Association of Androgen Deprivation Therapy With Alzheimer's Disease: Unmeasured Confounders

The recent report by Nead et al,¹ in which an informatics approach was used to extract routine administrative and clinical data from electronic medical records of two major academic centers in the United States, found a positive and seemingly duration-dependent association between androgen deprivation therapy (ADT) and Alzheimer's disease (AD) among a cohort of 16,888 men with prostate cancer. The authors should be commended for their novel data-mining approach to address a salient clinical question. The methods may represent the foundation for many big data studies to come.

We have several methodologic concerns. First, presence and duration of ADT is based on the presence of any one of 29 different words in electronic medical records, which refer to a heterogeneous group of medications with disparate mechanisms and physiologic effects. For example, gonadotrophin-releasing hormone (GnRH) agonists downregulate the hypothalamic-pituitary-gonadal axis by chronic stimulation of GnRH receptors in the anterior pituitary and, thus, cause an initial surge in luteinizing hormone (LH) and testosterone. Other medications block GnRH or androgen receptors, which causes no such surge. Furthermore, different forms of ADT have different effects on gonadotropin levels: GnRH agonists mainly reduce LH, whereas GnRH antagonists reduce follicle-stimulating hormone and LH. Antiandrogens increase both. Given that receptors for GnRH, LH, and follicle-stimulating hormone are found in a wide variety of substrates—some with important inflammatory, vascular, and metabolic roles—it is unsurprising that differential adverse effects may be seen between forms of ADT.^{2,3}

The data bear this out. A recent study that examined multiple phase III drug trials found lower risks of cardiovascular adverse effects in GnRH antagonists compared with agonists.⁴ Another study found worse cardiovascular, thromboembolic, and metabolic outcomes in GnRH agonist therapy compared with bilateral orchiectomy—despite the fact that both achieved castrate levels of androgens.⁵ As such, it is disappointing that the authors do not perform a more granular analysis of the effect of each drug class on the development of AD. In addition, it would be remiss to completely exclude patients who received ADT in the form of bilateral orchiectomy. This may be a missed opportunity to shed light on the mechanisms behind the purported neurocognitive adverse effects of ADT.

Second, ADT necessitates frequent outpatient visits. Patients who receive ADT may need injections every several months and are at an advanced stage of disease that requires more checkups.⁶ Given that study outcomes were identified by using administrative data, individuals with more frequent visits may be more likely to be diagnosed with adverse events because of a greater number of

physician encounters and more numerically likely to have an instance of the defined study outcome term appear in the medical record as a result of a greater number of records.

Third, two recent studies found that patients with prostate cancer who receive ADT have higher rates of impaired cognitive performance at baseline,^{7,8} which may contribute to the eventual development of AD. Of note, these studies included patients with both nonmetastatic and asymptomatic metastatic disease. A third study of men with only localized prostate cancer assessed cognitive function by using 14 different tests that covered eight domains; there were no adverse effects on cognitive function among those who received ADT compared with those who did not.⁹ Taken together with the fact that men with higher stage disease are more likely to require ADT, these results suggest that disease stage is likely an important confounder of ADT and AD. Nead et al¹ were unable to account for disease stage in their study, which they rightly acknowledge.

As such, on the topic of confounding, advanced statistical techniques, such as propensity matching or instrumental variable analysis, will never be able to completely account for every possible confounder. It is possible, however, to perform sensitivity analyses to determine how strong an unmeasured confounder would need to be to explain away the point estimate of the observed hazard ratio.¹⁰ To do this, we have to consider the relationships: between an unmeasured confounder (eg, localized v metastatic disease) with the exposure (ie, ADT use), and between the unmeasured confounder and the outcome (ie, development of AD). We found that if the latter relationship had a negative value (likelihood of developing AD < 1), that is, patients with metastatic prostate cancer who are less likely to develop AD, then regardless of the relationship between unmeasured confounder(s) and exposure, the result would be nonsignificant (Table 1). Therefore, this calls into question the robustness of the results of this study. Although there may truly be an association between ADT and AD, the inability to account for important unmeasured confounding, in particular, stage of disease, limits its validity; therefore, we urge readers to interpret any conclusions in light of this.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Table 1. Magnitudes of the Joint Bounding Factor for Different Combinations of the Odds of Receiving Androgen Deprivation Therapy and Likelihood of Developing Alzheimer's Disease, Both in Presence of Unmeasured Confounders

