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# BMJ Open

## Cohort Profile: Rationale and Methods of UK Biobank Repeat Imaging Study Eye Measures

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# 1 Cohort Profile: Rationale and Methods of UK Biobank Repeat Imaging Study Eye

## 2 Measures

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2  
3 35 **ABSTRACT**  
4  
5

6 36 **Purpose:** To describe the rationale and methodology of eye and vision assessments in the UK  
7  
8 37 Biobank Repeat Imaging study.  
9

10 38 **Participants:** UK Biobank is a large-scale, multicentre, prospective cohort containing in-  
11  
12  
13 39 depth genetic, lifestyle, environmental and health information from half a million participants  
14  
15 40 aged 40-69 enrolled across the UK. A subset (up to 60,000 participants) of the cohort will be  
16  
17 41 invited to the UK Biobank Repeat Imaging Study to collect repeated brain, cardiac and  
18  
19 42 abdominal magnetic resonance imaging (MRI) scans, whole-body DEXA (Dual-energy x-ray  
20  
21 43 absorptiometry), carotid ultrasound, as well as retinal optical coherence tomography (OCT)  
22  
23 44 and colour fundus photographs.  
24  
25

26 45 **Findings to date:** UK Biobank has helped make significant advances in understanding risk  
27  
28 46 factors for many common diseases, including for dementia and cognitive decline. Ophthalmic  
29  
30 47 genetic and epidemiology studies have also benefited from the unparalleled combination of  
31  
32 48 very large numbers of participants, deep phenotyping, and longitudinal follow-up of the  
33  
34 49 cohort, with comprehensive health data linkage to disease outcomes. In addition, we have  
35  
36 50 used UK Biobank data to describe the relationship between retinal structures, cognitive  
37  
38 51 function and brain MRI-derived phenotypes.  
39  
40  
41

42 52 **Future plans:** UK Biobank is one of the largest prospective cohorts worldwide with  
43  
44 53 extensive data on ophthalmic diseases and conditions. The collection of eye-related data (e.g.  
45  
46 54 OCT), as part of the UK Biobank Repeat Imaging study, will take place between 2022-2028.  
47  
48 55 The depth and breadth and longitudinal nature of this dataset, coupled with its open-access  
49  
50 56 policy, will create a major new resource for dementia diagnostic discovery and to better  
51  
52 57 understand its association with co-morbid diseases.  
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## 59 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

### 60 *Strengths*

- 61 • World's largest prospective, longitudinal multi-modal imaging cohort with
- 62 unprecedented power for analysis of determinants of a wide range of health outcomes.
- 63 • Exceptional added value from the size, depth, and quality of the cross-sectional and
- 64 longitudinal MRI data on the eye, brain, body and imaging of heart, carotids, together
- 65 with linkage to electronic health records, through which overt dementia and
- 66 Alzheimer's disease can be identified.
- 67 • Optimal timing to study cognitive impairment (age distribution: ~80%  $\geq$  60 years and
- 68 ~65%  $\geq$  65 years)

### 69 *Limitations*

- 70 ○ Consistency of measurements between imaging devices over time, particularly with
- 71 use of different OCT devices.
- 72 ○ Healthier participants compared to the general population.

73

## 74 INTRODUCTION

75 Dementia refers to a heterogeneous group of neurodegenerative disorders affecting 46.8  
76 million people globally.[1-3] Alzheimer's disease (AD) is the commonest, affecting 60-80%  
77 of people with dementia.[4, 5] Usually, a long prodromal period of up to 20 years of  
78 progressive cerebral atrophy is detectable on magnetic resonance imaging (MRI) scans and  
79 using body fluid biomarkers for neurodegeneration before AD is diagnosed.[2] These  
80 observations lead to a biological, rather than a clinical definition of AD.[6] To date, the  
81 majority of candidate drugs for slowing cognitive decline in AD or other dementias have  
82 failed in clinical trials[7], probably because they are used too late in the natural history when  
83 irreversible, advanced degeneration has already set in.[8, 9] Global rollout of screening and  
84 disease progression monitoring strategies for AD based on MRI scans is precluded by their  
85 high cost and frequently limited availability. Body fluid biomarkers might provide ways of  
86 stratifying or diagnosing dementias but will remain complimentary to structural imaging  
87 biomarkers because of their lack of diagnostic specificity and are not recommended as a  
88 screening test.[10]

