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## The Cognitive Costs of Social Isolation

**Author(s):**

Lawrence Whalley, MD<sup>1</sup>

**Corresponding Author:**

Lawrence Whalley  
l.j.whalley@abdn.ac.uk

**Affiliation Information for All Authors:** 1. University of Aberdeen, Institute of Applied Health Sciences

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Advances in molecular genetics and neuroimaging now support novel integrative studies of complex behavioral traits and brain disease.<sup>1</sup> These phenomena connect multiple etiologies with common clinical endpoints of which Alzheimer Disease (AD) is probably best known. Twin studies reliably estimate the impact of the environment on AD at about 20%<sup>2</sup> but how to disentangle genetic and environmental factors in AD remains one of the great challenges in clinical neuroscience. The task requires understanding a complex matrix of data that comprises the myriad physical manifestations of neurodegenerative diseases arising in a multidimensional research space and occurring at multiple possible levels of enquiry that includes neurogenetics, neuroimaging and covers neurodevelopment and aging, childhood adversities, occupation, physical and mental health and

more. The potential reward is great: identification of neural pathways underpinning harmful effects and novel types of intervention to prevent or delay AD. In this issue of *Neurology*, Shen et al<sup>3</sup> used UK Biobank data to make a unique contribution to this problem and to show how, following a complex integrative analysis of epidemiological, neuroimaging and molecular genetic data, social isolation is linked to incident dementia. They added strong evidence of plausible pathways by showing an association between social isolation and reduced grey matter (GM) volumes and under-expressed genes already linked to AD.

Loneliness is an involuntary, unpleasant feeling state that differs from social isolation. The dull ache of loneliness corresponds to a discrepancy between a desired optimum and the reality of a perceived level of social isolation. Loneliness is distinct from the choice of solitude with uninterest in social activities. From an evolutionary perspective, loneliness alerts an individual to their need for social engagement with benefits for survival and reproductive success<sup>4</sup> that has a strong genetic underpinning.<sup>5</sup> Current high rates of solitary living and reported loneliness bring about much misery and suffering with strong links to increased morbidity and mortality<sup>6</sup> and are important but neglected public health problems. Hitherto, the ill-effects of social isolation were explained by the harm caused by the distress of loneliness to critical brain structures. Shen et al<sup>3</sup> improve on this: they distinguish the effects of social isolation from loneliness and show it is social isolation acting alone and not loneliness that increases the incidence of dementia. By itself, this is a useful conclusion, consolidating earlier work, and translates easily into community actions to address health concerns of old people living socially isolated lives. But Shen et al<sup>3</sup> go further and explore this association in ways anticipated by Siebner et al<sup>1</sup>. They show that social isolation can be linked to lower than expected GM volumes in brain structures already implicated in the pathogenesis of AD signs and symptoms. Their analytical model was then extended to show under-expression of AD-related genes in participants with identified GM reductions.

The success of this approach of Shen et al<sup>3</sup> to the complex problem of gene-environment interaction in AD has important implications for research in many neurological diseases. The goal of some clinical research in neurology is to show how best to use genetically informed brain imaging data to understand the pathogenesis of signs and symptoms in neurological diseases. This understanding, it is argued, will pinpoint where treatment advances will most likely be made and underpin the future directions of many major research programs. The prevention of age-related neurodegeneration lies at the heart of much clinical research in AD. Older people living socially isolated lives are more likely to be lonely, but loneliness alone is insufficient to increase their dementia risk. The determinants of social isolation in late life are well-known and interventions to reduce isolation are widely implemented in many Western societies. Personal characteristics that include poor health/mobility, poverty and some personality traits are suggested but community structures (for example, high crime areas) are also important.<sup>7</sup> Shen et al<sup>3</sup> set new tasks for progress in dementia prevention. The first is to show where social isolation appears as a primary agent leading to dementia and is not a consequence of cognitive impairment. What follows becomes an intellectual challenge to reveal the substructure of social isolation and to identify those elements most relevant to dementia risk. Emotional components in light of the Shen et al study<sup>3</sup> appear less important than supposed. The problem might be resolved using psychometric methods to uncover latent factors modulating cognitive impairments seen more often among the socially isolated and show their relevance to dementia risk. An alternate approach to the problem of “how and why social isolation is risky for health”<sup>8</sup> might address the quality of fieldwork in future studies. For example, structural anthropology has developed methods that rely less on self-reports of social interaction and provide, for example, a better understanding of the role of language within cultural institutions and kinships. Such an approach could prove critical to understanding why social isolation is so harmful to humankind, sometimes disastrously so, to our fundamental cognitive processes. The absence of supportive social attachments and a paucity in the use of language by the socially isolated may together be sufficient to increase dementia risk. The close observation of different cultural groups

will be necessary to establish the generalizability of the harm to health caused by social isolation. Fieldwork that improves on the methods used in the UK Biobank may prove to be productive. In parallel, the concept of computational psychiatry<sup>9</sup> suggests how misinterpretations of reality could arise in social isolation. Conversely, social interactions may protect an older adult and help avoid acceptance of computational errors of judgement and the accumulation of those errors that underpin the psychopathology of the dementias.

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