This is an Accepted Manuscript for *International Psychogeriatrics* as part of the
Cambridge Coronavirus Collection.
DOI: 10.1017/S1041610223000339

Applying the construct of social determinants of health to imaging-based brain changes

David C. Steffens, M.D., M.H.S.

Professor and Chair, Department of Psychiatry, University of Connecticut School of Medicine
Farmington, Connecticut, U.S.A.

The past decade has seen an explosion of research on social determinants of health (SDoH), defined by the World Health Organization as the non-medical factors that influence health outcomes and include the conditions in which people are born, grow up, and live and the wider set of forces and systems that shape the conditions of daily life (Jeste, 2022). Factors such as housing, employment, family income, education, food insecurity, rural versus urban setting, neighborhood characteristics, childhood adversity, racial discrimination, and access to health services have been studied to their contributions to occurrence of health conditions and to a variety of health outcomes. While considerable research on SDoH has focused on non-geriatric populations, recent research has examined how social factors affect health outcomes of older adults. For example, ageism as a social determinant has become a focus of research, with one study finding that ageism was associated with a marked increase in prevalence and cost (estimated at $63 billion) of the eight most expensive diseases in the United States (Levy *et al*., 2020).

A recent issue of *International Psychogeriatrics* focused on ageism and other non-medical SDoH. In a study of 1,570 participants, Ayalon and Cohn-Schwartz (2022) examined self-perceptions of aging (SPA) and age-based discrimination among three groups: Veteran Israelis, Israeli Arabs and immigrants from the Former Soviet Union. Among Israeli Arabs, being older was related to better SPA, whereas among the immigrants being older was related to worse SPA. As immigrants became older, they were more likely to report ageist experiences. Israeli Arabs reported higher levels of ageist experiences. In another study focused on awareness of positive and negative age-related changes, Sabatini *et al*. (2022) administered questionnaires to 609 United Kingdom participants and reported responses that were expected, (e.g., experiencing negative changes and attitudes toward aging) and unexpected (e.g., engagement in purposeful activities or in activities that distract from age-related thoughts). Other articles in the issue focused on governmental policies during the COVID pandemic in Uganda and effects on access to food and adequate nutrition (Giebel *et al*., 2022), and the importance of improving problem-solving skills and providing support to family caregivers of people with dementia in Canada (2022).

One extension of research on SDoH in the elderly to consider is in the area of healthy versus unhealthy brain aging. A recent study focused on developing the construct of social health and connected it to brain health (Vern00ij-Dassen *et al*., 2022). Drawing from theoretical, conceptual and epidemiological research, the authors defined social health as wellbeing that relies on capacities both of the individual and the social environment. Thus, both individual (e.g., social participation) and social (e.g., social network) environmental elements (e.g., social network) are key for preserving social health. The authors suggested that maintenance of social health taps into cognitive reserve, which can then slow cognitive impairment or maintain cognitive functioning. In addition, social health factors such as lower loneliness and volunteering, along with higher education and greater physical activity, have been associated with higher optimism and lower pessimism, while low social support was associated with higher pessimism (Craig *et al*., 2023). In turn, higher optimism and lower pessimism support healthy ageing.

Definitions of healthy brain aging often rely on neuroimaging findings. A review of 2,246 articles related to magnetic resonance imaging (MRI) of healthy brain aging examined expected MRI-based brain changes with normal aging (MacDonald and Pike, 2021). They reported that the brain loses approximately 7% of its volume between the 20s and 60s and continues to decline thereafter. Brain volume is easy to obtain from MRI analysis and is important because it correlates with cognitive performance. As brain volume decreases with age, there is a concomitant increase in ventricular size and cerebrospinal fluid volume. Similar volumetric changes with aging affect the cerebral cortices and white matter. Interestingly, subcortical gray matter volume in totality appears to shrink at a slower rate than cortical gray matter. The authors also reviewed studies examining white matter hyperintensities (WMH) associated with aging, noting that while total volume of WMH increases with age, WMH in normal aging are generally confined to the periventricular region. They conclude that all of these measures can be combined to estimate brain age and compare with chronological age to get a sense of healthy versus “premature” aging. Similarly, Blinkouskaya *et al*. (2022) reviewed the literature on structural studies of brain aging (10). They identified and quantified global brain volume changes as well as changes in volumes of gray matter, cortex, white matter, ventricles, and WMH.

