) |
|                     |               |                     |                     | P<0.001            |

Additive scale: Synergy index (95%CI)

Unadjusted

|                     | 1.0            | 1.32 (0.79-2.20)    | 0.88 (0.31-2.46)    |                     |
|                     |               | p=0.29              | p=0.81              |                     |

Adjusted for confounders

|                     | 1.0            | 1.03 (0.50-2.13)    | 0.80 (0.17-3.87)    |                     |
|                     |               | p=0.94              | p=0.79 b            |                     |

Multiplicative scale: POR (95%CI) from LR interaction term

Unadjusted

|                     | 1.0            | 1.43 (0.77-2.64)    | 1.46 (0.43-4.98)    |                     |
|                     |               | p=0.26              | p=0.55              |                     |

Adjusted for confounders

|                     | 1.0            | 1.33 (0.63-2.81)    | 2.58 (0.58-11.50)   |                     |
|                     |               | p=0.45              | p=0.22              |                     |

Note: The synergy index is a measure of interaction on the additive scale; it has the same distribution as the POR, viz., 0 to plus infinity with 1.0 as the equivalency point indicating no association. The ratio of the PORs, obtained from the interaction term in a logistic regression analysis, is a measure of interaction on the multiplicative scale. The potential confounders controlled for in the adjusted models include: age (years), sex (M, F), service branch (Army [referent], Navy, Air Force, Marines), rank (officer, enlisted), active duty vs Guard/Reserve, special strata (yes, no), Combat Exposure Scale (0=missing, 1=light [referent], 2=light to moderate, 3=moderate to heavy and heavy). One subject’s missing age was imputed to the mean age of the sample. The analyses included 504 cases and 502 controls; 4 cases and 6 controls were excluded for missing genotype data. Abbreviations: BChE, butyrylcholinesterase; CI, confidence interval; POR, prevalence odds ratio; RERI, relative excess risk due to interaction.

a Rare AChE genotypes include K/K, K/UK, U/A, and U/AK; other rare genotypes were not represented in the study sample.

b Adjusted RERI = -0.46 (95% CI -2.57 – 3.23)
Table S9. Interaction on the additive and multiplicative scales of hearing nerve agent alarms and butyrylcholinesterase (BChE) enzyme activity level on GWI.

| BChE activity level | 4<sup>th</sup> quartile (lowest risk) | 3<sup>rd</sup> quartile (mid-low risk) | 2<sup>nd</sup> quartile (mid-high risk) | 1<sup>st</sup> quartile (highest risk) | POR (95% CI) for BChE activity quartiles within strata of alarms |
|---------------------|--------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|-------------------------------------------------------------|
| N cases/controls    | POR (95% CI)                         | N cases/controls                     | POR (95% CI)                         | N cases/controls                     |POR (95% CI) for alarms within strata of BChE activity |
| Yes                 | 102/46                               | 87/61                                | 89/59                                | 119/65                               | 3<sup>rd</sup> vs 4<sup>th</sup> quartile | 2<sup>nd</sup> vs 4<sup>th</sup> quartile | 1<sup>st</sup> vs 4<sup>th</sup> quartile |
| No                  | 30/71                                | 29/66                                | 29/86                                | 23/64                                | 0.80 (0.44-1.45)                                           | 0.64 (0.40-1.04)                                           | 0.68 (0.42-1.10)                                           | 0.98 (0.61-1.57)                                           |

Additive scale: Synergy index (95% CI)

|                  | Unadjusted                           | Adjusted for confounders             |
|------------------|--------------------------------------|--------------------------------------|
|                  | 1.0                                  | 0.55 (0.29-1.05)                     | 0.64 (0.33-1.22)                     | 1.01 (0.54-1.86)                     |
|                  | p=0.07                               | p=0.07                               | p=0.17                               | p=0.99                               |

Multiplicative scale:
POR (95% CI) from LR interaction term

|                  | Unadjusted                           | Adjusted for confounders             |
|------------------|--------------------------------------|--------------------------------------|
|                  | 1.0                                  | 0.62 (0.28-1.34)                     | 0.85 (0.40-1.84)                     | 1.15 (0.52-2.54)                     |
|                  | p=0.22                               | p=0.02                               | p=0.68                               | p=0.74                               |

Note: The synergy index is a measure of interaction on the additive scale; it has the same distribution as the OR, viz., 0 to plus infinity with 1.0 as the equivalency point indicating no association. The ratio of the PORs, obtained from the interaction term in a logistic regression analysis, is a measure of interaction on the multiplicative scale. The potential confounders controlled for in the adjusted models include: age (years), sex (M, F), service branch (Army [referent], Navy, Air Force, Marines), rank (officer, enlisted), active duty vs Guard/Reserve, special strata (yes, no), Combat Exposure Scale (0=missing, 1=light [referent], 2=light to moderate, 3=moderate to heavy and heavy). One subject’s missing age was imputed to the mean age of the sample. The analyses included 508 cases and 508 controls. Abbreviations: BChE, butyrylcholinesterase; CI, confidence interval; POR, prevalence odds ratio; RERI, relative excess risk due to interaction.

a Adjusted RERI = 0.720 (95% CI -1.98 – 3.31)
Table S10. Interaction on the additive and multiplicative scales of having taken pyridostigmine bromide and butyrylcholinesterase (BChE) genotype on GWI.

| BChE K variant genotype | UK | Rare genotypes<sup>a</sup> | POR for BChE genotypes within strata of pyridostigmine |
|-------------------------|----|-----------------------------|----------------------------------------------------------|
|                         | UU | UK                          | N cases/controls | POR (95%CI) | N cases/controls | POR (95%CI) | N cases/controls | POR (95%CI) | UK vs UU | Rare vs UU |
| Took pyridostigmine     |    |                             |                |             |                |             |                |             |          |             |
| No                      | 97/175 | 1.0                      | 45/77 | 1.06 (0.68-1.64) p=0.81 | 6/21 | 0.52 (0.20-1.32) p=0.17 | 1.06 (0.68-1.64) p=0.81 | 0.52 (0.20-1.32) p=0.17 |
| Yes                     | 225/143 | 2.84 (2.05-3.93) p<0.001 | 111/71 | 2.82 (1.91-4.16) p<0.001 | 20/15 | 2.41 (1.18-4.91) p=0.02 | 0.99 (0.69-1.43) p=0.97 | 0.85 (0.42-1.71) p=0.64 |
| POR (95%CI) for pyridostigmine within strata of genotypes | 2.84 (2.05-3.93) p<0.001 | 2.68 (1.67-4.29) p<0.001 | 4.67 (1.51-14.41) p=0.007 |

