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LETTER TO THE EDITOR

Rethinking Alzheimer's disease susceptibility and heterogeneity. Comment on Miller et al.

Dear Editors,

We read with great interest the article by Miller and colleagues, "Neurodevelopment and neural environment inform Alzheimer's disease age at onset and phenotype."[1] By pioneering a life-spanning integrative framework, Miller and colleagues offer unprecedented evidence and novel perspectives for addressing critical unresolved questions regarding the factors that shape the clinical manifestations of neurodegenerative diseases.

Neurodegenerative diseases are characterized by substantial heterogeneity in both clinical presentation and age at onset.[2] Even within the same pathological entity, individuals may differ in symptom profile, disease trajectory, and timing of clinical manifestation.[3] Despite extensive efforts to identify genetic, biological, and environmental risk factors, it remains unclear why some individuals develop focal, non-amnestic syndromes at a relatively young age, whereas others present later in life with more typical amnestic phenotypes.[4] One compelling hypothesis is that disease expression reflects differences in individual susceptibility, shaped by a complex interplay between neurodevelopmental factors, lifetime environmental exposures, neuropathologic burden, and genetic background.[5,6] In this context, by analyzing data from more than 10,000 clinically characterized individuals across multiple independent cohorts, and by integrating developmental history, health-related factors, and age-at-onset modeling, Miller et al. identified neurodevelopmental (non–right-handedness, learning disabilities) and neural–environmental (seizure, autoimmune disease) factors as enriched in early-onset and non-amnestic presentations of Alzheimer's disease (AD). This interpretative framework offers a novel methodological approach that goes beyond traditional risk paradigms and allows for a more nuanced description of disease susceptibility and phenotypic variability across AD subtypes. In particular, the distinction between neurodevelopmental, neural environmental, and vascular factors, and the way each domain relates to age at onset and clinical presentation, represents one of the most compelling aspects of this work. A key strength of the study is its ability to link well-established clinical observations, such as the higher prevalence of focal, non-amnestic presentations in early-onset AD, to a biologically plausible model. The findings show that neurodevelopmental and neural environmental factors become progressively more relevant as age at onset decreases, whereas vascular factors exert a stronger influence later in life. This difference in age-related patterns suggests that early-onset and non-amnestic forms of AD may be not primarily driven by the traditional vascular risk factors associated with aging, but rather by brain vulnerabilities rooted in development and by neural environmental influences acting across the lifespan. This is particularly compelling, as it supports the idea of a lifespan model in which patterns of brain organization established during early development continue to modulate disease vulnerability decades later.

Equally important is the proposal to move beyond the rigid early-onset AD/late-onset AD (EOAD/LOAD) dichotomy and to adopt data-driven age-at-onset epochs (<70, 70–85, >85 years). This choice reflects a clear commitment to empirical evidence and supports a more flexible and biologically informed classification system, one that can adapt to generational changes in risk factors such as vascular burden and access to early-life education. The proposed framework also appears particularly well-suited for extension in future studies involving populations with different demographic, educational, and health characteristics.

Beyond these results, this study offers important avenues for further discussion. As the authors aptly note, vascular risk profiles, developmental conditions, and environmental exposures are neither static nor equally distributed, but vary across time and contexts. In this light, it would be particularly informative to examine how the relative contributions of vascular, neurodevelopmental, and neural environmental factors differ across populations shaped by distinct sociocultural, geographical, and ethnic backgrounds, thereby clarifying population-level variability in disease susceptibility.[7] Given the growing attention to cross-population differences in cognitive reserve and inflammatory or vascular profiles, such extensions could further strengthen the translational relevance of the proposed framework.[8,9] Furthermore, the work by Miller et al. encourages future prospective studies to consider and investigate not only the presence of specific risk factors, but also how changes in exposure to these factors across the lifespan interact to influence AD risk and phenotype. Such considerations could substantially contribute to a more dynamic and comprehensive understanding of disease susceptibility and inform interventions targeting neurodevelopmental conditions, vascular risk factors, or social determinants to potentially reduce the risk of neurodegenerative diseases.

Overall, the authors have developed an elegant model that invites further testing and refinement, and that is likely to have a lasting impact on how AD risk and clinical presentation are conceptualized. Hence, this study not only offers a convincing reinterpretation of AD heterogeneity, but also provides a flexible conceptual structure upon which future population-based, biomarker-driven, comparative and longitudinal studies, as well as personalized diagnostic and therapeutic approaches, can be built.

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