Functional imaging modalities have also been used to examine healthy brain aging including both functional MRI and positron emission tomography (PET) studies. For example, fMRI has been employed to show resting-state functional connectivity (rsFC) differences between cognitive normal older adults and patients with mild cognitive impairment (MCI) and Alzheimer’s disease (Behfar *et al*., 2020). The investigators found increased rsFC among healthy aging and MCI in cognition-related brain regions of the middle frontal gyrus, precentral gyrus and superior parietal lobe. This increase in rsFC occurred despite local atrophy among these groups, indicating a possible compensatory mechanism in MCI and healthy aging. Thus, healthy brain aging may be associated with a preserved ability to compensate for brain aging with functionally adaptive changes to brain activity. In a PET study, the investigators assessed healthy brain aging using [^{18}F]FDG as a measure of cerebral glucose consumption and [^{11}C]UCB-J PET as an indicator of synaptic density (Andersen *et al*., 2022). They confirmed earlier reports of synaptic density stability with normal aging.

Various imaging modalities have been used to characterize unhealthy or pathological brain aging. As noted above, some imaging studies define pathological aging in relation to brain changes beyond what is expected in the normal aging process (MacDonald and Pike, 2021). Other studies highlight the constructs of “cognitive reserve” and “brain reserve” in both normal aging and in conditions associated with cognitive decline (Stern *et al*., 2020). Cognitive reserve (CR) refers to the breadth of memory and thinking abilities, including flexibility and adaptability of attentional processes (conscious and subconscious) commonly subserving daily function (i.e., work, play, and leisure). Brain reserve (BR) refers to physical and neuroanatomical structures of the brain. In terms of measurement, CR is challenging to measure directly, but rather relies on methods that incorporate SDoH, e.g., education, intelligence, occupational complexity, leisure and physical activity. On the other hand, measurement of BR relies on imaging-based measures

https://doi.org/10.1017/S1041610223000339 Published online by Cambridge University Press

such as gray matter volume, cortical surface area, cortical thickness, PET measures of synaptic integrity, and white matter microstructural properties.

The literature on social factors and unhealthy brain aging has mainly focused on cognitive decline as a proxy for pathological brain aging. For example, neighborhood environmental variation has been linked to dementia risk, and may be related to extent of physical inactivity, depression, obesity, hypertension, diabetes, and social isolation (Finlay *et al*., 2022). Geographic areas with limited walkability and the presence of polluting sites had a significant negative association with cognitive function after controlling for individual and neighborhood factors (Yu *et al*., 2023). In the United States, neighborhood characteristics may explain some racial differences in cognitive decline and dementia risk. Compared to Black participants living in higher segregation-lower neighborhood socioeconomic status (NSES) areas, Black participants living in lower segregation-lower NSES areas or higher segregation-higher NSES areas experienced slower decline in episodic memory over time (Meyer *et al*., 2023).

Recent literature has also focused on cognitive consequences of presence of personality factors, especially neuroticism, the tendency to experience negative emotions, such as anger, anxiety, and depressed mood. The link between neuroticism and cognitive decline is consistent with the notion that not only is stress bad for the brain, but that it is especially harmful in older individuals with neuroticism, whose brains may be poorly equipped to deal with stress. In a large community-based longitudinal study, compared with older adults scoring in the lowest quartile of neuroticism, those scoring in the highest quartile had a three-fold increased risk of incident Alzheimer's disease (Terraciano *et al*., 2014). A meta-analysis found that neuroticism increased risk of both dementia and mild cognitive impairment (Low *et al*., 2013). Among depressed older adults, one-year neuroticism change with depression treatment was inversely associated with three-year change in cognitive performance such that, compared with individuals with decreased neuroticism scores, those with lack of improvement in neuroticism scores experienced greater cognitive decline (Steffens *et al*., 2022). Improvement in stress may have cognitive benefits. Dickinson *et al*. (2021) found the among older adults with and without depression, a decline in the total number of stressors was associated with a subsequent improvement on a global measure of cognition.