Additive scale: Synergy index (95%CI)

|                         | Unadjusted | Adjusted for confounders |
|-------------------------|------------|--------------------------|
| Unadjusted              | 1.0        | 0.96 (0.52-1.77) p=0.91  |
| Adjusted for confounders| 1.0        | 0.82 (0.37-1.84) p=0.64  |

Multiplicative scale: POR (95%CI) from LR interaction term

|                         | Unadjusted | Adjusted for confounders |
|-------------------------|------------|--------------------------|
| Unadjusted              | 1.0        | 0.94 (0.53-1.67) p=0.84  |
| Adjusted for confounders| 1.0        | 0.87 (0.43-1.78) p=0.71  |

Note: The synergy index is a measure of interaction on the additive scale; it has the same distribution as the POR, viz., 0 to plus infinity with 1.0 as the equivalency point indicating no association. The ratio of the PORs, obtained from the interaction term in a logistic regression analysis, is a measure of interaction on the multiplicative scale. The potential confounders controlled for in the adjusted models include: age (years), sex (M, F), service branch (Army [referent], Navy, Air Force, Marines), rank (officer, enlisted), active duty vs Guard/Reserve, special strata (yes, no), Combat Exposure Scale (0=missing, 1=light [referent], 2=light to moderate, 3=moderate to heavy and heavy). One subject’s missing age was imputed to the mean age of the sample. The analyses included 504 cases and 502 controls; 4 cases and 6 controls had missing BChE genotypes.

Abbreviations: BChE, butyrylcholinesterase; CI, confidence interval; POR, prevalence odds ratio; RERI, relative excess risk due to interaction.

<sup>a</sup> Rare AChE genotypes include K/K, K/UK, U/A, and U/AK; other rare genotypes were not represented in the study sample.

<sup>b</sup> Adjusted RERI = -0.67 (95% CI -2.39 – 1.22)
Table S11. Interaction on the additive and multiplicative scales of *having taken pyridostigmine bromide* and *butyrylcholinesterase (BChE) enzyme activity level* on GWI.

| BChE activity level | 4th quartile (lowest risk) | 3rd quartile (mid-low risk) | 2nd quartile (mid-high risk) | 1st quartile (highest risk) | POR (95% CI) for BChE activity quartiles within strata of pyridostigmine |
|---------------------|----------------------------|-----------------------------|-----------------------------|-----------------------------|---------------------------------------------------------------------|
|                     | N cases/controls | POR (95% CI) | N cases/controls | POR (95% CI) | N cases/controls | POR (95% CI) | N cases/controls | POR (95% CI) | 3rd vs 4th quartile | 2nd vs 4th quartile | 1st vs 4th quartile |
| Took pyridostigmine |                           |                       |                            |                          |                                                      |                                                      |                                                      |                                                      |                        |                          |                        |
| No                  | 42/68                | 1.0                  | 36/61                      | 0.96 (0.54-1.68) p=0.87 | 37/83                 | 0.72 (0.42-1.25) p=0.24 | 34/62                 | 0.89 (0.50-1.57) p=0.68 | 0.96 (0.54-1.68) p=0.87 | 0.72 (0.42-1.25) p=0.24 | 0.89 (0.50-1.57) p=0.68 |
| Yes                 | 90/49                | 2.97 (1.77-5.00) p<0.001 | 80/66                      | 1.96 (1.19-3.25) p=0.009 | 81/62               | 2.12 (1.27-3.51) p=0.004 | 108/57               | 3.07 (1.86-5.06) p=0.001 | 0.66 (0.41-1.06) p=0.09 | 0.71 (0.44-1.15) p=0.16 | 1.03 (0.64-1.66) p=0.90 |

PORs (95% CI) for alarms within strata of BChE activity

Additive scale: Synergy index (95% CI)

| Unadjusted | Adjusted for confounders |
|------------|--------------------------|
| 1.0        | 1.0                      |
| 0.69 (0.33-1.45) p=0.33 | 0.69 (0.33-1.45) p=0.33 |

Adjusted RERI = -0.17 (95% CI -2.29 – 1.19)

Multiplicative scale: POR (95% CI) from LR interaction term

| Unadjusted | Adjusted for confounders |
|------------|--------------------------|
| 1.0        | 1.0                      |
| 0.69 (0.33-1.45) p=0.33 | 0.69 (0.33-1.45) p=0.33 |

Note: The synergy index is a measure of interaction on the additive scale; it has the same distribution as the OR, viz., 0 to plus infinity with 1.0 as the equivalency point indicating no association. The ratio of the PORs, obtained from the interaction term in a logistic regression analysis, is a measure of interaction on the multiplicative scale. The potential confounders controlled for in the adjusted models include: age (years), sex (M, F), service branch (Army [referent], Navy, Air Force, Marines), rank (officer, enlisted), active duty vs Guard/Reserve, special strata (yes, no), Combat Exposure Scale (0=missing, 1=light [referent], 2=light to moderate, 3=moderate to heavy and heavy). One subject’s missing age was imputed to the mean age of the sample. The analyses included 508 cases and 508 controls. Abbreviations: BChE, butyrylcholinesterase; CI, confidence interval; POR, prevalence odds ratio; RERI, relative excess risk due to interaction.
**Table S12.** Interaction on the additive and multiplicative scales of hearing nerve agent alarms and PON1 Q192R type R isoenzyme activity level on GWI.

