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HUMAN DEVELOPMENT, BIRTH TO DEATH

Moffitt & Caspi
Genes Environment Health Behavior

Concept Paper Form

Provisional Paper Title: Neighborhood Aggregation of Dementia Diagnoses and Midlife Dementia Risk
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Today's Date: 3/6/2023

Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

50 million individuals worldwide are currently living with Alzheimer's disease and related dementias (ADRD), a number expected to triple within the next thirty years as the global population of older adults grows.[1] With no existing interventions that can effectively halt or delay dementing illness progression,[2] primary prevention of disease has become a critical global goal.

After decades of evidence have accrued to indicate that individual behavior choices can lower disease risk (e.g., drinking less alcohol, eating a Mediterranean diet, pursuing daily physical activity),[3] attention has now shifted to examining the spaces in which individual behavior choices occur.[4–7] The neighborhoods in which older adults live greatly constrain the social, recreational, and dietary choices that they may make on a daily basis, with potential implications for the health of their aging brains.[4–7] Neighborhoods also determine the physical and chemical nervous-system stressors that these adults may be regularly exposed to, including air and water pollutants, noise, temperature extremes, and potential natural and human-caused disasters.[4–7]

Accordingly, dementia diagnoses and preclinical dementia antecedents (e.g., cognitive decline) have been found to aggregate in neighborhoods with disadvantageous physical, social and economic characteristics over and above the personal risk-demographics of individuals living in those neighborhoods (i.e., age, sex, social class position).[8–11] This suggests that neighborhood-based interventions could offer a new avenue for primary dementia prevention – an avenue that could leverage existing resources outside the healthcare sector, influence whole communities at once, and operate without necessarily requiring individual behavior change. For example, existing interventions targeting individuals at-risk for disease due to neighborhood conditions, such as voucher programs facilitating neighborhood mobility, have shown surprising efficacy for

reducing intractable chronic disease outcomes, such as obesity and diabetes.[8] Interventions and natural experiments targeting whole neighborhoods, meanwhile, such as vacant-lot greening initiatives and redevelopment programs, have been found to influence wide segments of the population simultaneously, with moderate to large effects recorded in RCTs in domains as diverse as criminal behavior,[9] diet,[10] and mental health.[11]

However, many questions remain to be answered about the nature of neighborhood-based risk for dementia. A primary one is when in the lifespan such risk emerges. The lion's share of the evidence about neighborhood-ADRD associations arrives from studies of older adults who have either received diagnoses, donated their brains for autopsy study, or been observed longitudinally over the last years of their life.[8–11] This limits causal inference and the identification of intervention pathways for three reasons. First, it does not rule out reverse causation, whereby individuals in the long preclinical phase of ADRDs migrate to less desirable neighborhoods as a consequence of their illness (e.g., cognitive decline forces early outflow from the labor market). Second, it does not rule out the accumulation in disadvantaged neighborhoods of individuals at-risk for ADRDs due to pre-existing shared risk factors (e.g., low educational attainment earlier in life). Third, it does not indicate when neighborhood-based interventions (e.g., mobility vouchers) would need to be delivered to be effective.

The proposed study will address existing gaps in the literature on neighborhoods and ADRD risk by turning to the New Zealand population and a deeply phenotyped population-representative New Zealand birth cohort followed to midlife (the Dunedin Study) to ask: 1) if dementia diagnoses follow neighborhood socioeconomic gradients in the country of New Zealand and, if so, 2) whether this geographic patterning of dementia is preceded by a neighborhood socioeconomic gradient in dementia risk factors and antecedents by midlife, decades before ADRD endpoints emerge.

Data analysis methods:

This study will operate at two levels within the New Zealand population.

