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HUMAN DEVELOPMENT, BIRTH TO DEATH

Moffitt & Caspi
Genes Environment Health Behavior

Concept Paper Form

Provisional Paper Title: ADRD Risk index in midlife
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Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

Objective of the study:

The unit team recently collected new data in the Dunedin Study, by gathering the AD8 for cohort members' grandparents and parents. We will ascertain indicators of which cohort members have a family history of ADRD. We will ask: How do other midlife ADRD risk factors measured in the Dunedin Study relate to an individual's family history of ADRD, and how do they relate to each other? Can we build a midlife risk index for ADRD? Drugs for ADRD are in the pipeline, and economists predict that when these become available, there will be a flood of midlife individuals asking their family doctors for these preventive drugs. However, the drugs are extremely costly, and if people must take them for years, no health provider can cover the cost. Thus, there will need to be an easy, low-cost, and valid method that family doctors can use to triage which of the patients under their care are at greatest risk for ADRD and warrant a prescription. If risk is not used as the basis of access to preventive drugs, then only the wealthy will be able to have them, thereby exacerbating inequalities in ADRD.

SPECIFIC AIMS:

We will carry out statistical analyses to identify which among 40 putative midlife risk factors for ADRD are most closely related to family ADRD history. Among those midlife risk factors that turn out to be related to family ADRD history, analyses will evaluate their relations to each other. We will construct a prototype midlife predictive tool for familial ADRD risk. We plan to eventually test the prediction tool in larger cohorts with older participants who have ADRD outcome data.

RESEARCH STRATEGY AND APPROACH:

We recently conducted a literature search of the known or suspected midlife risk factors for ADRD, and established that our protocol for the age-45 assessment of the Dunedin cohort already includes 40 of the 41 published risk factors (only brain amyloid-beta is missing from

the Dunedin Study data base). The list of risk factors is shown in a table at the end of this document.
We wish to model the inter-relations among these 40 ADRD risk factors. Modelling could generate a measurement tool to quantify presumed cumulative risk level for ADRD in a midlife adult (similar to the Framingham Heart Age tool). Modelling can also detect latent classes of risk factors that cluster together, which might inform the study of heterogeneity within the ADRD phenotype. Risk factors for ADRD have been studied before, but inter-relationships among all 40 of them have never been examined in the same cohort of individuals. There is further potential to detect novel ADRD risk factors.
The technical problem to solve is that the Dunedin cohort, at age 45, lacks the clinical ADRD outcome point to use as a criterion benchmark. We propose the solution of using familial load for ADRD as a proxy (a surrogate for the ADRD phenotype outcome). Work would construct a criterion measure of each cohort member's familial load of ADRD in his or her immediate ancestors: grandparents and parents. In essence, an index of familial ADRD load would make it possible to "post-dict" ancestral ADRD load from the 40 risk factors, ascertaining for each risk factor how strongly it is associated with familial ADRD load.
We accept that post-dicting to family ADRD history is not a perfect solution. Nevertheless, consider the alternative. To our knowledge no other data set that has all of the ADRD risk factors already ascertained in midlife, and if there were one, it too would have to wait many years for the clinical diagnosis of ADRD.
There is a useful precedent for the approach we propose: In the UK Biobank, a successful genome-wide association analysis of ADRD was conducted using family history of ADRD as a proxy phenotype. Only 55 participants in Biobank have dementia, but of their parents, 60,000 had ADRD. New replicated risk loci for ADRD were discovered in that GWAS by using family history, as we aim to do here (Liu, Erlich, & Pickrell, 2017, Nature Genetics, doi:10.1038/ng.3766).

Data analysis methods:

Data analysis approaches. Our data analysis will involve three steps.
First, we will examine the associations of each of the risk factors with family ADRD history. The purpose of this analytic step is to establish if there are any risk factors that are not associated with family ADRD history. These will be eliminated from further consideration. We have grouped the risk factors on a **Table** at the end of this document, shown by whether they are measured in the Dunedin Study on a continuous distribution, or are dichotomous categories. Within the dichotomous categorical measures, the table shows which categorical variables have at least 10% prevalence in the cohort which will insure sufficient statistical power.
Second, we will examine the associations between the risk factors, to establish the extent of overlap and independence between the various risk factors. In addition, we will apply data reduction tools (factor analysis, latent class analysis) to test the extent to which different risk factors aggregate into a smaller number of dimensions/classes. Ultimately, this will allow us to test the extent to which different classes or groups of variables (whether classified conceptually or empirically) add to overall model prediction. For example, do genetics tell us anything that we cannot already observe with clinical phenotypes? Does having MRI brain data really improve prediction?
Third, we will develop a prototype risk prediction tool using family ADRD history as the

criterion. The goal is to construct a risk-factor predictor of ADRD history in the Dunedin Study, and to then export this predictor to other studies in order to validate it. We have experience with such statistical approaches in other areas. For example, we recently developed a methylation predictor of smoking status. The purpose of such a predictor is to provide a tool for researchers who need to control for smoking in studies of DNA methylation, but have not collected observed smoking phenotypes. We used elastic-net regression to develop a predictor using epigenome-wide association analysis results about tobacco smoking in our cohort. The final elastic net analysis selected 32 probes to include in the predictor, which was, in turn, highly accurate in discriminating smokers from non-smokers in other independent cohorts (Area Under the Curve > .90).