|                  | PON1 Q192R type R isoenzyme activity level | POR (95% CI) for PON1 type R activity quartiles within strata of alarms |
|------------------|---------------------------------------------|-------------------------------------------------------------------------|
|                  | 4th quartile (lowest risk) | 3rd quartile (mid-low risk) | 2nd quartile (mid-high risk) | 1st quartile (highest risk) | 3rd vs 4th quartile | 2nd vs 4th quartile | 1st vs 4th quartile |
|                  | N cases/controls | POR (95% CI) | N cases/controls | POR (95% CI) | N cases/controls | POR (95% CI) | N cases/controls | POR (95% CI) | N cases/controls | POR (95% CI) | N cases/controls | POR (95% CI) |
| **Heard nerve agent alarms** | | | | | | | | | | | |
| No               | 25/61 | 1.0 | 30/67 | 1.09 (0.58-2.06) | p=0.78 | 13/30 | 1.06 (0.48-2.35) | p=0.89 | 43/129 | 0.81 (0.46-1.45) | p=0.48 |
| Yes              | 118/46 | 6.26 (3.52-11.14) | p<0.001 | 110/49 | 5.48 (3.08-9.73) | p<0.001 | 39/22 | 4.33 (2.15-8.71) | p<0.001 | 130/104 | 3.05 (1.79-5.19) | p<0.001 |
| **PORs (95% CI) for alarms within strata of PON1 type R activity** | | | | | | | | | | | | 6.26 (3.52-11.14) | p<0.001 | 5.01 (2.90-8.66) | p<0.001 | 4.09 (1.78-9.43) | p<0.001 | 3.75 (2.44-5.77) | p<0.001 |
| **Additive scale: Synergy index (95% CI)** | | | | | | | | | | | | Unadjusted | 1.0 | 0.84 (0.47-1.50) | p=0.56 | 0.63 (0.28-1.39) | p=0.25 | 0.40 (0.23-0.72) | p=0.002 |
|                  | Adjusted for confounders | 1.0 | 0.83 (0.39-1.74) | p=0.63 | 0.59 (0.21-1.70) | p=0.34 | 0.36 (0.17-0.78) | p=0.009 a |
| **Multiplicative scale: POR (95% CI) from LR interaction term** | | | | | | | | | | | | Unadjusted | 1.0 | 0.80 (0.36-1.77) | p=0.58 | 0.65 (0.24-1.80) | p=0.41 | 0.60 (0.29-1.23) | p=0.16 |
|                  | Adjusted for confounders | 1.0 | 0.83 (0.32-2.17) | p=0.71 | 0.56 (0.16-1.94) | p=0.36 | 0.50 (0.21-1.20) | p=0.12 |

Note: The synergy index is a measure of interaction on the additive scale; it has the same distribution as the OR, viz., 0 to plus infinity with 1.0 as the equivalency point indicating no association. The ratio of the PORs, obtained from the interaction term in a logistic regression analysis, is a measure of interaction on the multiplicative scale. The potential confounders controlled for in the adjusted models include: age (years), sex (M, F), service branch (Army [referent], Navy, Air Force, Marines), rank (officer, enlisted), active duty vs Guard/Reserve, special strata (yes, no), Combat Exposure Scale (0=missing, 1=light [referent], 2=light to moderate, 3=moderate to heavy and heavy). One subject’s missing age was imputed to the mean age of the sample. The analyses included 508 cases and 508 controls. Abbreviations: CI, confidence interval; PON1, paraoxonase-1; POR, prevalence odds ratio; RERI, relative excess risk due to interaction.

a Adjusted RERI = -1.46 (95% CI -5.34 – 0.21)
Table S13. Interaction on the additive and multiplicative scales of hearing nerve agent alarms and PON1 paraoxonase enzyme activity level on GWI.

| PON1 paraoxonase enzyme activity level | 4th quartile (lowest risk) | 3rd quartile (mid-low risk) | 2nd quartile (mid-high risk) | 1st quartile (highest risk) | POR (95% CI) for PON1 paraoxonase activity quartiles within strata of alarms |
|----------------------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|--------------------------------------------------------------------------------|
|                                        | N cases/controls             | POR (95% CI)                | N cases/controls             | POR (95% CI)                | N cases/controls             | POR (95% CI) |
| Heard nerve agent alarms               |                             |                             |                             |                             |                             |               |
| No                                     | 26/66                       | 1.0                         | 32/68                       | 1.20 (0.64-2.22) p=0.57     | 29/77                       | 0.96 (0.51-1.78) p=0.89 |
|                                        | 24/76                       | 0.80 (0.42-1.53) p=0.50     |                             |                             |                             |               |
| Yes                                    | 124/45                      | 7.00 (3.97-12.34) p<0.001   | 102/53                      | 4.89 (2.78-8.57) p<0.001     | 79/61                       | 3.29 (1.87-5.78) p<0.001 |
|                                        |                             |                              |                             |                             |                             |               |
| PORs (95% CI) for alarms within strata of PON1 paraoxonase activity | 7.00 (3.97-12.34) p<0.001 | 4.09 (2.39-6.98) p<0.001    | 3.44 (2.00-5.91) p<0.001    | 4.70 (2.68-8.23) p<0.001    |
| Additive scale: Synergy index (95% CI) |                             |                             |                             |                             |                             |               |
| Unadjusted                              | 1.0                         | 0.63 (0.35-1.12) p=0.11     | 0.38 (0.20-0.72) p=0.003    | 0.48 (0.26-0.88) p=0.02     |
| Adjusted for confounders               | 1.0                         | 0.69 (0.35-1.34) p=0.28     | 0.40 (0.19-0.86) p=0.02     | 0.46 (0.22-0.95) p=0.04 a   |
| Multiplicative scale: POR (95% CI) from LR interaction term |                             |                             |                             |                             |                             |               |
| Unadjusted                              | 1.0                         | 0.58 (0.27-1.28) p=0.18     | 0.49 (0.22-1.08) p=0.08     | 0.67 (0.30-1.49) p=0.33     |
| Adjusted for confounders               | 1.0                         | 0.53 (0.21-1.38) p=0.19     | 0.48 (0.19-1.20) p=0.11     | 0.59 (0.22-1.60) p=0.30     |

Note: The synergy index is a measure of interaction on the additive scale; it has the same distribution as the OR, viz., 0 to plus infinity with 1.0 as the equivalency point indicating no association. The ratio of the PORs, obtained from the interaction term in a logistic regression analysis, is a measure of interaction on the multiplicative scale. The potential confounders controlled for in the adjusted models include: age (years), sex (M, F), service branch [Army [referent], Navy, Air Force, Marines], rank [officer, enlisted], active duty vs Guard/Reserve, special strata [yes, no], Combat Exposure Scale (0=missing, 1=light [referent], 2=light to moderate, 3=moderate to heavy and heavy). One subject’s missing age was imputed to the mean age of the sample. The analyses included 508 cases and 508 controls. Abbreviations: CI, confidence interval; PON1, paraoxonase-1; POR, prevalence odds ratio; RERI, relative excess risk due to interaction. Serum paraoxonase catalytic activity for sarin is mediated mostly by the R isoenzyme.

