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:** Is poor sleep associated with accelerated pace of aging as estimated from a single brain scan?

**Proposing Author:** Ethan Whitman, Aric Prather

**Author's Email:** ethan.whitman@duke.edu, Aric.Prather@ucsf.edu

**P.I. Sponsor:** Ahmad Hariri
(if the proposing author is a student or colleague of an original PI)

**Today's Date:** 9/5/24

---

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

## Objective of the study:

Sleep disturbance and short sleep duration (e.g., <6 hours of sleep per night) are implicated in the incidence and progression of a host of age-related conditions, including several neurodegenerative diseases such as Alzheimer's disease[1–4]; however, the biological mechanisms linking sleep and these diseases of aging are unknown. Recent research has demonstrated associations between poor sleep and markers of biological aging[5], including metrics based on DNA methylation patterns (i.e., epigenetic clocks)[6,7,8]. Indeed, data for the Health and Retirement Study found that older adults reporting short sleep duration (<6 hours) and insomnia symptoms showed statistically significantly faster DunedinPACE compared to non-disturbed sleepers[6].

Innovations in deep learning methods using neuroanatomic MRI data have led to alternative aging metrics that may be more strongly associated with sleep than blood-based aging measures[9,10]. Further, growing evidence supports the predictive utility of MRI-based brain age metrics with respect to classifying the risk of neurodegenerative diseases that are observed at high rates among those with sleep disturbance. That said, no study has investigated whether sleep is associated with MRI-derived brain aging outcomes.

The aim of the present study is to investigate whether self-reported sleep measures, including measures of sleep duration, overall sleep quality, and insomnia symptoms, are associated with the brain-derived measure the Dunedin Pace of Aging from NeuroImaging or DunedinPACNI. We have recently found that faster DunedinPACNI predicts cognitive decline, dementia conversion, chronic disease risk, and mortality in the UK Biobank and Alzheimer's Disease Neuroimaging Initiative (ADNI) datasets[11]. We will extend these findings using sleep data from the Dunedin Study, UK Biobank, and ADNI.

## Data analysis methods[1]:

**Question 1: Is poor sleep associated with accelerated aging among midlife and older adults?** To answer this question, we will first ask whether Dunedin Study members who report worse quality sleep on

[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 Pittsburgh Sleep Quality Index (PSQI) have faster Pace of Aging and DunedinPACNI scores at age 45. We will control for age and sex in these analyses. Furthermore, we will also test the contemporaneous association between age 45 Pace of Aging and age 38 sleep quality also measured using the PSQI. This will allow us to determine the sequence of any causal link that may exist between accelerated aging and poor sleep.

**Question 2: Is poor sleep associated with faster DunedinPACNI in participants of the UK Biobank?** Using DunedinPACNI, we will attempt to replicate the association between poor sleep and faster Pace of Aging in UK Biobank. We will further test if people who self-report a history of insomnia diagnosis have faster DunedinPACNI compared to those who do not. We will control for age and sex in these analyses.

**Question 3: Is poor sleep associated with faster DunedinPACNI among people with neurodegenerative disease?** We will use data collected from 764 ADNI participants to test again test for an association between poor sleep and faster DunedinPACNI. We will further test if associations between poor sleep quality and faster DunedinPACNI are stronger in older adults with Mild Cognitive Impairment and dementia. We will control for age and sex in these analyses.

**Question 4: Are associations between poor sleep and faster DunedinPACNI explained by more general risk for Alzheimer's disease?** As other risk factors for dementia (e.g., a history of psychiatric disease, traumatic brain injuries, etc.) could drive both poor sleep and faster DunedinPACNI scores, we will conduct sensitivity analyses repeating the primary analyses while including the top ADRD Risk Index available in each cohort as a covariate control. As the CAIDE (Cardiovascular Risk Factors, Aging, and Incidence of Dementia) Dementia Risk Score is a validated ADRD risk index available in all three cohorts, it will be the primary control variable used. The CAIDE is incorporates various cardiovascular and socioeconomic risk factors including hypertension, obesity, hypercholesterolemia, and low educational attainment, has been shown to predict dementia across up to 40 years[12], and correlates well with other larger ADRD Risk Indexes composed of more diverse risk factors (r's of .55 to .63)[13].

**Question 5: Is poor sleep associated with an epigenetic measure of accelerated pace of aging?** Lastly, we will test whether poor sleep is associated with an epigenetic measurement of accelerated rate of aging, DunedinPACE. This will allow us to determine whether poor sleep is associated with accelerated aging measured using multiple modalities. We will conduct these analyses in the Dunedin and ADNI datasets, since these datasets have DNA methylation data available. We will control for age and sex in these analyses.

