

# Letters

## COMMENT & RESPONSE

### Agent Orange Exposure and Dementia Diagnosis in US Veterans of the Vietnam Era

**To the Editor** We were pleased to see the attention of Martinez et al<sup>1</sup> to dementia in veterans of the Vietnam era. However, we are troubled by several important concerns about their study: study population characterization, exposure definition, dementia ascertainment, and a failure to recognize the total environmental exposure milieu of deployment that included Agent Orange.

The study population is described as a 2% sample of veterans of the Vietnam era, based on the period of military service (August 5, 1964, to May 7, 1975), who received care from the Veteran Health Administration. Period of service is a self-reported variable recorded during Veteran Health Administration health care encounters. Department of Defense data on dates and location of deployments would have strengthened population identification.<sup>1</sup>

Requiring self-reported Agent Orange exposure from at least 1 inpatient and 1 outpatient encounter likely introduced misclassification bias,<sup>1</sup> because this method excludes an unknown proportion of individuals with mild and moderate cases that did not require inpatient care. Furthermore, no specification was provided as to the identification of those who were unexposed.<sup>1</sup>

It is unclear what approach the authors<sup>1</sup> used for screening out prevalent cases at baseline. The included references use different methods, but no specification was provided regarding the specific approach taken for this study.<sup>1</sup> When and how long was the baseline period used to rule out prevalent cases of dementia? Similarly, using a single encounter to identify incident dementia is recognized as resulting in increased false-positive results. For example, ascertainment using a single occurrence of a multiple sclerosis-associated diagnostic code overestimated cases by as much as 40% compared with a medical record review.<sup>2</sup> The ascertainment methods used by Martinez et al<sup>1</sup> not only include incident dementia but likely include an unknown proportion of so-called rule-out cases.

The Agent Orange Act of 1991<sup>3</sup> created a legal framework for awarding veterans' benefits. The law recognized in-

country service as a presumptive exposure for benefit determinations. The authors<sup>1</sup> use of presumption of exposure is not scientifically defensible for assessing a putative association of exposure and disease. Admittedly, direct measurement of herbicide exposure via biological assay is challenging.<sup>4</sup> Agent Orange was just 1 of many potential environmental exposures in the Vietnam war theater; types and amounts of these exposures were variable and dependent on military occupation, timing, and location.

The limitations noted<sup>1</sup> are substantial, and along with absence of an informed presentation about the complex exposure milieu of combat deployment, they preclude any meaningful conclusions regarding Agent Orange and dementia in veterans of the Vietnam era. We recommend a follow-up study addressing these concerns.

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