a Adjusted RERI = -4.02 (95% CI -12.47 – 0.28)
**Table S14. Interaction on the additive and multiplicative scales of hearing nerve agent alarms and PON1 arylesterase (phenylacetate) enzyme activity level on GWI.**

| PON1 arylesterase (phenylacetate) enzyme activity level | 4th quartile (lowest risk) | 3rd quartile (mid-low risk) | 2nd quartile (mid-high risk) | 1st quartile (highest risk) |
|--------------------------------------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| N cases/controls | POR (95% CI) | N cases/controls | POR (95% CI) | N cases/controls | POR (95% CI) | N cases/controls | POR (95% CI) |
| Heed nerve agent alarms                                |                             |                             |                             |                             |                             |                             |                             |
| No                                                      | 25/71                       | 31/82                       | 27/70                       | 28/64                       | 1.07 (0.58-1.99) p=0.82   | 1.10 (0.58-2.07) p=0.78   | 1.24 (0.66-2.35) p=0.50 |
| Yes                                                     | 89/59                       | 107/55                      | 87/59                       | 114/48                      | 4.28 (2.44-7.52) p=0.001 | 5.53 (3.16-9.67) p<0.001 | 4.19 (2.39-7.35) p<0.001 |
| PORs (95% CI) for alarms within strata of PON1 arylesterase activity |                             |                             |                             |                             | 4.28 (2.44-7.52) p=0.001 | 5.15 (3.04-8.71) p<0.001 | 3.82 (2.20-6.65) p=0.001 |
| Additive scale: Synergy index (95% CI)                  |                             |                             |                             |                             |                             |                             |                             |
| Unadjusted                                              | 1.0                         | 1.35 (0.73-2.50) p=0.35     | 0.94 (0.50-1.77) p=0.87     | 1.63 (0.88-3.00) p<0.12    |
| Adjusted for confounders                                | 1.0                         | 1.42 (0.62-3.28) p=0.42     | 1.31 (0.58-2.96) p=0.53     | 1.59 (0.75-3.35) p=0.23 a |
| Multiplicative scale: POR (95% CI) from LR interaction term |                             |                             |                             |                             | 1.20 (0.56-2.59) p=0.64   | 0.89 (0.41-1.96) p=0.78   | 1.27 (0.57-2.80) p=0.56 |
| Unadjusted                                              | 1.0                         | 1.38 (0.56-3.44) p=0.49     | 1.80 (0.68-4.76) p=0.23     | 1.30 (0.50-4.42) p=0.59    |
| Adjusted for confounders                                | 1.0                         |                             |                             |                             | 1.27 (0.57-2.80) p=0.56   | 1.27 (0.57-2.80) p=0.56   |

Note: The synergy index is a measure of interaction on the additive scale; it has the same distribution as the OR, viz., 0 to plus infinity with 1.0 as the equivalency point indicating no association. The ratio of the PORs, obtained from the interaction term in a logistic regression analysis, is a measure of interaction on the multiplicative scale. The potential confounders controlled for in the adjusted models include: age (years), sex (M, F), service branch (Army [referent], Navy, Air Force, Marines), rank (officer, enlisted), active duty vs Guard/Reserve, special strata (yes, no), Combat Exposure Scale (0=missing, 1=light [referent], 2=light to moderate, 3=moderate to heavy and heavy). One subject’s missing age was imputed to the mean age of the sample. The analyses included 508 cases and 508 controls. Abbreviations: CI, confidence interval; PON1, paraoxonase-1; POR, prevalence odds ratio; RERI, relative excess risk due to interaction. Serum arylesterase catalytic activity for sarin is mediated by both Q and R isoenzymes.

a Adjusted RERI = 1.92 (95% CI -1.61 – 6.81)
Table S15. Interaction on the additive and multiplicative scales of hearing nerve agent alarms and PON1 diazoxonase enzyme activity level on GWI.

| N cases/controls | POR (95% CI) for 4th quartile (lowest risk) | N cases/controls | POR (95% CI) for 3rd quartile (mid-low risk) | N cases/controls | POR (95% CI) for 2nd quartile (mid-high risk) | N cases/controls | POR (95% CI) for 1st quartile (highest risk) |
|------------------|--------------------------------------------|------------------|--------------------------------------------|------------------|--------------------------------------------|------------------|--------------------------------------------|
|                  | Unadjusted                                 | Adjusted for confounders |                                | Unadjusted                                 | Adjusted for confounders |                                | Unadjusted                                 | Adjusted for confounders |                                |
|                  |                                             | Summary Statistics |                                |                                             | Summary Statistics |                                |                                             | Summary Statistics |                                |
|                  |                                             |                  |                                |                                             |                  |                                |                                             |                  |                                |
|                  | N cases/controls | POR (95% CI) | N cases/controls | POR (95% CI) | N cases/controls | POR (95% CI) | N cases/controls | POR (95% CI) |
| Heard nerve agent alarms | Yes | 79/61 | 3.48 (2.06-5.89) | p=0.001 | 92/73 | 3.39 (2.04-5.64) | p<0.001 | 89/43 | 5.56 (3.23-9.60) | p=0.001 | 137/44 | 8.36 (4.93-14.21) | p<0.001 |
|                  | No | 32/86 | 1.0 | 22/84 | 0.70 (0.38-1.31) | p=0.27 | 28/64 | 1.18 (0.64-2.15) | p=0.60 | 29/53 | 1.47 (0.80-2.70) | p=0.21 |
|                  |                                             |                  |                                |                                             |                  |                                |                                             |                  |                                |
| Additive scale: Synergy index (95% CI) | Unadjusted | 1.0 | 1.09 (0.53-2.27) | p=0.82 | 1.72 (0.86-3.42) | p=0.12 | 2.50 (1.32-4.71) | p=0.005 |
|                  | Adjusted for confounders | 1.0 | 1.18 (0.45-3.09) | p=0.75 | 1.89 (0.76-4.71) | p=0.17 | 2.84 (1.22-6.59) | p=0.02 |
| Multiplicative scale: POR (95% CI) from LR interaction term | Unadjusted | 1.0 | 1.38 (0.64-2.98) | p=0.41 | 1.36 (0.62-2.96) | p=0.44 | 1.63 (0.76-3.54) | p=0.21 |
|                  | Adjusted for confounders | 1.0 | 1.67 (0.68-4.12) | p=0.26 | 1.80 (0.68-4.72) | p=0.23 | 2.40 (0.94-6.11) | p=0.07 |

Note: The synergy index is a measure of interaction on the additive scale; it has the same distribution as the OR, viz., 0 to plus infinity with 1.0 as the equivalency point indicating no association. The ratio of the PORs, obtained from the interaction term in a logistic regression analysis, is a measure of interaction on the multiplicative scale. The potential confounders controlled for in the adjusted models include: age (years), sex (M, F), service branch (Army [referent], Navy, Air Force, Marines), rank (officer, enlisted), active duty vs Guard/Reserve, special strata (yes, no), Combat Exposure Scale (0=missing, 1=light [referent], 2=light to moderate, 3=moderate to heavy and heavy). One subject’s missing age was imputed to the mean age of the sample. The analyses included 508 cases and 508 controls. Abbreviations: CI, confidence interval; OR, prevalence odds ratio; RERI, relative excess risk due to interaction. Serum diazoxonase catalytic activity for sarin is mediated mostly by the Q isoenzyme.