OR _{EU} †	HR _{UD} *									
	0.8	0.9	1.1	1.2	1.3	1.5	1.8	2	2.5	3
1.2	1.96 (1.15 to 3.33)	1.91 (1.12 to 3.26)	1.85 (1.08 to 3.15)	1.83 (1.07 to 3.11)	1.81 (1.06 to 3.08)	1.78 (1.04 to 3.02)	1.74 (1.02 to 2.96)	1.72 (1.01 to 2.93)	1.69 (0.99 to 2.88)	1.67 (0.98 to 2.84)
1.3	1.99 (1.16 to 3.38)	1.93 (1.13 to 3.28)	1.84 (1.08 to 3.13)	1.81 (1.06 to 3.08)	1.78 (1.04 to 3.03)	1.74 (1.02 to 2.95)	1.69 (0.99 to 2.87)	1.66 (0.97 to 2.83)	1.62 (0.95 to 2.76)	1.59 (0.93 to 2.71)
1.5	2.04 (1.19 to 3.47)	1.95 (1.14 to 3.32)	1.82 (1.07 to 3.1)	1.78 (1.04 to 3.02)	1.74 (1.02 to 2.95)	1.67 (0.98 to 2.84)	1.6 (0.94 to 2.73)	1.57 (0.92 to 2.67)	1.5 (0.88 to 2.56)	1.46 (0.86 to 2.49)
1.8	2.09 (1.22 to 3.56)	1.97 (1.15 to 3.36)	1.8 (1.06 to 3.07)	1.74 (1.02 to 2.96)	1.69 (0.99 to 2.87)	1.6 (0.94 to 2.73)	1.51 (0.88 to 2.57)	1.46 (0.86 to 2.49)	1.38 (0.81 to 2.35)	1.32 (0.77 to 2.25)
2	2.12 (1.24 to 3.6)	1.98 (1.16 to 3.38)	1.79 (1.05 to 3.05)	1.72 (1.01 to 2.93)	1.66 (0.97 to 2.83)	1.57 (0.92 to 2.67)	1.46 (0.86 to 2.49)	1.41 (0.83 to 2.4)	1.32 (0.77 to 2.24)	1.25 (0.73 to 2.13)
2.5	2.16 (1.27 to 3.68)	2.01 (1.17 to 3.41)	1.78 (1.04 to 3.03)	1.69 (0.99 to 2.88)	1.62 (0.95 to 2.76)	1.5 (0.88 to 2.56)	1.38 (0.81 to 2.35)	1.32 (0.77 to 2.24)	1.2 (0.7 to 2.05)	1.13 (0.66 to 1.92)
3	2.19 (1.28 to 3.73)	2.02 (1.18 to 3.44)	1.77 (1.03 to 3.01)	1.67 (0.98 to 2.84)	1.59 (0.93 to 2.71)	1.46 (0.86 to 2.49)	1.32 (0.77 to 2.25)	1.25 (0.73 to 2.13)	1.13 (0.66 to 1.92)	1.04 (0.61 to 1.78)
4	2.23 (1.31 to 3.8)	2.04 (1.19 to 3.47)	1.75 (1.03 to 2.98)	1.65 (0.96 to 2.8)	1.55 (0.91 to 2.65)	1.41 (0.83 to 2.4)	1.25 (0.73 to 2.13)	1.18 (0.69 to 2)	1.03 (0.61 to 1.76)	0.94 (0.55 to 1.6)
5	2.26 (1.32 to 3.84)	2.05 (1.2 to 3.48)	1.74 (1.02 to 2.97)	1.63 (0.95 to 2.77)	1.53 (0.9 to 2.61)	1.38 (0.81 to 2.35)	1.21 (0.71 to 2.06)	1.13 (0.66 to 1.92)	0.98 (0.57 to 1.66)	0.88 (0.51 to 1.49)
6	2.27 (1.33 to 3.87)	2.05 (1.2 to 3.5)	1.74 (1.02 to 2.96)	1.62 (0.95 to 2.76)	1.52 (0.89 to 2.58)	1.36 (0.79 to 2.31)	1.18 (0.69 to 2.01)	1.1 (0.64 to 1.87)	0.94 (0.55 to 1.6)	0.84 (0.49 to 1.42)
8	2.29 (1.34 to 3.9)	2.06 (1.21 to 3.51)	1.73 (1.01 to 2.95)	1.61 (0.94 to 2.73)	1.5 (0.88 to 2.55)	1.33 (0.78 to 2.27)	1.15 (0.67 to 1.96)	1.06 (0.62 to 1.8)	0.89 (0.52 to 1.52)	0.78 (0.46 to 1.33)
10	2.3 (1.35 to 3.92)	2.07 (1.21 to 3.52)	1.73 (1.01 to 2.94)	1.6 (0.94 to 2.72)	1.49 (0.87 to 2.54)	1.32 (0.77 to 2.24)	1.13 (0.66 to 1.92)	1.03 (0.61 to 1.76)	0.86 (0.51 to 1.47)	0.75 (0.44 to 1.28)

Abbreviations: HR, hazard ratio; OR, odds ratio.

*The strength of association (HR) of the unmeasured confounder, *U* (ie, localized v metastatic disease) on the outcome, *O* (ie, developing Alzheimer's disease).†The strength of association relating the exposure, *E* (ie, androgen deprivation therapy use) and the unmeasured confounder, *U* (ie, localized v metastatic disease).

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