First, using the New Zealand Integrated Data Infrastructure's (IDI) collection of deidentified whole-of-population administration information on dementia diagnoses in New Zealand we will ask whether dementia diagnoses aggregate along neighborhood socioeconomic gradients. Analyses will utilize the NZ Index of Deprivation (NZDep), an area-level socioeconomic ranking of neighborhoods generated from NZ census records, which is integrated into the IDI. Analyses will produce descriptive statistics on neighborhoods and dementia incidence in New Zealand and calculate associations of disadvantaged neighborhood residence with risk of a dementia diagnosis across a 20-year potential observation period (1999 to 2019). Analyses will be restricted to the individuals in the IDI dataset with valid neighborhood information. NZDep information from individuals' first address will be the primary independent variable to limit the potential for reverse causation, although a mean neighborhood deprivation score will also be investigated to capture residence changes across the study period (up to 20 residences) and the potential influence of cumulative exposure to disadvantageous neighborhoods. Analyses will follow the general methods of Richmond-Rakerd et al.[12]

Second, using the longitudinal Dunedin Study's high-resolution information on dementia risk factors and antecedents utilized by Reuben et al.,[3] we will ask whether midlife dementia risk factors (as captured by the top 4 existing ADRD risk indexes and the Dunedin Study's comprehensive risk benchmark, the DunedinARB) and preclinical antecedents (MRI-assessed brain structure and objective and subjective cognitive function) follow neighborhood socioeconomic gradients many years before dementia diagnoses typically emerge (e.g., after age 65). Neighborhood status will be indexed by the NZDep for the approximately 75% of Study Members living in New Zealand across the study period, and the matched Australian Index of Relative Socioeconomic Advantage and Disadvantage (IRSAD) for the 15% of Study Members living in Australia. Analyses will produce descriptive statistics on neighborhoods and dementia risks / antecedents in the Cohort and calculate continuous associations of disadvantaged neighborhood residence with ADRD risk index scores and ADRD antecedents. Neighborhood information from Study Member home address at age 45 will be the primary independent variable, although a mean neighborhood deprivation score will also be investigated to capture residence changes across the previous two decades (covering phases 26, 32, and 38) and the potential influence of cumulative exposure to disadvantageous neighborhoods. Analyses will follow the general methods of Reuben et al.[3] Additional statistical adjustments will be made to take into account Study Member individual-level social class position (i.e., occupation). If space allows, follow-up sensitivity tests may investigate potential shared childhood antecedents of both neighborhood disadvantage residence *and* ADRD risk, including poor age 3 brain health and low educational attainment earlier in life.

Variables needed at which ages:

IDI variables will be utilized on-site at the NZ Stats data use offices and are excluded from the variable request component of this concept note.

Dunedin Study variables to be used will include:

Exposure variables:

- Neighborhood socioeconomic status as indexed by the NZDep or IRSAD for the neighborhood in which Study Members were living at phase 26, 32, 38, and 45.

Age 45 outcome variables:

- Dementia Risk Indexes from Reuben et al.[3]
    - The 4 ADRD Risk indexes and comprehensive DunedinARB, including the 10 risk domains of the DunedinARB. Individual components of the DunedinARB may be requested in amendments to this concept note to conduct post-hoc sensitivity or follow-up tests.
- Dementia Antecedents from Reuben et al.[3]
    - The 6 ADRD antecedents: MRI assessed brainAGE, WMHV, hippocampal volume; full-scale IQ, IQ decline from childhood, subjective cognitive complaints.

Potential covariates:

- Sex

- Individual social class position (SES) at phase 26, 32, 38, and 45
- Educational attainment by age 38
- Poor age 3 brain health

Significance of the Study (for theory, research methods or clinical practice):
The proposed study will answer novel questions about the potential aggregation of dementia diagnoses along neighborhood socioeconomic gradients, including better characterizing the lifespan timing of these associations. Such information will expand our capacity to investigate and consider neighborhood-based interventions for ADRDs, opening a potential new avenue in disease prevention for this hard-to-treat and costly late-life disease of global importance.