89 The eye provides insights into the risk or presence of all systemic diseases, including  
90 hypertension and diabetes, as well as changes associated with cognitive ageing and  
91 neurodegeneration.[11-13] As an alternative to MRI or plasma biomarkers, optical coherence  
92 tomography (OCT) offers a rapid, low-cost and non-invasive method for obtaining high-  
93 resolution (3-5 $\mu$ m) images of the retina at the back of the eye – the only part of the central  
94 nervous system (CNS) that can be visualized directly. The laminated structure of the retina  
95 enables the direct monitoring of neurodegeneration at a near cellular level *in vivo* at a  
96 resolution that is more detailed than for any other non-invasive, *in vivo* imaging modalities.  
97 There is strong evidence that quantitative OCT measurements are associated with concurrent  
98 cognitive impairment and future cognitive decline and dementia.[14, 15] Additionally, OCT

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2  
3 99 methods may directly monitor related vascular pathology: amyloid microangiopathy affects  
4  
5 100 retinal and choroidal vasculature, as well as that in the cerebrum with AD.[16] Thus, retinal  
6  
7 101 OCT scans offer the means to identify individuals at high risk of developing AD, providing  
8  
9 102 them with opportunities to change their lifestyles or enter drug trials to delay or avert the  
10  
11 103 onset of dementia. OCT scans are also a sensitive way to monitor patients for neurotoxic  
12  
13 104 side-effects of novel drug treatments. The ability to directly measure specific neuronal layers  
14  
15 105 and microvascular characteristics in detail may provide a surrogate outcome marker for the  
16  
17 106 CNS more generally and potentially enhance the power to detect disease much earlier than  
18  
19 107 methods based on clinical history and genetic factors.  
20  
21  
22  
23 108 Several genetic (e.g. *APOE*), comorbid (e.g. diabetes, hypertension, depression, obesity), and  
24  
25 109 lifestyle factors (e.g. low educational attainment and smoking) have been associated with  
26  
27 110 increased AD risk.[17-19] However, observational epidemiological studies cannot distinguish  
28  
29 111 cause from effect and are vulnerable to bias from reverse causation and confounders. The  
30  
31 112 analyses by Norton and Larsson illustrate how different disease risk factors can co-exist and  
32  
33 113 are often correlated, but they do not independently increase the risk of AD.[19, 20] It also  
34  
35 114 highlights the importance of identifying causal risk factors for dementia in designing  
36  
37 115 upstream public health policies and social policies to reduce disease risk, clinical trials for  
38  
39 116 new AD drugs and basic science research to understand the underlying mechanisms of  
40  
41 117 dementia development. Using quantitative measurements from OCT scans, it may be possible  
42  
43 118 to assess causal relationships between risk factors and retinal biomarkers related to dementia.  
44  
45 119 The large size of the cohort and the associated healthcare, imaging and genetic data make UK  
46  
47 120 Biobank uniquely valuable for disambiguation of associations from causal comorbidities both  
48  
49 121 for patient stratification and for elucidation of underlying mechanisms.  
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52  
53 122 The research gaps, as mentioned earlier, motivated us to develop a major new resource for  
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55 123 dementia diagnostic discovery and to better understand the association with co-morbid  
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3 124 diseases by adding rapid, low-cost OCT to the anticipated UK Biobank Repeat Imaging  
4  
5 125 study, alongside ancillary testing of autorefraction/keratometry and fragmented letter test  
6  
7 126 (FLT).[21] The objectives of this article are to describe (1) the process of test selection (2)  
8  
9 127 the methodology for eye and vision measures in the UK Biobank Repeat Imaging study; (3)  
10  
11 128 the baseline characteristics of the study population in this study.  
12  
13  
14

## 15 129 **COHORT DESCRIPTION**

### 16 130 *UK Biobank*

17  
18 131 UK Biobank is a large-scale biomedical database and research resource containing in-depth  
19  
20 132 genetic and health information from over 500,000 participants aged 40-69 enrolled across the  
21  
22 133 UK between 2006 and 2010. Detailed study protocols are available on the UK Biobank  
23  
24 134 website (<https://www.ukbiobank.ac.uk/>). It has become the pre-eminent biomedical research  
25  
26 135 platform for studying the aetiology of common diseases of later life. During the baseline  
27  
28 136 assessment, extensive sociodemographic, lifestyle, and health-related information was  
29  
30 137 collected through a touch screen questionnaire and oral interview, and a wide range of  
31  
32 138 physical measurements was performed.[22, 23] Participants also provided biological samples  
33  
34 139 for genotyping, haematological, biochemistry, metabolomics and proteomics assays for the  
35  
36 140 full cohort.[24]  
37  
38 141 UK Biobank received approval from the National Information Governance Board for Health  
39  
40 142 and Social Care and the National Health Service Northwest Centre for Research Ethics  
41  
42 143 Committee (Ref: 11/NW/0382). UK Biobank is compliant with the previous Data Protection  
43  
44 144 Act and the more recent General Data Protection Regulation (GDPR) implemented in 2018.  
45  
46 145 For the GDPR, participants were contacted by email or post to explain how UK Biobank  
47  
48 146 meets the requirements of the new regulations (<https://www.ukbiobank.ac.uk/gdpr/>).  
49  
50 147 At the baseline assessment in 2006-2010, various eye measures including visual acuity,  
51  
52 148 autorefraction, keratometry, intraocular pressure, corneal biomechanics, and retinal imaging  
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3 149 comprising disc/macular digital colour photographs and a 3D macular OCT were performed  
4  
5 150 on a subset of the UK Biobank participants – e.g., over 110,000 participants have completed  
6  
7 151 the visual acuity, refractive error, and intraocular pressure measurements; and ~67,000  
8  
9 152 participants underwent retinal imaging. Detailed information on the baseline eye and vision  
10  
11 153 measures has been published elsewhere [22].  
12  
13  
14

