Appendix Section B(2): CONCEPT PAPER TEMPLATE

DUNEDIN MULTIDISCIPLINARY HEALTH AND DEVELOPMENT STUDY

(The Dunedin Study)

CONCEPT PAPER TEMPLATE

(July 2024)

DUNEDIN STUDY CONCEPT PAPER

Provisional Paper Title: Neighborhood Deprivation and the Pace of Aging

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(if the proposing author is a student or colleague of an original PI)

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Please describe your proposal in 2-3 pages with sufficient detail for helpful review by addressing all areas outlined below.

Objective of the study:

Elevated risk for disease and premature mortality tends to follow socioeconomic gradients at both individual and area (neighborhood) levels in countries with and without robust social safety nets.[1–4] Many proposed mechanisms putatively underly this broad trend but most fall within the "cumulative weathering" or allostatic load frameworks whereby individuals with lower socioeconomic attainment experience greater daily stress on their body systems resulting in enhanced or premature biological aging.[5,6] This physiological stress can arise from individually experienced factors such as physically demanding jobs (e.g., rotating shift work that disrupts circadian rhythms) or collectively experienced factors such as airborne chemical contaminants (e.g., fine particulate air pollution).

Recent studies have begun to leverage epigenetic signatures of systemic biological aging to test the hypothesis that low or "deprived" socioeconomic status at both individual and area levels is associated with enhanced biological aging across the lifespan and before the onset of debilitating chronic diseases. While this field of investigation remains young, studies using such epigenetic aging "clocks" have consistently reported negative socioeconomic gradients in epigenetic "age," although effect sizes have tended to vary, predictably, by the clock used (so-called first, second, or third generation clocks) and the population under study.[e.g., 7–10]

This existing early evidence is compelling and suggests that aging can be quantified early in life (i.e., before old age) and linked to factors potentially modifiable by intervention (e.g., working conditions, neighborhood conditions, etc.). As of yet, however, the implications of this evidence base are limited by several factors. First, most studies, particularly of area-level socioeconomic deprivation, have utilized small or non-representative samples – a characteristic common to early studies in a field using new methods or testing novel hypothesis. Second, nearly all studies have relied exclusively on epigenetic aging clocks. While relatively efficient as a cross-sectionally collected measure of a putatively longitudinal process, these clocks have their own limitations, including potential over-sensitivity to specific exposures (e.g., tobacco smoking), unknown biological relevance or potential for "reversal," and poorer

performance in minority populations, among other challenges.[11–13] Third, few studies have yet attempted to investigate the potential interplay of individual and area-level socioeconomic deprivation in the enhancement of biological aging, limiting our ability to identify potentially useful intervention targets at either level.

Here we propose to address these limitations in the literature via a series of matched investigations in separate population-representative cohorts in separate countries with assessed neighborhood socioeconomic deprivation exposure and distinct measures of biological aging. First, in the prospective longitudinal New Zealand-based Dunedin cohort (N = 938) we will test the association of multidecade residence in deprived neighborhoods with the pace of whole-body biological aging across adulthood assessed via direct repeated measurement of multiple organ health indicators across two decades (the Dunedin "Pace of Aging"). Second, in the multi-age Scotland-based Generation Scotland cohort (N = 16,121) we will test the association of residence in deprived neighborhoods with the pace of biological aging assessed via a whole-blood DNA methylation-based epigenetic clock trained on the Dunedin Pace of Aging (the third generation Dunedin PACE clock).[14] Third, in the United Kingdom-based prospective UK Biobank study we will test the association of residence in deprived neighborhoods with the pace of biological aging assessed via a brain-MRI-based aging biomarker trained on the Dunedin Pace of Aging (Dunedin PACNI) (N = 33,314).[15] If main effects of neighborhoods with aging are identified, pre-planned follow-up tests will then ask whether there is an interaction between individual-level socioeconomic status and neighborhood-level socioeconomic status in the prediction of pace of aging. Educational attainment will be utilized for these analyses given its role as a key indicator of socioeconomic attainment, its recently published association with the pace of aging, and its modifiability at the population level.[16,17] These tests will ask, in effect, whether neighborhoods are more weakly associated with the pace of aging among individuals with greater levels of educational attainment.

