CONCEPT PAPER TEMPLATE

Provisional Paper Title:	Quantification of the pace of biological aging through retinal imaging
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Objective of the study:

Ageing has become an urgent problem worldwide, with the proportion of elders over 60 years old project to double from 12% to 20% between 2015 and 2050.[1] As we age, the risk that we will experience chronic diseases (e.g., heart disease) and declining capacities (e.g., poorer memory) increases. The rate of ageing is heterogeneous at an individual level.[2] While many individuals continue to live in their nineties with relatively good quality of life, others experience body function decline and mortality at younger ages. Thus, chronological age is, at best, an imperfect basis for aging quantification.

To help explain why some adults experience age-related decline faster than others, extensive efforts have been made to accurately quantify biological ageing process. Dunedin Pace of Ageing (DunedinPoA) has been validated as a reliable measure of midlife biological ageing, determined by a panel of 19 biomarkers obtained at ages 26, 32, 38, and 45 from Dunedin study.[3]

The retina provides a window to the microvascular and nervous systems of the body and can be easily recorded by retinal photography. Recently novel ageing biomarkers, Reti-Age and RetinaAGE, have been developed based on fundus images using deep-learning.[5,7] Reti-Age quantifies the difference on the retina of people aged of 65 years old and older from those who were younger. Its predictive power over the risk of all-cause, cardiovascular, and cancer-related mortality was validated on external UK Biobank population.[7] RetinaAGE, retinal age gap estimation, is another biological aging marker developed to calculate the residual of the model predicting calendar age from retinal photos. The residual, retinal age gap, that is the difference between predicted age from the fundus image and chronological age have been verified as an independent predictor for future risk of mortality, cardiovascular disease and Parkinson's disease.[4-6]

In this study, we propose to investigate effects of midlife biological ageing indexed by DunedinPoA from ages 26 to 45 on ageing indicators at age 45 based on retinal images (Reti-Age and RetinaAGE), and further investigate cross-sectional associations between retinal ageing biomarkers (Reti-AGE and RetinaAGE at age 45) and age-related outcomes at age 45, including neuroimaging measures, cognitive difficulties, sensorimotor functional capacity, and perceptions of ageing.

Hypothesis:

1) We propose that DunedinPoA is significantly associated with retinal aging markers in the Dunedin birth cohort.

2) We propose that retinal aging markers are significantly associated age-related outcomes in the Dunedin birth cohort.

Data analysis methods:

1. Distribution of Reti-Age and RetinaAGE in midlife (Aim 1).

   1.1 Method: We will leverage in-house developed and externally-validated retinal age deep learning algorithm to fundus images collected at age 45.

   1.2 Details:

   The Reti-Age will be provided using application user interface (API) for securely uploading the raw retinal images to algorithm server.

   The RetinaAGE software will be provided and the results of retinal age can be obtained after running the software through raw retinal images.

   Given the raw retinal images of Dunedin Study have been stored in Singapore, the scoring will be done in Singapore.

2. Association between DunedinPoA and Reti-Age and RetinaAGE (Aim 2).

   2.1 Method: We will investigate the associations between DunedinPoA from ages 26 to 45 and Reti-Age and RetinaAGE at age 45.

   2.2 Details: Linear regression models will be applied to investigate associations between DunedinPoA from ages 26 to 45 and retinal aging markers at age 45. The model will adjust for sex (Model I) as the primary analysis. Further adjustments of smoking, BMI, mean arterial blood pressure, and history of diabetes and chronic conditions will be included in the full model.

3. Association between Reti-Age and RetinaAGE and key age-related outcomes (Aim 2).

   3.1 Method: We will investigate the associations between Reti-Age and RetinaAGE and key age-related outcomes at age 45.

   3.2 Details: Linear regression models will be applied to investigate associations between Reti-Age and RetinaAGE and key age-related outcomes including brain age, adult intelligence quotient (IQ) scores and factor score of physical function tests . All models will be adjusted for sex. Further adjustments of smoking, BMI, mean arterial blood pressure, and history of diabetes and chronic conditions will be included in the full model.

Variables needed at which ages:

1. Retinal age (obtained via retinal fundus images at phase 45).
2. Pace of ageing (a panel of 19 biomarkers obtained at ages 26, 32, 38, and 45 years).
3. Brain age (obtained via deep learning algorithm at age 45);

4. Adult intelligence quotient (IQ) scores at age 45 and adult intelligence quotient (IQ) residualized of baseline childhood status;
5. Factor score of physical function tests at age 45;
6. Potential covariates:
   - Sex
   - Smoking (age 45)
   - BMI (age 45)
   - Mean arterial blood pressure (age 45)
   - Diseases diagnosis (age 45)

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

1. Concerning public health, accelerated biological ageing is a common cause of age-related chronic diseases (e.g., heart disease). An accurate quantification of the biological ageing process is clinically significant for risk stratification and to enable targeted, personalised interventions (e.g., quit smoking). The non-invasive, fast, easy and cost-effective nature of retinal imaging enables it to be an accessible and scalable screening tool to identify people at an increased risk of biological ageing.

2. Concerning geroscience research, measures to quantify biological aging in response to intervention are needed to evaluate geroprotective interventions for humans. The emerging anti-aging interventions that can achieve slowing of biological ageing promise to improve quality of life and yield substantial healthcare savings.

3. Concerning policy, many social programs, including pensions and Medicare, are designed to offset the economic and health burdens that accrue as individuals age. Eligibility for these benefits has been determined on the basis of chronological age. Biological aging measures could represent an alternative to using birth-dates when determining the allocation of healthcare and financial support for those suffering from the sequelae of aging.

References:

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