## Variables needed at which ages:

Dunedin Study:
-Pace of Aging scores at age 45
-DunedinPACNI scores at age 45
-PSQI data phase 45
-PSQI data phase 38
-sex
-CAIDE Dementia Risk Index
-DunedinPACE scores at age 45

UK Biobank:
-DunedinPACNI scores
-self-reported sleep duration (Field ID = 1160)
-self-reported history of insomnia diagnosis (Field ID = 1200)
-sex
-age
-CAIDE Dementia Risk Index

ADNI:

-DunedinPACNI scores
-Cognitive status/diagnosis
-informant-reported sleep disturbance from the Neuropsychiatric Inventory Examination (NPI)
-informant-reported severity of sleep disturbance from the NPI
-sex
-age
-CAIDE Dementia Risk Index
-DunedinPACE scores

## Significance of the Study (for theory, research methods or clinical practice):

Epidemiologic and experimental data demonstrate sleep's importance in supporting physical and mental health, including brain health. Furthermore, sleep represents an actionable behavioral target; however, there is a pressing need for surrogate endpoints that precede frank disease. An examination of associations between sleep and DunedinPACNI will provide important data to guide intervention development and future clinical trials.

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

This research will not include separate analysis of specific ethnic groups. Nevertheless, any findings will likely be generalizable to the Māori community. Indeed, we know already that DunedinPACNI follows an expected socioeconomic gradient of health inequities[11]. Linking poor sleep quality to faster DunedinPACNI will further underscore the importance of good sleep for physical and mental health especially amongst socioeconomically disadvantaged people.

## References:

1. Chen JC, Espeland MA, Brunner RL, Lovato LC, Wallace RB, Leng X, Phillips LS, Robinson JG, Kotchen JM, Johnson KC, Manson JE, Stefanick ML, Sarto GE, Mysiw WJ. Sleep duration, cognitive decline, and dementia risk in older women. Alzheimer's & Dementia. 2016 Jan 1;12(1):21–33.

2. Macedo AC, Balouch S, Tabet N. Is Sleep Disruption a Risk Factor for Alzheimer's Disease? J Alzheimers Dis. 2017;58(4):993–1002. PMID: 28550253

3. Shi L, Chen SJ, Ma MY, Bao YP, Han Y, Wang YM, Shi J, Vitiello MV, Lu L. Sleep disturbances increase the risk of dementia: A systematic review and meta-analysis. Sleep Med Rev. 2018 Aug;40:4–16. PMID: 28890168

4. Yao CW, Pelletier A, Fereshtehnejad SM, Cross N, Dang-Vu T, Postuma RB. Insomnia symptom subtypes and manifestations of prodromal neurodegeneration: a population-based study in the Canadian Longitudinal Study on Aging. J Clin Sleep Med. 2022 Feb 1;18(2):345–359. PMCID: PMC8804990

5. Carroll JE, Prather AA. Sleep and Biological Aging: A Short Review. Curr Opin Endocr Metab Res. 2021 Jun;18:159–164. PMCID: PMC8658028

6. Kusters CDJ, Klopack ET, Crimmins EM, Seeman TE, Cole S, Carroll JE. Short Sleep and Insomnia Are Associated With Accelerated Epigenetic Age. Psychosom Med. 2024 Jun 1;86(5):453–462. PMCID: PMC10879461

7. Lee HS, Kim B, Park T. The association between sleep quality and accelerated epigenetic aging with metabolic syndrome in Korean adults. Clin Epigenetics. 2024 Jul 16;16(1):92. PMCID: PMC11253334

8. Carroll JE, Irwin MR, Levine M, Seeman TE, Absher D, Assimes T, Horvath S. Epigenetic Aging and Immune Senescence in Women With Insomnia Symptoms: Findings From the Women's Health Initiative Study. Biol Psychiatry. 2017 Jan 15;81(2):136–144. PMCID: PMC5536960

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

9. Yin C, Imms P, Cheng M, Amgalan A, Chowdhury NF, Massett RJ, Chaudhari NN, Chen X, Thompson PM, Bogdan P, Irimia A, Alzheimer's Disease Neuroimaging Initiative. Anatomically interpretable deep learning of brain age captures domain-specific cognitive impairment. Proc Natl Acad Sci U S A. 2023 Jan 10;120(2):e2214634120. PMCID: PMC9926270

10. Cole JH, Poudel RPK, Tsagkrasoulis D, Caan MWA, Steves C, Spector TD, Montana G. Predicting brain age with deep learning from raw imaging data results in a reliable and heritable biomarker. NeuroImage. 2017 Dec 1;163:115–124.

11. Ethan T. Whitman, Maxwell L. Elliott, Annchen R. Knodt, Wickliffe C. Abraham, Tim J. Anderson, Nick Cutfield, Sean Hogan, David Ireland, Tracy R. Melzer, Sandhya Ramrakha, Karen Sugden, Reremoana Theodore, Benjamin S. Williams, Avshalom Caspi, Terrie E. Moffitt, & Ahmad R. Hariri1 for The Alzheimer's Disease Neuroimaging Initiative. An estimate of the longitudinal pace of aging from a single brain scan predicts dementia conversion, morbidity, and mortality.

12. Exalto, L. G. *et al.* Midlife risk score for the prediction of dementia four decades later. *Alzheimers. Dement.* **10**, 562–570 (2014).
13. Reuben, A. *et al.* Improving risk indexes for Alzheimer's disease and related dementias for use in midlife. *Brain Commun.* **4**, fcac223 (2022).