Adjusted RERI = 4.17 (95% CI 1.15 – 10.04)
Table S16. Sensitivity analysis for correcting for unmeasured confounding the adjusted RERI for the effect of the GxE interaction of hearing alarms and PON1 RR vs QQ genotype\(^a\) on GWI on the additive scale.

| Stipulated | Calculated | Stipulated | Calculated |
|------------|------------|------------|------------|
| \(P_0\)    | \(P_1\)    | \(PRR_{Ud}\) | \(k\) | \(aRERI_c\) | 95% CI | \(P_0\)    | \(P_1\)    | \(PRR_{Ud}\) | \(k\) | \(aRERI_c\) | 95% CI |
| 1          | 1.0        | 1          | 1.000      | 7.69\(^b\) | 3.64-18.64\(^a\) | 0.3      | 0.9        | 5          | 2.714      | 2.81       | 1.23-6.68 |
| 0.5        | 0.7        | 1          | 1.000      | 7.69       | 3.64-18.64       | 0.3      | 0.9        | 7          | 3.250      | 3.34       | 0.95-5.58 |
| 0.5        | 0.7        | 3          | 1.250      | 6.15       | 2.91-14.86       | 0.3      | 0.9        | 9          | 3.667      | 3.07       | 0.80-4.93 |
| 0.5        | 0.7        | 5          | 1.364      | 5.63       | 2.65-13.60       | 0.1      | 0.3        | 1          | 1.000      | 7.69       | 3.64-18.64 |
| 0.5        | 0.7        | 7          | 1.429      | 5.37       | 2.53-12.96       | 0.1      | 0.3        | 3          | 1.167      | 6.59       | 3.12-15.94 |
| 0.5        | 0.7        | 9          | 1.471      | 5.22       | 2.46-12.57       | 0.1      | 0.3        | 5          | 1.211      | 6.35       | 3.00-15.35 |
|            |            |            |            |            |                  | 0.1      | 0.3        | 7          | 1.231      | 6.24       | 2.95-15.09 |
| 0.5        | 0.9        | 1          | 1.000      | 7.69       | 3.64-18.64       | 0.1      | 0.3        | 9          | 1.242      | 6.18       | 2.93-14.95 |
| 0.5        | 0.9        | 3          | 1.667      | 4.60       | 2.17-11.07       | 0.1      | 0.5        | 1          | 1.000      | 7.69       | 3.64-18.64 |
| 0.5        | 0.9        | 5          | 2.143      | 3.57       | 1.63-8.55        | 0.1      | 0.5        | 3          | 1.400      | 5.48       | 2.55-13.23 |
| 0.5        | 0.9        | 7          | 2.500      | 3.05       | 1.36-7.28        | 0.1      | 0.5        | 5          | 1.533      | 5.00       | 2.36-12.03 |
| 0.5        | 0.9        | 9          | 2.778      | 2.74       | 1.196-53         | 0.1      | 0.5        | 7          | 1.600      | 4.79       | 2.26-11.53 |
| 0.3        | 0.5        | 1          | 1.000      | 7.69       | 3.64-18.64       | 0.1      | 0.5        | 9          | 1.640      | 4.67       | 2.21-11.25 |
| 0.3        | 0.5        | 3          | 1.200      | 6.40       | 3.03-15.49       |          |            |            |            |            |            |
| 0.3        | 0.5        | 5          | 1.267      | 6.06       | 2.87-14.66       | 0.1      | 0.7        | 1          | 1.000      | 7.69       | 3.64-18.64 |
| 0.3        | 0.5        | 7          | 1.300      | 5.91       | 2.79-14.28       | 0.1      | 0.7        | 3          | 1.750      | 4.38       | 2.06-10.53 |
| 0.3        | 0.5        | 9          | 1.320      | 5.82       | 2.75-14.07       | 0.1      | 0.7        | 5          | 2.091      | 3.66       | 1.68-8.77  |
| 0.3        | 0.7        | 1          | 1.000      | 7.69       | 3.64-18.64       | 0.1      | 0.7        | 9          | 2.412      | 3.17       | 1.42-7.55  |
| 0.3        | 0.7        | 3          | 1.500      | 5.11       | 2.42-12.32       |          |            |            |            |            |            |
| 0.3        | 0.7        | 5          | 1.727      | 4.44       | 2.08-10.68       | 0.1      | 0.9        | 1          | 1.000      | 7.69       | 3.64-18.64 |
| 0.3        | 0.7        | 7          | 1.857      | 4.12       | 1.91-9.93        | 0.1      | 0.9        | 3          | 2.333      | 3.27       | 1.49-7.81  |
| 0.3        | 0.7        | 9          | 1.941      | 3.94       | 1.82-9.50        | 0.1      | 0.9        | 5          | 3.286      | 2.31       | 0.94-5.52  |
| 0.3        | 0.9        | 1          | 1.000      | 7.69       | 3.64-18.64       | 0.1      | 0.9        | 7          | 4.000      | 1.89       | 0.71-4.51  |
| 0.3        | 0.9        | 3          | 2.000      | 3.83       | 1.769-20         |          |            |            |            |            |            |

Abbreviations: \(PRR_{Ud}\), stipulated prevalence rate ratio in the underlying population for the association of the unmeasured confounder (U) with GWI; \(P_0\), stipulated probability of U in those in the underlying population who did not hear alarms; \(P_1\), stipulated probability of U in those in the underlying population who heard alarms; \(PRR_U\), the association of U with hearing alarms, assumed equal to \(PRR_{Ud}\); \(k\), adjustment factor calculated by the first equation below; aOR, the odds ratio from a logistic regression for the gene-environment interaction adjusted for the measured confounders; \(aRERI_c\), relative excess risk due to interaction on the additive scale, adjusted for measured confounders and corrected for unmeasured confounding, calculated by the second equation below; 95% CI, asymmetrical 95% confidence limits of \(aRERI_c\) calculated by bootstrapping with 5,000 repetitions; plausible values of \(P_0\) and \(P_1\) are \(>0\) to \(<1\) and of \(PRR_U\), \(>1\) to \(<10\).