Variables needed at which ages:

TABLE:

N=40 midlife risk factors for Alzheimer's Disease and Related Dementias available in the Dunedin cohort which will be used in our research: Established midlife risk factors for ADRD were identified by searching Google Scholar for these five key words: Alzheimer's, Dementia, Risk, review, meta-analysis. We also identified risk factors examined by the 2011 NIH State of the Science Consensus Panel on ADRD risk factors (Daviglus, Plassman, Pirzada et al., 2011, Risk factors and preventive interventions for Alzheimer disease: state of the science, Archives of Neurology).

Continuously distributed risk measures available in Dunedin:
Family history of ADRD by self and parent report
Diabetes (HBA1C, medical records)
Obesity (BMI)
Hypertension
Hyperlipidemia (elevated cholesterol assay)
Inflammation (hsCRP assay)
Plasma homocysteine (assay)
Personality, including Neuroticism, Conscientiousness
Low education
Manual unskilled occupation
Mild Cognitive Impairment (via repeated neuropsychological testing, self-reports, and informant reports)
Cognitive activity/engagement (protective)
Cognitive decline by midlife (ascertained via repeated testing since childhood)
Physical inactivity
Smoking (pack years)

Dichotomous categorical risk measures with prevalence >10% in Dunedin:
Depression diagnosis
Low alcohol intake (protective)
Mediterranean diet (protective)
APOE4 (Dunedin has actual genotype, not imputed from snp arrays)
Traumatic brain injury history (TBI by self-report and medical record)

NSAID intake (protective, by pharmaceutical NHS record)

Dichotomous categorical risk measures with prevalence <10% in Dunedin:
Folic acid intake
Occupational pesticide exposure
Arthritis (protective)

Additional potential risk factors available in the Dunedin Study that will be used in our research. These appear in the literature, but no meta-analysis was found:

Continuously distributed risk measures in Dunedin:
GWAS-based polygenic scores for ADRD (derived by IGAP, UKBiobank)
Accelerated Midlife Pace of Aging (Belsky et al. 2015, PNAS)
Structural neuroimaging ascertained by MRI (e.g., hippocampal volume)
Diffusion tensor neuroimaging fractional anisotropy (e.g., of the right cingulum)
Vascular abnormalities in digital retinal imaging
Gait/mobility disturbance via Gaitrite technology (with and without cognitive challenge)
Sensory deficits in vision paradigms that challenge the central nervous system such as Contrast Sensitivity
Sensory deficits in hearing paradigms that challenge the central nervous system such as the Speech in Noise Test
Physical function paradigms that challenge the central nervous system such as One-leg Balance test
Epigenetic methylation profiles (published epigenetic clocks), and transcriptomic marker profiles
Cytokines

Dichotomous categorical risk measures with prevalence >10% in Dunedin:
Sleep disorders (insomnia, poor sleep quality)
Childhood lead exposure (blood lead >10 mg/DL; an environmental risk factor with cognitive effects that should be unrelated to family history of ADRD)

Dichotomous categorical risk measures with prevalence <10% in Dunedin:
Social isolation
Sensory deficits in olfaction ascertained in the Smell Test
Chronic migraine headache history
Chronic pain

Brain Amyloid-beta (**this is the only published risk factor we found that is not available in the Dunedin cohort**)

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

SIGNIFICANCE AND INNOVATION:

Our NIA grant was not focused on ADRD as an outcome, because the cohort is only 45 years old. However, the path to ADRD is lifelong, and it crosses generations. Because there is no cure, prevention is the holy grail. Prevention will require an accurate tool for ascertaining presumptive ADRD risk during midlife, before the onset of clinically diagnosed ADRD. Such a tool is needed, but lacking. Moreover, studying risk factors for ADRD in midlife adults as we propose here avoids mortality selection, a serious methodological problem in older cohorts. When older samples are used, many individuals with the highest concentration of risk factors have already died and their data are therefore missing, moreover surviving participants can be highly selected. For example, in a recent report beta amyloid predicted cognitive decline in cognitively healthy individuals (Donohue, Sperling et al. 2017, JAMA), but participants' mean age was 74 and mean education was university graduate.

References cited: