UK Biobank Eye & Vision Consortium

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In this Newsletter:

Publication News

The VAMPIRE team, lead by Tom McGillivray & Manuel Trucco, have submitted a manuscript **'Suitability of UK Biobank retinal images for automatic analysis of morphometric properties of the vasculature',** to PLOS ONE which has been accepted for publication. A PDF version will be published on our website in due course.

Visual health inequalities: Findings from UK Biobank

The findings of a study by Phillipa Cumberland and Jugnoo Rahi investigating socioeconomic influences on visual health the UK Biobank cohort has been published online as an abstract in The Lancet. Using multinomial and ordinal regression analyses, it was found that as well as the frequency of normal bilateral vision decreasing with age, the risk of visual impairment across severity categories was associated with increased demographic and socioeconomic variables such as deprivation. In addition, these patterns were not explained by risk of underlying eye disease. The authors concluded that There are consistent patterns of associations between visual impairment across the full spectrum including, importantly, people with mild impairment, and known health determinants as well as key social outcomes.

Cumberland, Phillippa M., and Jugnoo S. Rahi. "Visual health inequalities: findings from UK Biobank." The Lancet 384 (2014): 527.

Annual Consortium Meeting Summary

The 4th annual meeting of the consortium took place in **February 2015** at the Wellcome Trust Convention Centre on Euston Road in London.

The collection of seven-day physical activity data, measured using accelerometer, from 60,000 out of 100,000 participants has been completed.

The Visual Impairment & Retinal Grading group, headed by Martin McKibbin, have successfully obtained fundus photo image files from UK Biobank and are currently assessing images from people with visual impairment.

Dr David Steel joined the UK Biobank Eye & Vision consortium and will be looking at vitreo-macular interface abnormalities as well as abnormalities of optic disc, excluding glaucoma.

Michelle Chan presented her findings on the associations with IOPg and IOPcc with physical and demographic factors in the UK Biobank cohort. The results confirmed many known associations, such as systolic blood pressure being the strongest determinant of IOP. However, we were able to demonstrate for

the first time that IOPg and IOPcc had distinctly different directions of associations with height, self-reported diabetes, smoking and ethnicity. This indicated that these factors have strong relationships with corneal biomechanics, and that IOPg and IOPcc may reflect different biological characteristics.The study findings were presented in the Association for Research in Vision and Ophthalmology meeting in Denver, USA in May.

The Crowd sourcing group have created a modifiable webpage that applies crowd sourcing to classify retinal images (Retinalannotation.com). The webpage has an intuitive interface where users are given the knowledge needed to complete the task and given the opportunity to practice classifying retinal images and given feedback on their performance. There is also a section that allows researchers to manage and review annotation results. From a 100-image dataset, accuracy for correct class for masters was 66% and non-masters 56%. In terms of labelling healthy vs non-healthy masters had a sensitivity of 88% and specificity 84%, while non-masters sensitivity of 82% and specificity 79%. Using 4 different approaches (baseline to highly skilled), crowd sourcing for image analysis showed that sensitivity for Mild AB ranged between 0.55 - 0.72, for Normal = 0.64 - 0.86 and Severe AB= 0.90–0.99, showing that this tool demonstrates proof in principle. However, more complex diagnostic questions are likely to require a more detailed/complex questionnaire design in order to in order to benefit from crowd sourcing. Retinal Annotation is aiming to perform large scale image analysis, to clarify variables contributing to accuracy, as well as make improvements to the training and reward system. Retinal Annotations also aims to plug in more datasets including non-retinal data.

The cataract research group have set up a project where they aim to determine and quantify risk factors and disease associations for cataract on the full dataset of 500,000 people. This will be a case control study looking at those that had cataract diagnosis vs those that did not and those that cataract surgery vs not that had not. The study will be investigating a range of risk factors including genetic, environmental, biometric, biomarkers, lifestyle and demographics. No further updates as yet.

As part of UK Biobank, 67,321 people received spectral domain optical coherence (SDOCT) imaging of the retina. Topcon automated segmentation were applied to ETDRS subfields to obtain retinal thickness, at each of 9 boundaries -- ILM, NFL/GCL, IPL/INL, INL/OPL, ELM, IS/OS, OS/RPE, BM/choroid. The group then excluded those whose image quality indicators were inadequate, leaving 38,406 right eyes and 38,689 left eyes with high-quality SDOCT scans. Analysis has been performed to describe distribution of full retinal thickness, NFL thickness, and RPE thickness among normal people and its associations. For the purposes of retina/cognition, the group have also performed preliminary analysis associating

Current Genotyping Details & Timescale

Following on from our previous issue, Genotyping using the Affymetrix UK Biobank Axiom Array is well underway. Genotyping is underway in all 500,000 participants, and is due to be completed during 2016. The full list of the 820,967 markers Affymetrix Axiom array can be found online at www.ukbiobank.ac.uk, these include specific markers, rare variants & GW coverage. Showcase has now been updated to enable researchers applying to use the UK Biobank resource to select the genotyping data they require for their research project, in advance of the release date, so that the datasets can be sent as soon as possible after the genotyping data are available for release. The release of QA'd genome wide data for the first 150,000 is set for this month (May 2015), after which we can expect imputation of this data, while late 2015 we expect QA'd Genome wide data for the entire cohort. Full imputation is expected by Spring 2016. These timelines are all provisional.