Assumption: \(PRR_{Ud} = PRR_U\)

\(^a\) Equations for calculating \(aRERI_c\) adapted from Corollary 3B in section 5 and the second example in section 6 of VanderWeele et al.\(^5\)

\[k = \frac{1+(1/PRR_{EU}-1)(P_0)}{1+(1/PRR_{EU}-1)(P_1)}\]

\[aRERI_c = \frac{1}{k} aOR_{11} - aOR_{10} - \frac{1}{k} aOR_{01} + 1\]

\(^b\) This row, using 1.0 for the 3 stipulated parameters for validation, represents the values uncorrected for unmeasured confounding. This \(aRERI\) agrees exactly with the RERI adjusted for measured confounders in Table 2 calculated by Zou’s SAS macro; whereas, its asymmetrical 95% CI from bootstrapping is slightly less conservative than that from Zou’s method.
Table S17. Sensitivity analysis for correcting for unmeasured confounding the adjusted prevalence odds ratio for the effect of the GxE interaction of hearing alarms and PON1 RR vs QQ genotype on GWI on the multiplicative scale.

| Stipulated    | Calculated | Stipulated | Calculated |
|---------------|------------|------------|------------|
| P0  | P1 | PRRUD | Bmult | aPORc | 95% CI | P0  | P1 | PRRU | Bmult | aPORc | 95% CI |
| 1.0 | 1.0 | 1.000 | 3.41b | 1.20 - 9.72b | 0.3 | 0.9 | 5.000 | 1.26 | 0.44 - 3.58 |
| 0.5 | 0.7 | 1.250 | 2.73 | 0.96 - 7.77 | 0.3 | 0.9 | 9.000 | 0.93 | 0.33 - 2.65 |
| 0.5 | 0.7 | 1.364 | 2.50 | 0.88 - 7.13 | 0.1 | 0.3 | 1.000 | 3.41 | 1.20 - 9.72 |
| 0.5 | 0.7 | 1.429 | 2.39 | 0.84 - 6.80 | 0.1 | 0.3 | 3.000 | 2.92 | 1.03 - 8.33 |
| 0.5 | 0.7 | 1.471 | 2.32 | 0.81 - 6.61 | 0.1 | 0.3 | 5.000 | 2.82 | 0.99 - 8.03 |
| 0.5 | 0.9 | 1.000 | 3.41 | 1.20 - 9.72 | 0.1 | 0.3 | 7.000 | 2.77 | 0.97 - 7.90 |
| 0.5 | 0.9 | 1.667 | 2.05 | 0.72 - 5.83 | 0.1 | 0.3 | 9.000 | 2.74 | 0.96 - 7.82 |
| 0.5 | 0.9 | 2.143 | 1.59 | 0.56 - 4.53 | 0.1 | 0.5 | 1.000 | 3.41 | 1.20 - 9.72 |
| 0.5 | 0.9 | 2.500 | 1.36 | 0.48 - 3.89 | 0.1 | 0.5 | 3.000 | 2.44 | 0.85 - 6.94 |
| 0.5 | 0.9 | 2.778 | 1.23 | 0.43 - 3.50 | 0.1 | 0.5 | 5.000 | 2.22 | 0.78 - 6.34 |
| 0.3 | 0.5 | 1.000 | 3.41 | 1.20 - 9.72 | 0.1 | 0.5 | 9.000 | 2.08 | 0.73 - 5.93 |
| 0.3 | 0.5 | 1.200 | 2.84 | 1.00 - 8.10 | 0.1 | 0.7 | 1.000 | 3.41 | 1.20 - 9.72 |
| 0.3 | 0.5 | 1.267 | 2.69 | 0.94 - 7.67 | 0.1 | 0.7 | 3.000 | 1.95 | 0.68 - 5.55 |
| 0.3 | 0.5 | 1.300 | 2.62 | 0.92 - 7.47 | 0.1 | 0.7 | 5.000 | 1.63 | 0.57 - 4.65 |
| 0.3 | 0.7 | 1.000 | 3.41 | 1.20 - 9.72 | 0.1 | 0.7 | 7.000 | 1.49 | 0.52 - 4.25 |
| 0.3 | 0.7 | 1.500 | 2.27 | 0.80 - 6.48 | 0.1 | 0.7 | 9.000 | 1.41 | 0.50 - 4.03 |
| 0.3 | 0.7 | 1.727 | 1.97 | 0.69 - 5.63 | 0.1 | 0.9 | 1.000 | 3.41 | 1.20 - 9.72 |
| 0.3 | 0.7 | 1.857 | 1.84 | 0.64 - 5.23 | 0.1 | 0.9 | 3.000 | 1.46 | 0.51 - 4.16 |
| 0.3 | 0.7 | 1.941 | 1.76 | 0.62 - 5.01 | 0.1 | 0.9 | 5.000 | 1.04 | 0.36 - 2.96 |
| 0.3 | 0.9 | 1.000 | 3.41 | 1.20 - 9.72 | 0.1 | 0.9 | 7.000 | 0.85 | 0.30 - 2.43 |
| 0.3 | 0.9 | 2.000 | 1.71 | 0.60 - 4.86 | 0.1 | 0.9 | 9.000 | 0.75 | 0.26 - 2.13 |

Abbreviations: PRRUD, stipulated prevalence rate ratio in the underlying population for the association of the unmeasured confounder (U) with GWI; P0, stipulated probability of U in those in the underlying population who did not hear alarms; P1, stipulated probability of U in those in the underlying population who heard alarms; PRRU, the association of U with hearing alarms, assumed equal to PRRUD; Bmult, estimate of the bias from unmeasured confounding on the multiplicative scale; aPORc, prevalence odds ratio of the interaction term of logistic regression estimating interaction on the multiplicative scale, adjusted for measured confounders and corrected for unmeasured confounding by dividing the aPOR by Bmult; 95% CI, asymmetrical 95% confidence limits of aPORc calculated by dividing the original 95% CI of the aPOR by Bmult; plausible values of P0 and P1 are >0 to <1 and of PRRU, >1 to <10.