References cited:

1. Alzheimer's Association. *Changing the Trajectory of Alzheimer's Disease: How a Treatment by 2025 Saves Lives and Dollars*. Alzheimer's Association; 2015. Accessed March 27, 2017. http://www.alz.org/alzheimers_disease_trajectory.asp#quickfacts

2. Mehta D, Jackson R, Paul G, Shi J, Sabbagh M. Why do trials for Alzheimer's disease drugs keep failing? A discontinued drug perspective for 2010–2015. *Expert Opin Investig Drugs*. 2017;26(6):735-739. doi:10.1080/13543784.2017.1323868

3. Reuben A, Moffitt TE, Abraham WC, et al. Improving risk indexes for Alzheimer's disease and related dementias for use in midlife. *Brain Commun*. 2022;4(5):fcac223. doi:10.1093/braincomms/fcac223

4. Chen X, Lee C, Huang H. Neighborhood built environment associated with cognition and dementia risk among older adults: A systematic literature review. *Soc Sci Med 1982*. 2022;292:114560. doi:10.1016/j.socscimed.2021.114560

5. Vassilaki M, Petersen RC, Vemuri P. Area Deprivation Index as a surrogate of resilience in aging and dementia. *Front Psychol*. 2022;13:930415. doi:10.3389/fpsyg.2022.930415

6. Zuelsdorff M, Larson JL, Hunt JFV, et al. The Area Deprivation Index: A novel tool for harmonizable risk assessment in Alzheimer's disease research. *Alzheimers Dement N Y N*. 2020;6(1):e12039. doi:10.1002/trc2.12039

7. Firouraghi N, Kiani B, Jafari HT, et al. The role of geographic information system and global positioning system in dementia care and research: a scoping review. *Int J Health Geogr*. 2022;21(1):8. doi:10.1186/s12942-022-00308-1

8. Ludwig J, Sanbonmatsu L, Gennetian L, et al. Neighborhoods, Obesity, and Diabetes — A Randomized Social Experiment. *N Engl J Med*. 2011;365(16):1509-1519. doi:10.1056/NEJMsa1103216

9. Branas CC, South E, Kondo MC, et al. Citywide cluster randomized trial to restore blighted vacant land and its effects on violence, crime, and fear. *Proc Natl Acad Sci*. 2018;115(12):2946-2951. doi:10.1073/pnas.1718503115

10. Richardson AS, Collins RL, Ghosh-Dastidar B, et al. Improvements in Neighborhood Socioeconomic Conditions May Improve Resident Diet. *Am J Epidemiol*. 2021;190(5):798-806. doi:10.1093/aje/kwaa220

11. South EC, Hohl BC, Kondo MC, MacDonald JM, Branas CC. Effect of greening vacant land on mental health of community-dwelling adults: A cluster randomized trial. *JAMA Netw Open*. 2018;1(3):e180298-e180298. doi:10.1001/jamanetworkopen.2018.0298

12. Richmond-Rakerd LS, D'Souza S, Milne BJ, Caspi A, Moffitt TE. Longitudinal Associations of Mental Disorders With Dementia: 30-Year Analysis of 1.7 Million New Zealand Citizens. *JAMA Psychiatry*. 2022;79(4):333-340. doi:10.1001/jamapsychiatry.2021.4377

Data Security Agreement

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☒	I am current on Human Subjects Training (CITI (www.citiprogram.org) or equivalent)
☒	My project is covered by the Duke ethics committee OR I have /will obtain ethical approval from my home institution.
☒	I will treat all data as "restricted" and store in a secure fashion. My computer or laptop is: a) encrypted (recommended programs are FileVault2 for Macs, and Bitlocker for Windows machines) b) password-protected c) configured to lock-out after 15 minutes of inactivity AND d) has an antivirus client installed as well as being patched regularly.
☒	I will not "sync" the data to a mobile device.
☒	In the event that my laptop with data on it is lost, stolen or hacked, I will immediately contact Moffitt or Caspi.
☒	I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper.
☒	I will not post data online or submit the data file to a journal for them to post. *Some journals are now requesting the data file as part of the manuscript submission process. Study participants have not given informed consent for unrestricted open access, so we have a managed-access process. Speak to Temi or Avshalom for strategies for achieving compliance with data-sharing policies of journals.*
☒	I will delete all data files from my computer after the project is complete. Collaborators and trainees may not take a data file away from the office. This data remains the property of the Study and cannot be used for further analyses without an approved concept paper for new analyses.
☒	I have read the Data Use Guidelines and agree to follow the instructions.

Signature: ***Aaron Reuben***