Letter to the Editor

Environmental factors influencing the link between APOE ε4 and Alzheimer's disease (AD) risk

While APOE ε4 allele is considered a genetic risk factor for Alzheimer's disease (AD), no relation existed between APOE ε4 and AD in the Yoruba in Nigeria among cohorts included in early prevalence waves. The authors' explanation that other disease susceptibilities may provoke earlier mortality is inconsistent with the Yoruba having a lower incidence of disease risk factors. Cohort enrichment in 2001 has altered the authors' conclusions; Yorba participants homozygous, and not heterozygous, for the ε4 allele had significantly increased risk for AD (HR = 2.95, p = 0.0002) (Hendrie *et al.*, 2014). This is a critical revelation, yet it is not clear why such a temporal relationship exists between risk genotypes and AD among the Yoruba. This letter proposes an explanation.

Economists have shown that the use of anthropogenic nitrogen fertilizers in agriculture drives structural economic changes and elevates non-agricultural labor productivity growth. The USA and Nigeria show major differences in the share of total nitrogen used that is synthetically derived, with increases in total nitrogen adoption and application in Nigeria accompanying crop yield gains since the 1980s (Lassaletta *et al.*, 2014). The costs of such agricultural innovation remain and include environmental contamination. Nitrous oxide (N_2O) is a modern health medicine, valued for its role as an inhalational anesthetic adjuvant/analgesic, though the compound also exists as a pervasive air pollutant, derived primarily from anthropogenic nitrogen use in agriculture.

Given that both population-based and molecular studies indicate that general anesthesia exposures, including N_2O, may increase caspase-3 activation and thereby elevate AD risk, we tested whether lagged county anthropogenic nitrogen is linked to age-adjusted AD mortality. County-level anthropogenic nitrogen use was determined by the United States Geological Survey (U.S.G.S.) (Gronberg and Spahr, 2012). County age-adjusted AD mortality rate was derived from the Centers for Disease Control and Prevention (CDC) (G30) (CDC, 2018). A two-way fixed effects regression analysis indicates that a ten-year lag logged measure of anthropogenic nitrogen among only counties >75 percentile in anthropogenic nitrogen use

and controlling for non-farm use is significantly positively associated with the county age-adjusted AD mortality rate per 100,000 persons ($B = 3.60$, S.E. = 1.52, p-value <0.05, $n = 377$ counties, $T = 17$ years, $N = 3{,}270$). Other criteria pollutants from the Environmental Protection Agency (EPA) showed no association with AD mortality rate (*data not shown*). These population-based data indicate that lagged county anthropogenic nitrogen used in agriculture (as valid N_2O proxy) may be related to county age-adjusted AD mortality.

Postoperative cognitive decline among elderly exposed to inhalational, compared to intravenous, anesthetics was significantly higher, with a greater proportion of the former group showing reduced MMSE scores (<25). Interestingly, the decline was strongly associated with APOE ε4 (Cai *et al.*, 2012). Moreover, total lipoproteins from APOE ε4/4 sera appear to be less effective than total lipoproteins from other APOEε variants in suppressing caspase 3/7 activity, a marker of apoptosis (DeKroon *et al.*, 2003). Given that N_2O induces caspase-3 activation (Zhen *et al.*, 2009), it can be speculated that bearing the APOE ε4 variant makes one less able to counter the effects of N_2O (i.e. N_2O-induced caspase activation and nicotinic acetylcholine receptor dysregulation, as proposed; Fluegge, 2018). With evidence that the APOE ε4 allele occurs more frequently in some sub-Saharan populations and yet only temporally contributes to dementia burden in developing economies, this suggests a contextual specificity of the allele's dominant role in AD pathology, representing a new gene–environment interaction. We suggest that unmeasured N_2O emissions, predominantly derived from anthropogenic nitrogen use in agriculture, can be considered as a possible risk factor for dementia pathogenesis, especially APOE ε4 related AD incidence.

Conflict of interest

None.

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