Assumption: PRRUD = PRRU

a Adapted from Corollary 2A in section 4 of VanderWeele et al.5

b This row, using 1.0 for the 3 stipulated parameters for validation, represents the values uncorrected for unmeasured confounding. Both the aPOR and its 95% CI agree exactly with the POR from the LR interaction term adjusted for measured confounding in Table 2.
| Reference | Ascertainment method | Study design | Reported question | Outcome association |
|-----------|----------------------|--------------|-------------------|---------------------|
| Haley and Kurt 1997<sup>6</sup> | Written questionnaire | Supervised survey of a battalion sample | “experienced likely chemical weapons attack” | PRR 7.8 (2.3-25.9) for GWI (syndrome 2) |
| Nisenbaum et al. 2000<sup>7</sup> | Written questionnaire | Study of an Air National Guard unit and airmen at 3 U.S. Air Force bases | “belief that biological or chemical weapons were being used against them” | OR 6.05 (3.43-19.68 for severe GWI; 2.52 (1.83-3.48) for mild-moderate GWI |
| White et al. 2001<sup>8</sup> | Written questionnaire | Supervised survey and neuropsycho-logical testing and interviews of 3 cohorts: 2 Gulf-deployed and 1 deployed to Germany | “poison gas or germ warfare” | Neuropsychological measures of mood, memory, and attention/executive function, P<0.05 |
| Kang et al. 2002<sup>9</sup> | Mailed questionnaire survey | Mailed survey of random sample of GWV population | Checklist of exposures: “Nerve gas” | RR 9.17 (7.69-10.93) for GWI (4 most typical symptoms) |
| Lindem et al. 2003<sup>10</sup> | Written questionnaire | Supervised survey and neuropsycho-logical testing and interviews in a subset from the White et al. study | Checklist: “Chemical or biological warfare agents” | Neuropsychological measures of attention, executive function, and memory, p<0.01 |
| Proctor et al. 2006<sup>11</sup> | Khamisiyah computer exposure plume model | Supervised survey and neuropsycho-logical testing and interviews in a subset from the White et al. study | Not applicable (nerve agent exposure estimated by unit location in computer-modeled atmospheric dispersion from demolition of ammunition depot) | Neuropsychological measures of psychomotor function and visuospatial abilities, P<0.01 |
| Heaton et al. 2007<sup>12</sup> | Khamisiyah computer exposure plume model | Volumetric analysis of brain MRI in GWI cases and controls from White et al. study | Not applicable | White matter and brain volume reduction associated with estimated sarin/cyclosarin exposure |
| Steele et al. 2012<sup>13</sup> | Telephone interview questionnaire | Cases and controls recruited from Kansas GW veterans | “Heard chemical alarms sounded” | OR 1.31 (0.83-2.07) for GWI |
| Haley and Tuite 2013<sup>14</sup> | CATI questionnaire telephone interview | National telephone interview survey (USMHS) of a random sample of 1991 U.S. military population | “Did the alarms on the chemical warfare detection devices in areas where you were living or working ever go off while you were present there?” if yes, “on how many days . . .” | aOR 4.13 (2.51-6.80) Trend test p<0.001 for overall GWI |
| Chao et al. 2010,2011, 2014,2015,2016,2018<sup>15-20</sup> | Written questionnaire | Volunteer GW veterans recruited by public ads in Northern California | “Did you hear chemical alarms sound?” If yes, “How many days did you hear chemical alarms?” | Various measures of abnormal brain structure and function and white matter integrity in those who recalled hearing alarms |
| Barth et al. 2017<sup>21</sup> | Khamisiyah computer exposure plume model | National random sample survey | Not applicable | aRR for brain cancer 2.71 (1.25-5.87) |
| Reference(s) | Experimental model | Finding |
|------------|-------------------|---------|
| Spiegelberg 1961\textsuperscript{22} | Hypothesis- raising clinical description | Description of a previously unsuspected chronic encephalopathic symptoms similar to GWI in workers who had repetitive subclinical sarin exposures in German nerve agent factories during World War II. |
| Duffy et al. 1979\textsuperscript{23} | Hypothesis- raising clinical description | Description of a previously unsuspected chronic encephalopathic symptoms similar to GWI in workers who had repetitive subclinical sarin exposures in U.S. nerve agent factories during the Cold War, associated with unusual EEG changes. |
| Burchfiel et al. 1976, 1982\textsuperscript{24,25} | Laboratory experiments | Administration of subclinical doses of sarin to Rhesus monkeys (1 μg/kg i.m. weekly x 10) produced chronic electroencephalographic (EEG) changes similar to those reported in the Duffy et al. study. |
| Henderson et al. 2001, 2002\textsuperscript{26,27} | Laboratory experiments | Inhalation administration of subclinical doses of sarin to rats (0, 0.2, or 0.4 mg/m\textsuperscript{3} of sarin for 1 h/day for 1, 5, or 10 days; follow-up at 30 d) produced persistent alteration in the numbers of muscarinic cholinergic M1 and M3 receptors in cortical and hippocampal brain regions, compatible with cognitive dysfunction. |
| Kassa et al. 2001,2001\textsuperscript{28,29} | Laboratory experiments | Inhalation administration of subclinical doses of sarin to rats (1.25 μL/L x 3 over 7 d; follow-up at 3 mo) resulted in increased CNS excitability and impaired gait and mobility, memory and cognitive behavior and altered immune function. |
| Scremin et al. 2003\textsuperscript{30} | Laboratory experiments | Administration of subclinical doses of sarin to rats (62.5 μg/kg [0.5 LD\textsubscript{50}] s.c. 3x per wk x 3 wks; follow-up at 16 wks) altered behavioral measures associated with down-regulation of muscarinic receptors in hippocampus, caudate putamen, and mesencephalon, not seen after PB alone or PB plus sarin. |
| Pena-Phillippides et al. 2007\textsuperscript{31} | Laboratory experiments | Inhalation administration of subclinical doses of sarin to rats (0.4 mg/m\textsuperscript{3}/day x 5d; follow-up at 2-4 wks) suppressed serum corticosterone and ACTH levels. |
| Van Helden et al. 2003,2004\textsuperscript{32,33} | Laboratory experiments | Inhalation administration of sarin vapor to marmosets at concentration-time doses below the dose producing miosis or detectable by military field devices (≤150 μg/m\textsuperscript{3} for 5 h; follow-up at 1 yr) produced persisting EEG changes like those reported by Duffy and Burchfiel (above) that increased in severity over time. |
| Mach et al.2008\textsuperscript{34} | Laboratory experiments | Administration of subclinical doses of sarin (64 μg/kg [0.4 LD\textsubscript{50}] s.c. daily x 3; follow-up at 21 d) with shaker stress to rats produced delayed behavioral change and catecholamine depletion in adrenal glands, suggesting autonomic dysfunction. |
| Morris et al.2007\textsuperscript{35} | Laboratory experiments | Administration of subclinical doses of sarin to mice (8 μg/kg [0.05 LD\textsubscript{50}] s.c. on 2 consecutive days; follow-up at 10 wks) produced delayed chronic reduction in high frequency heart rate variability and increased tyrosine hydroxylase mRNA in locus coeruleus and dorsal vagal complex of brain, indicating abnormal central autonomic activity similar to that in GWI\textsuperscript{36,37}. |
| Shewale et al. 2012\textsuperscript{38} | Laboratory experiments | Administration of subclinical doses of sarin to mice (64 μg/kg [0.4 LD\textsubscript{50}] s.c. on 2 consecutive days; follow-up at 8-12 wks) produced reduced cardiac responsive-ness to beta-adrenergic stimulation, reduced adrenal tyrosine hydroxylase mRNA, corticosterone, and stress response in HPA axis indicating autonomic impairment. |
| Oswal et al. 2013\textsuperscript{39} | Laboratory experiments | Administration of subclinical doses of sarin to mice (64 μg/kg [0.4 LD\textsubscript{50}] s.c. on 2 consecutive days; follow-up at 4-8 wks) produced alterations in dopamine turnover in the frontal cerebral cortex, amygdala and caudate nuclei of the brain capable of mediating long-term behavioral and neuropsychological changes. |
| O’Callaghan et al. 2015; Ashbrook et al. 2018; Belgrad et al. 2019; Michalovich et al. 2020\textsuperscript{40-43} | Laboratory experiments | Administration of corticosterone in drinking water daily x 5 or 7 d followed by sarin surrogate DFP (diisopropyl fluorophosphate, 1.5 mg/kg s.c.) initiated chronic neuroinflammation in the brains of mice with adverse effects on oligodendrocytes and epigenetic modification of genes related to the brain’s immunologic and cognitive systems. |
| Alsheh et al. 2020\textsuperscript{44} | Clinical study | Neuroinflammation was recently demonstrated in veterans with GWI by in vivo positron-emission-tomography (PET) imaging of the brain. |
| Deshpande et al. 2010, 2016, 2018, 2020\textsuperscript{45-48} | Laboratory experiments | Administration of a subclinical dose of DFP to rats (0.5 mg/kg daily s.c. x 5d; follow-up at 3-6 mo) was followed by behavioral abnormalities analogous to chronic depression, anxiety and memory impairment as well as hippocampal neuronal damage leading to a chronic elevation of intracellular calcium concentration, all largely corrected by 2 previously FDA-approved drugs. |
Table S20. Prior experimental evidence establishing that the PON1 Q192R type Q isoenzyme activity is the property of the PON1 gene that best protects the brain from the neurotoxic effects of low-level sarin nerve agent.