Data analysis methods[1]:

Primary tests: Ordinary least squares multivariable linear regression will test the association of neighborhood socioeconomic status ("deprivation) with biological aging in each cohort while adjusting for age and sex. Given the known influence of tobacco consumption on most biological aging biomarkers, models will be re-run with the addition of the best smoking-status indicator available in each cohort. To identify whether neighborhoods are associated with biological aging even in the absence of documented physical illness, additional sensitivity tests may add measures of physical comorbidities (e.g., diabetes and heart, kidney, or liver disease) to the models.

Follow-up tests of educational attainment: Follow-up tests in each cohort will test whether level of education modifies potential neighborhood-aging associations. First, primary tests will be re-run stratefied for education to examine the similarity of slopes across education levels. Then, in non-stratefied tests, educational level will be added to

[1] A key concern for the Dunedin Study is superficial analyses of data that simply identify differences or deficits between ethnic groups or other communities where inequities exist (e.g. persons with disabilities, Pasifika peoples, members of migrant and SOGIESC (Sexual Orientation, Gender Identify and Expression and Sexual Characteristics) communities). The cumulative effect of these types of studies is stigmatising and not of benefit. Any research that identifies differences must (a) incorporate information on the broader context (e.g. historical or political factors); (b) where possible undertake additional analyses to examine the source of the difference/s, and (c) include policy recommendations for its resolution.

the covariate adjustment as well as a neighborhood-by-education interaction term. These interaction tests will first utilize the full cohort samples available but then stratefy by age-band to accommodate different opportunities, requirements, and expectations for education by generation in those cohorts with wide age-ranges (Generation Scotland, UK Biobank). If interaction terms are found to be significant they will be probed using standard approaches, such as centering above and below the mean on the predictor variables. If space allows, other individual-level socioeconomic indicators, in particular occupational attainment, may be utilized in sensitivity tests of the individual and area-level SES interaction.

Variables needed at which ages:
For the Dunedin cohort requested variables include:

Exposure variable: Cumulative Neighborhood Disadvantage, ages 26 to 45 years (composite variable created via factor analysis for Reuben et al., 20204, Alzheimer's & Dementia)

Outcome variable: Pace of Aging, composite of ages 26 to age 45 years

Covariates

- Sex
- Educational attainment by age 45
- Occupational attainment by age 45
- Smoking status at age 45 + pack years smoked by age 45
- Physical health comorbidities (diabetes, heart, liver, and kidney disease status) by age 45

Additional variables: Though not planned for inclusion in the main study tests, DunedinPACE and DunedinPACNI are also requested to enable sensitivity testing of the neighborhood-aging association using different biomarkers of aging.

- DunedinPACE at age 45
- DunedinPACNI at age 45

Significance of the Study (for theory, research methods or clinical practice):
The hypothesis that low socioeconomic attainment (particularly at the neighborhood-level) enhances biological aging must be rigorously tested in multiple samples and countries using aging biomarkers from multiple tissues and levels of analysis. If neighborhood socioeconomic deprivation is found to predict rates of biological aging it would identify one potentially causal mechanism linking neighborhoods to disease. This in turn would suggest that intervening on neighborhood characteristics could improve health upstream of individual diseases (e.g., in the years leading up to morbidity) – something for which existing interventions (e.g., housing mobility programs) could be scaled up to address or new interventions developed (e.g., neighborhood health programs). Knowledge of the potential interplay of individual socioeconomic attainment with area-level socioeconomic attainment would, moreover, identify further potential intervention pathways (e.g., through expanded education opportunities for example).

How the paper will contribute to Māori health advancement and/or equitable health outcomes[2]

Māori residents of New Zealand are more likely to live in neighborhoods ranked as socioeconomically deprived. Evidence of neighborhood-aging associations would identify enhanced biological aging as one potential pathway to explain health disparities at the nation-level in New Zealand, potentially opening up new neighborhood-based health interventions before health disparities emerge.

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[2] Helpful information can be found here: https://www.hrc.govt.nz/sites/default/files/2020-01/NZ%20Prioritisation-Framework-FA-web_0.pdf

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