

Letters

COMMENT & RESPONSE

In Reply We thank Schneiderman and colleagues for their interest in our article, in which we reported that US veterans of the Vietnam era with presumptive Agent Orange (AO) exposure have nearly a 2-fold increased risk of being diagnosed with dementia.¹ They raise several concerns about our methods, which we address here.

First, they note that the period of service variable we used to identify veterans from the Vietnam era is based on self-reporting.¹ We agree that linkage with Department of Defense data on dates and location of deployment would have improved the accuracy of our cohort identification. We would be interested in merging Department of Defense and Veterans Health Administration data to address this concern in the future. Nonetheless, there is no evidence or reason to believe that veterans would falsely report their period of service. Also, the age range of our cohort¹ was consistent with what would be expected for veterans of the Vietnam era.

Second, we clarify that our definition of presumptive AO exposure required more than at least 1 inpatient and 1 outpatient encounter with self-reported AO exposure.¹ Specifically, we required that the patient self-report AO exposure (inpatient) and a clinician indicate that at least 1 health care encounter (inpatient or outpatient) was associated with AO exposure. We believe that requiring clinician confirmation improved the specificity of our AO definition. Veterans with only 1 of these criteria were excluded. Veterans with neither of these criteria were considered unexposed. Schneiderman et al correctly point out that the patient self-report variable is only available from inpatient files, and this approach may have excluded mild or moderate cases that did not require inpatient care. Therefore, we agree that our results¹ may not generalize to veterans with lower levels of AO exposure. We believe it would be helpful to record veterans' self-reports of AO exposure in outpatient as well as inpatient records.

Third, we clarify that we defined prevalent dementia at baseline as having a single dementia diagnosis code at the random selection date or during the 2 previous years, using the 2016 Veterans Health Administration Dementia *International Classification of Diseases, Ninth Revision* Diagnostic Code list.² We agree that requiring a single diagnosis rather than 2 diagnoses of dementia prioritizes sensitivity over specificity.

We feel this is appropriate because dementia is underdiagnosed.³

Fourth, we disagree that use of the term *presumptive exposure* in our article¹ is not scientifically defensible. There is no gold standard for determining AO exposure, and we specifically chose to include this word to highlight for readers that we did not have direct measures of AO exposure. In addition, we emphasize throughout our article¹ that we are describing an observed association that does not necessarily reflect a causal effect.

Finally, we agree that AO was one of many environmental exposures in the Vietnam war and types and amounts of these exposures varied. However, AO was the most common of the herbicides sprayed, which is why it has been the focus of most prior research and reports from the National Academies of Sciences, Engineering, and Medicine.⁴

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1. Martinez S, Yaffe K, Li Y, Byers AL, Peltz CB, Barnes DE. Agent Orange exposure and dementia diagnosis in US veterans of the Vietnam Era. *JAMA Neurol*. 2021;78(4):473-477. doi:10.1001/jamaneurol.2020.5011
2. Barnes DE, Byers AL, Gardner RC, Seal KH, Boscardin WJ, Yaffe K. Association of mild traumatic brain injury with and without loss of consciousness with dementia in US military veterans. *JAMA Neurol*. 2018;75(9):1055-1061. doi:10.1001/jamaneurol.2018.0815
3. Bradford A, Kunik ME, Schulz P, Williams SP, Singh H. Missed and delayed diagnosis of dementia in primary care: prevalence and contributing factors. *Alzheimer Dis Assoc Disord*. 2009;23(4):306-314. doi:10.1097/WAD.0b013e3181a6bebc
4. National Academies of Sciences, Engineering and Medicine. *Veterans and Agent Orange: update 11*. The National Academies Press; 2018. <https://doi.org/10.17226/25137>