

Concept Paper Template 2018

Provisional Paper Title: A Deep Learning System for Automated Measurement of Retinal Vessel Caliber from Fundus Photographs to Quantify Cardiovascular Risk

Proposing Author: Carol Y. Cheung, Tien Y. Wong

Author's Email:

carolcheung@cuhk.edu.hk
wong.tien.yin@singhealth.com.sg

P.I. Sponsor:

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

N.A.

Today's Date: 18Feb2019

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

Objective of the study:

The caliber of the retinal vessels is influenced by blood pressure, diabetes and predictive of cardiovascular and retinal disease such as stroke and diabetic retinopathy. However, the measurement of retinal vascular caliber requires significant human efforts, and a fully automated and reliable system that can measure retinal vascular caliber accurately will have substantial research and clinical use. We aim to develop and validate a deep learning system (DLS) for automated measurement of retinal vessel calibers from retinal photographs. We will compare the correlation of the DLS with human measurement (SIVA-human) and then evaluated the DLS's measurement (SIVA-DLS) with CVD risk factors using external independent datasets in diverse clinical settings

Data analysis methods:

First, to assess distribution and agreement in caliber measurements between SIVA-human and SIVA-DLS, we will perform paired t-test, compute the intra-class correlation coefficient (ICC) between the two methods, and construct Bland-Altman plot. In the Bland-Altman plot analyses, the 95% limits of agreement (LOA) are defined as mean difference $\pm 1.96 \times SD$. Second, we will use multiple linear regression models to correlate each CVD risk factors (age, gender, MABP, BMI, smoking, HbA1c and total cholesterol level) and caliber measurements,

adjusting for age (except the models of age), gender (except the models of gender), and fellow caliber. We will compare the fit of the models between SIVA-DLS and SIVA-human based on the adjusted R².

Variables needed at which ages:

Retinal data (retinal photographs, SIVA data), ethnicity, age, gender, MABP, BMI, smoking, HbA1c and total cholesterol level at age 38 and age 45.

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

The caliber of the retinal arterioles and venules (100 to 300 μm in diameter) have been proposed to be surrogate measures of systemic microvascular health and changes in caliber may reflect early microvascular damage or alterations in peripheral, cerebral and coronary small vessels. However, because current versions of retinal vessel caliber software such as SIVA require substantial human assessment and intervention, following standardized grading protocols, the ability to use retinal imaging for clinical CVD risk stratification and prediction is limited. Artificial intelligence (AI) using deep learning systems (DLSs) with convolutional neural networks (CNNs) have now been used in medical imaging. We aim to develop and validate a DLS for automated measurement of retinal vessel calibers from retinal photographs. The validation of AI-based DLS for automated measurement of retinal arteriolar and venular calibers from retinal photographs will have immediate research value in epidemiological and clinical studies, and can be further translated for clinical CVD prediction in the future.

References:

1. Liew G, Wang JJ, Mitchell P, Wong TY. Retinal vascular imaging: a new tool in microvascular disease research. *Circ Cardiovasc Imaging*. 2008;1(2):156-61.
2. Wong CW, Wong TY, Cheng CY, Sabanayagam C. Kidney and eye diseases: common risk factors, etiological mechanisms, and pathways. *Kidney Int*. 2014;85(6):1290-302.
3. Cheung CY, Ikram MK, Chen C, Wong TY. Imaging retina to study dementia and stroke. *Prog Retin Eye Res*. 2017;57:89-107.
4. Cheung CY, Ikram MK, Sabanayagam C, Wong TY. Retinal microvasculature as a model to study the manifestations of hypertension. *Hypertension*. 2012;60(5):1094-103.
5. Wang SB, Mitchell P, Liew G, Wong TY, Phan K, Thiagalingam A, et al. A spectrum of retinal vasculature measures and coronary artery disease. *Atherosclerosis*. 2018;268:215-24.
6. McGeechan K, Liew G, Macaskill P, Irwig L, Klein R, Klein BE, et al. Meta-analysis: retinal vessel caliber and risk for coronary heart disease.

- AnnInternMed. 2009;151(6):404-13.
7. McGeechan K, Liew G, Macaskill P, Irwig L, Klein R, Klein BE, et al. Prediction of incident stroke events based on retinal vessel caliber: a systematic review and individual-participant meta-analysis. *AmJ Epidemiol.* 2009;170(11):1323-32.
 8. Sun C, Wang JJ, Mackey DA, Wong TY. Retinal vascular caliber: systemic, environmental, and genetic associations. *SurvOphthalmol.* 2009;54(1):74-95.
 9. Cheung CY, Ikram MK, Klein R, Wong TY. The clinical implications of recent studies on the structure and function of the retinal microvasculature in diabetes. *Diabetologia.* 2015;58(5):871-85.
 10. Cheung CY, Tay WT, Ikram MK, Ong YT, De Silva DA, Chow KY, et al. Retinal microvascular changes and risk of stroke: the Singapore Malay Eye Study. *Stroke.* 2013;44(9):2402-8.
 11. Ho H, Cheung CY, Sabanayagam C, Yip W, Ikram MK, Ong PG, et al. Retinopathy Signs Improved Prediction and Reclassification of Cardiovascular Disease Risk in Diabetes: A prospective cohort study. *Sci Rep.* 2017;7:41492.
 12. Ting DSW, Cheung CY, Lim G, Tan GSW, Quang ND, Gan A, et al. Development and Validation of a Deep Learning System for Diabetic Retinopathy and Related Eye Diseases Using Retinal Images From Multiethnic Populations With Diabetes. *JAMA.* 2017;318(22):2211-23.
 13. Gulshan V, Peng L, Coram M, Stumpe MC, Wu D, Narayanaswamy A, et al. Development and Validation of a Deep Learning Algorithm for Detection of Diabetic Retinopathy in Retinal Fundus Photographs. *JAMA.* 2016;316(22):2402-10.
 14. De Fauw J, Ledsam JR, Romera-Paredes B, Nikolov S, Tomasev N, Blackwell S, et al. Clinically applicable deep learning for diagnosis and referral in retinal disease. *Nat Med.* 2018;24(9):1342-50.

Data Security Agreement

| | |
|-------------------------|--|
| Provisional Paper Title | A Deep Learning System for Automated Measurement of Retinal Vessel Caliber from Fundus Photographs to Quantify Cardiovascular Risk |
| Proposing Author | Carol Y. Cheung & Tien Y. Wong |
| Today's Date | 18Feb2019 |

Please keep one copy for your records and return one to the PI Sponsor

Please initial your agreement: (customize as necessary)

| | |
|---|---|
| √ | I am current on Human Subjects Training [CITI www.citiprogram.org] or equivalent. |
| √ | My project is covered by the Dunedin Study's ethics approval OR I have /will obtain ethical approval from my home institution (please specify). |
| √ | I will treat all data as "restricted" and store in a secure fashion. My computer or laptop is: <ul style="list-style-type: none"> • encrypted (recommended programs are FileVault2 for Macs, and Bitlocker for Windows machines) • password-protected • configured to lock-out after 15 minutes of inactivity AND • 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 my PI Sponsor or Study Director, Richie Poulton (richie.poulton@otago.ac.nz). |
| √ | 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. <i>Some journals are now requesting the data file as part of the manuscript submission process. The Dunedin Study Members have not given informed consent for unrestricted open access, so we have a managed-access process. Speak to your PI Sponsor or Richie Poulton for strategies for achieving compliance with data-sharing policies of journals.</i> |
| √ | 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. The data remains the property of the Study and cannot be used for further analyses without an approved concept paper for new analyses. |

Signature: _____

CAROL