RNFL thickness with self-reports of neurological diseases, including chronic/degenerative, motor neuron disease, multiple sclerosis, parkinson's, and dementia/Alzheimers. Of these, multiple sclerosis showed a significant association with thinner RNFL as compared to normals. This lead the group to conclude that the lack of association with other diseases is likely due to small numbers, and remain encouraged that there is potential for interesting findings between RNFL and cognition indices.

Formation of Eye and Cognition Group

A group for research into Eye and Cognition has been formulated consisting of the following collaborative groups:

Cognitive assessment – Dr John Gallacher (Cardiff): Dr Gallacher is based at the University of Cardiff and is also the director of Dementia's platform. Dr Gallacher will be contributing his expertise from his psychological and epidemiological background to this research group in order to inform research that, at first instance, analyses baseline eye data in UKBB alongside measures of cognition.

OCT imaging – Mr Praveen Patel, Dr Fang Ko, Prof Paul Foster, Miss Zaynah Muthy (Moorfields): Mr Patel and colleagues are aiming to analyse retinal features obtained from OCT, such as RNFL thickness, alongside diagnosed neurologic disease such as dementia and Parkinson's. The next steps are to conduct a detailed preliminary analysis of RNFL thickness with such diseases in the UKBB cohort.

Vascular morphometry (QUARTZ group) – Dr Chris Owen, Dr Alicja Rudnicka, Dr Sarah Barman (St Georges/Kingston): The purpose of the QUARTZ system, lead by Dr Owen, is to obtain sub-pixel measures of width and tortuosity of retinal vessels. This group aims to use data from the whole image and also aims determine whether in those with disease, this method can detect precursors to development. This automated segmentation programme is able to detect retinal vessels and meaningful data from them including width and tortuosity. The next steps include examining whether there are any prospective associations with neurological disease outcomes in UKBB, and also to assess whether the QUARTZ system has an assistive role in risk prediction or as a potentially useful screening tool for disease.

Vascular morphometry (VAMPIRE group) - Prof Manuel Trucco, Dr Tom McGillivray, Prof Bal Dhillon (Dundee/Edinburgh): The VAMPIRE group, as well as the QUARTZ group are starting to move beyond conventional measures (AVR, CRVE, CRAE and tortuosity in regions closeto the OD) to explore novel summative, statistical and regional descriptors of the retinal vasculature and anatomy in fundus images and ultra-wide-field-of-view SLO images. These systems will provide very rich as useful data that can be used to statistically analyse detailed retinal features with measures of cognitive performance in healthy as well as dementia-suffering subjects.

Retinal blood flow – Dr Gareth McKay (Belfast): Dr Gareth McKay has received funding to investigate retinal microvascular changes in diabetic patients at increased risk of renal or cardiovascular complications. This

research area has broadened to investigate retinal microvascular and nerve fibre layer variation with cognitive function in people with mild cognitive impairment and dementia, with colleagues Dr Ruth Hogg and Professor Usha Chakravarthy (ophthalmology) and Dr Bernadette McGuinness and Professor Peter Passmore (geriatrics). We have also received funding with Professor Jayne Woodside from the Centre for Ageing Research and Development in Ireland, to examine retinal microvascular changes in association with cognitive function/decline and potential dietary influences on the microvasculature, in a large prospective population-based study.

This group met last month to discuss how to proceed with research. It was suggested that a preliminary analysis looking at retinal functions against cognitive measures would be ideal and beneficial as an indicator to what hypotheses are worth exploring further. It was also suggested by John Gallacher that it would be worth utilising Dementia's Platform - a multi million pound partnership funded by the MRC to develop knowledge around dementia. The website to Dementia's Platform can be accessed here.

Formation of Nutrition & Eye Group

Over the past two decades there has been substantial progress in linking nutrition to sight threatening diseases such as age-related macular degeneration (AMD), glaucoma and diabetic retinopathy. The most notable associations have been found with respect to AMD, with both epidemiological studies and clinical trials demonstrating the benefits of antioxidant nutrients (vitamins C and E, zinc, carotenoids such as lutein and zeaxanthin, and fruit and vegetables rich in these nutrients). While regulation of blood sugar is essential for preventing sight threatening complications of diabetes some small studies have suggested that certain micro nutrients such as chromium, isoflavones with soy proteins and Vitamin E might provide additional benefits. There is also evidence highlighting the beneficial effects of dietary antioxidants in the prevention of Glaucoma. Recent research has also moved from investigating individual nutrients to looking at diets more holistically used dietary pattern analysis and dietary scores. Many studies to date however, are relatively small and often only cross-sectional in design limiting their power to detect associations, the UK Biobank provides an exciting opportunity to explore the relationships between diet and sight threatening ocular diseases in a very large well-characterised prospective cohort. In the longer term the sample size will enable gene-environment interactions to be explored in conjunction with the genetics group which will provide novel information on how genetic predisposition interacts with lifestyle in the development of AMD, Diabetic Retinopathy and Glaucoma. In the future the relationship between diet and other ocular disease may also be possible as grading of the ophthalmic images progresses.

Objectives:

1. To investigate the association between diet and AMD, Diabetic Retinopathy and Glaucoma.

2. Explore how these relationships relate or are modified by systemic factors identified by the blood biochemistry results e.g. markers of inflammation, redox balance etc.

3. Explore the existence of gene-environment interactions between dietary and lifestyle factors in AMD, Diabetic Retinopathy and Glaucoma.

Those wishing to collaborate on a project within the Nutrition & Eye research group are advised to contact Dr Ruth Hogg from Queen's University, Belfast.

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