With this background in social factors and cognitive aging in mind, we can turn to a nascent but growing literature on SDoH and brain aging. In this issue of *International Psychogeriatrics*, Rodriguez *et al*. (2023) extend the research on social determinants of health-related conditions to examine social determinants of white matter disease, a vascular pathology associated with unhealthy brain aging. Specifically, the authors sought to better understand the observation that socioeconomically deprived groups experience a higher burden of white-matter hyperintensities (WMH), a brain imaging marker of vascular disease, compared with other socioeconomic groups. They focused on two key drivers of socioeconomic status: education and income. Using data from the population-based Adult Study of the Leipzig Research Centre for Civilization Diseases (LIFE) based in Leipzig, Germany, the investigators identified 1,185 dementia-free individuals aged 40 to 80 enrolled in a population registry. The study relied on both interview data and neuroimaging data. Through standard interviews, they obtained clinical and social data, specifically information on a variety of physical health conditions as well as reported education and income. For imaging, they employed a 3T magnetic resonance imaging (MRI) scanner, using sequences to obtain WMH data, which were then examined to determine severity scores using the Fazekas 0-3 scoring system. While the authors initially found an association between income and WMH in unadjusted analyses, subsequent analyses adjusted for age, gender, arterial hypertension, heart disease, and apolipoprotein E (*APOE)* e4 allele status showed no association between income and WMH. With statistical correction, education was not associated with either nor with WMH. Subsequent analyses revealed significant associations between higher distress and more WMH as well as between obesity and greater deep WMH. The authors concluded that differences in health-related risk factors might explain previously observed differences in WMH in socioeconomically deprived groups.

Other studies have examined stress as a SDoH and cerebrovascular disease. One such factor is stress associated with socioeconomic circumstances. For example, early life socioeconomic circumstance (as measured by paternal occupation) was associated with burden of WMH in late life (Murray *et al*., 2014). Stress related to trauma and to racial discrimination have also been examined as cerebrovascular risk factors. Everyday racial discrimination was associated with faster accumulation of WMH over time among older Black adults (Zahodne *et al*., 2023). A trauma history, particularly sexual assault, was associated with greater WMH volume controlling for covariates, including depressive and post-traumatic symptoms. Sexual

https://doi.org/10.1017/S1041610223000339 Published online by Cambridge University Press

assault may place women at risk for poor brain health (Thurston *et al*., 20232). Research has also focused on examining links between accumulated recent stressors and cerebrovascular disease. In one study, increased stressor exposure was associated with greater increases in volume of WMH, while reductions in stressor exposure were associated with less increase in hyperintensity volume (Johnson *et al*., 2017). In a study quantifying stress using the Perceived Stress Scale (PSS), the investigators found that while increases in PSS score were associated with lower total brain volume and with increased odds of infarction, PSS scores were unrelated to WMH volume (Aggarwal *et al*., 2014).

Investigators have sought to elucidate putative mechanism linking stress and WMH. One group used laboratory-based mental stressors to determine degree of stress-induced blood pressure reactivity. After adjustment for age, gender, resting clinic blood pressure, and fasting glucose levels, higher systolic blood pressure reactivity was associated with an increased number of small silent infarcts and greater severity ratings of periventricular and deep WMH. Findings were similar for diastolic blood pressure reactivity (Walstein *et al*., 2004). This study provides a mechanistic framework for understanding links between stress and vascular-related structural brain changes.

In sum, the paper by Jacob *et al*. highlights a burgeoning area of research that focuses on social factors and biological measures of brain aging. As in this study, any investigation on this topic will need to incorporate the complex mix of biological, psychological and social factors inherent with geriatric research. Medical conditions, distress, educational background and social circumstances were shown to be salient in determining WMH volumes, and it is likely that these and other seemingly unconnected, but actually quite interrelated, factors will inform future studies of healthy and unhealthy brain aging.

https://doi.org/10.1017/S1041610223000339 Published online by Cambridge University Press

References

Aggarwal, N.T., *et al*. (2014). Perceived stress is associated with subclinical cerebrovascular disease in older adults. *American Journal of Geriatric Psychiatry*, 22, 53-62.

Andersen, K.B., *et al*. (2022). Healthy brain aging assessed with [(18)F]FDG and [(11)C]UCB-J PET. *Nuclear Medicine and Biology*, 112-113, 52-58.

Ayalon, L. and Cohn-Schwartz, E. (2022). Ageism from a cross-cultural perspective: results from a national survey of Israelis over the age of 50. *International Psychogeriatrics*, 34, 779-787.

Behfar, Q., *et al*. (2020). Graph theory analysis reveals resting-state compensatory mechanisms in healthy aging and prodromal Alzheimer's disease. *Frontiers in Aging Neuroscience*, 12, 576627.

Blinkouskaya, Y., Cacoilo, A., Gollamudi, T., Jalalian, S. and Weickenmeier, J. (2021). Brain aging mechanisms with mechanical manifestations. *Mechanisms of Ageing and Development*, 200, 111575.