| Reference(s)                      | Experimental model | Finding                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-----------------------------------|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Davies et al. 1996\(^{50}\)       | In vitro assays    | From assays of the rate of hydrolysis of sarin by the plasma from 93 human volunteers, plasma from PON1 QQ homozygotes had a mean hydrolysis rate of sarin 9.3 times that of RR homozygotes.                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| La Du et al. 2001\(^{51}\)        | In vitro assays    | Sera from 25 veterans with GWI and 20 well control veterans were assayed for rate of hydrolysis of sarin (sarinas activity) as well as serum hydrolytic activity of the PON1 Q and R isoenzymes. Sarinase activity was correlated with Q isoenzyme activity but not with R isoenzyme activity. The catalytic efficiency of the purified Q isoenzyme with sarin was over 4-fold greater than with the R isoenzymes. This study is particularly relevant because it shows that the Q isoenzyme can effectively hydrolyze sarin in blood at the low physiologic concentrations expected with low-level sub-symptomatic sarin exposure. |
| Kanamori-Kataoka and Seto 2009\(^{52}\) | In vitro assays    | The maximum rate of hydrolysis of sarin with purified PON1 Q and R isoenzymes from plasma of 63 civilian volunteers was 3.5 times greater with the Q isoenzyme than with the R isoenzyme, confirming the finding of Davies et al.                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Valiyyaveetti et al. 2010\(^{53}\) | In vitro assays    | Acetylcholinesterase (AChE) is exceptionally sensitive to inhibition by sarin nerve agent and considered its primary target. In a series of vitro assays, purified human PON1 type Q isoenzyme, at physiological concentrations present in blood, was shown to potently prevent inhibition of AChE by sub-micromolar concentrations of sarin.                                                                                                                                                                                                                                                                                                                                 |
| Valiyyaveetti et al. 2011\(^{54,55}\) | In vivo experiments | Intravenous treatment of guinea pigs with purified human PON1 type Q isoenzyme significantly increased survival, reduced physiologic signs of nerve agent exposure, and attenuated brain AChE inhibition after microinstillation inhalation exposure to 1.2 x LC\(_{50}\) of sarin.                                                                                                                                                                                                                                                                                                                                 |
Figure S1. Mean (SE) butyrylcholinesterase (BChE) serum activity by $BChE$ genotype. All variant genotype groups were significantly ($p<0.001$) different from the U/U group except for the U/A group. The number at the base of each bar is the group sample size in the full USMHS genotyping sample ($n=1,923$).
Figure S2. Prediction of irreversible or long-lasting health effects in soldiers exposed to airborne nerve agent above the U.S. Environmental Protection Agency’s Acute Exposure Guideline Level 2 (AEGL-2) but below the detection threshold of the widely deployed U.S. M8A1 nerve agent alarm device. On the basis of current science, the AEGL levels define the airborne concentration-time thresholds (expressed as mg/m³ per min) of a chemical as the level above which the general population, especially genetically susceptible individuals, could be expected to experience the following adverse effects: above AEGL-1 = notable discomfort, irritation, or certain asymptomatic nonsensory effects that are not disabling and are transient and reversible upon cessation of exposure; above AEGL-2 = irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape; above AEGL-3 = life-threatening health effects or death. As tens of thousands of M8A1 detection alarms sounded repeatedly following U.S. and Coalition bombing of Iraqi chemical weapon storage sites throughout the conflict period, most soldiers donned mission oriented protective posture (MOPP) impervious suits, masks and gloves. Since, however, the AEGL-2 threshold (0.087 mg/m³ for 10 min, 0.05 mg/m³ for 30 min, etc.) was substantially below the M8A1 detection threshold (0.11 mg/m³), there were undoubtedly periods of time before and after alarms sounded when soldiers were unprotected and exposed to AEGL-2 concentrations of nerve agent over the short times sufficient to cause irreversible or serious, long-lasting health effects, particularly for more genetically susceptible individuals. Thus, the detection threshold of the M8A1 detector would have prevented incapacitating or fatal nerve agent exposures (above AEGL-3) if they had occurred, but not AEGL-2 exposures, which did occur but in 1991 were not yet known to have long-lasting effects. The greater sensitivity of the Czech GSP-11 (0.05 mg/m³) and the French AP2C/APACC (0.01 mg/m³) detection devices explains the repeated Czech and French detections not detected by the ubiquitous U.S. M8A1 detectors. Figure reproduced from Neuroepidemiology 2013; 40: 160-177 by permission of S. Karger AG, Basel.
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