Craig, H. *et al*. (2023). Socioeconomic, behavioural, and social health correlates of optimism and pessimism in older men and women: a cross-sectional study. *International Journal of Environmental Research and Public Health*, 20, 3529.

Dickinson, W.J., Potter, G.G., Hybels, C.F., McQuoid D.R. and Steffens, D.C. (2011). Change in stress and social support as predictors of cognitive decline in older adults with and without depression. *International Journal of Geriatric Psychiatry*, 26, 1267-1274.

Finlay, J., Esposito, M., Langa, K.M., Judd, S. and Clarke, P. (2022). Cognability: an ecological theory of neighborhoods and cognitive aging. *Social Science & Medicine*, 309, 115220.

Giebel, C., Ivan, B., Burger, P. and Ddumba, I. (2022). Impact of COVID-19 public health restrictions on older people in Uganda: "hunger is really one of those problems brought by this COVID". *International Psychogeriatrics*, 34, 805-812.

Jeste, D.V. (2022). Non-medical social determinants of health in older adults. *International Psychogeriatrics*, 34, 755-756.

Johnson, A.D., McQuoid, D.R., Steffens, D.C., Payne, M.E., Beyer, J.L. and Taylor, W.D. (2017). Effects of stressful life events on cerebral white matter hyperintensity progression. *International Journal of Geriatric Psychiatry*, 32, e10-e17.

Levy, B.R., Slade, M.D., Chang, E.S., Kannoth, S. and Wang, S.Y. (2020). Ageism amplifies cost and prevalence of health conditions. *Gerontologist*, 60, 174-181.

Low, L.F., Harrison, F. and Lackersteen, S.M. (2013). Does personality affect risk for dementia? A systematic review and meta-analysis. *American Journal of Geriatric Psychiatry*, 21, 713-728.

MacDonald, M.E. and Pike, G.B. (2021). MRI of healthy brain aging: a review. *NMR in Biomedicine*, 34, e4564.

Meyer O.L., *et al*. (2023). Neighborhood socioeconomic status and segregation linked to cognitive decline. *Alzheimers & Dementia (Amsterdam, Netherlands)*, 15, e12401.

Murray, A.D., McNeil, C.J., Salarirad, S., Whalley, L.J., Staff, R.T. (2014). Early life socioeconomic circumstance and late life brain hyperintensities--a population based cohort study. *PLoS One*, 9, e88969.

Rodriguez, F., et al. (in press). Differences in white matter hyperintensities in socioeconomically deprived groups: results of the population-based LIFE Adult Study. *International Psychogeriatrics*.

Sabatini, S. *et al*. (2022). Exploring awareness of age-related changes among over 50s in the UK: findings from the PROTECT study. *International Psychogeriatrics*, 34, 789-803.

Sadavoy, J., Sajedinejad S. and Chiu, M. (2022). Evaluation of the Reitman Centre CARERS program for supporting dementia family caregivers: a pre-post intervention study. *International Psychogeriatrics*, 34, 827-838.

Steffens, D.C., Manning, K.J., Wu, R. and Grady, J.J. (2022). Association of 1-year change in neuroticism and 3-year change in cognitive performance among older depressed adults. *International Psychogeriatrics*, 34, 645-650.

Stern, Y., *et al*. (2020). Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimers & Dementia*, 16, 1305-1311.

Terracciano, A., *et al*. (2014). Personality and risk of Alzheimer's disease: new data and meta-analysis. *Alzheimers & Dementia*, 10, 179-186.

Thurston R.C., *et al*. (2022). Sexual assault and white matter hyperintensities among midlife women. *Brain Imaging and Behavior*, 16, 773-780.

Vernooij-Dassen M, *et al*. (2022). Recognition of social health: A conceptual framework in the context of dementia research. *Frontiers in Psychiatry*, 13, 1052009.

Waldstein, S.R., *et al*. (2004). Stress-induced blood pressure reactivity and silent cerebrovascular disease. *Stroke*, 35, 1294-1298.

Yu, W., Esposito, M., Li, M., Clarke, P., Judd, S. and Finlay, J. (2023). Neighborhood 'Disamenities': local barriers and cognitive function among Black and white aging adults. *BMC Public Health*, 23, 197.

Zahodne, L.B. *et al*. (2023). Longitudinal associations between racial discrimination and hippocampal and white matter hyperintensity volumes among older Black adults. *Social Science & Medicine*, 316, 114789.