#### 15 154 *The Repeat Imaging Sub-study*

16  
17  
18 155 In 2014, UK Biobank launched the world's largest multimodal imaging study, intending to  
19  
20 156 include baseline magnetic resonance imaging (MRI) of the brain, heart and abdomen, whole-  
21  
22 157 body DEXA (Dual-energy x-ray absorptiometry) and carotid Doppler ultrasound on up to  
23  
24 158 100,000 participants. Detailed methods of the UK Biobank imaging enhancement were  
25  
26 159 published elsewhere.[25] Although imaging 100,000 participants is a unique and powerful  
27  
28 160 enhancement to the UKB resource, many valuable insights could only be gained from  
29  
30 161 observing the change in imaging phenotypes over time. Recognising the importance of serial  
31  
32 162 measurements, up to 60,000 of those in the imaging enhancement study will be invited to  
33  
34 163 undergo repeat multimodal imaging between 2019-2028. As part of the repeat imaging study,  
35  
36 164 data collection of the eye measures (e.g., OCT) is anticipated to take place from 2022-2028.  
37  
38  
39  
40

41 165 The specific study design is as follows:

- 42  
43 166 • All UK Biobank participants who have previously attended a baseline brain and body  
44  
45 167 imaging visit will be invited to attend a repeat imaging visit (the invitation will  
46  
47 168 specify the same imaging centre as their baseline imaging visit to minimize  
48  
49 169 measurement error caused by differences between scanners at different centres).
- 50  
51 170 • Appointment slots are planned in groups of 3 to minimize equipment downtime and to  
52  
53 171 maximize participant throughput and data quality.
- 54  
55 172 • On arrival, those who accept will be asked to consent to the study, and each  
56  
57 173 participant will then undergo a pre-screening safety assessment.  
58  
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- 1  
2  
3 174 • The 3 participants would then progress to the imaging modalities as follows:  
4  
5 175 ○ Participant #1 => Brain MRI  
6  
7  
8 176 ○ Participant #2 => Abdomen and heart MRI  
9  
10 177 ○ Participant #3 => DeXA, ultrasound and OCT  
11  
12 178 • Each imaging modality “group” takes approximately 40 minutes, after which the  
13  
14 179 participants will move to the next modality, then switch again after 40 minutes so that  
15  
16 180 each member of the group of 3 has visited all three imaging measurement stations  
17  
18 181 over a 2-hour period.  
19  
20  
21 182 • The participants then all progress to the non-imaging parts of the visit where they will  
22  
23 183 complete questionnaires, have physical measures, and give biological samples, which  
24  
25 184 mirrors much of the initial (2006-2010) baseline visit.  
26  
27  
28 185 • As one group of 3 participants exits the imaging part of the visit, the next group of 3  
29  
30 186 are ready to enter, thus ensuring that the imaging part of the visit is fully utilized.  
31  
32  
33 187 • This process will repeat for five groups of 3 people (15 total) on 7 days per week at  
34  
35 188 each of UK Biobank’s 4 dedicated imaging centres.  
36  
37

### 38 189 *Study location*

39  
40  
41 190 This multisite study will be run from four dedicated UK Biobank Imaging Centres across the  
42  
43 191 UK (Newcastle upon Tyne, Stockport, Reading and Bristol). These 4 centres help ensure  
44  
45 192 most participants are within a reasonable distance to attend a scanning visit. As far as is  
46  
47 193 reasonably practical, maintaining the same instruments and software/firmware across the sites  
48  
49 194 and all phases of the UK Biobank project will ensure consistency and comparability of results  
50  
51 195 from the start of the baseline imaging project to the end of the repeat imaging program. UK  
52  
53 196 Biobank built the following strategies to reduce variability across the different sites:  
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- 1  
2  
3 197 • The sites are each populated with the same equipment (same manufacturer, same  
4  
5 198 model, same software/firmware etc.) configured with the same protocols and the same  
6  
7 199 settings.  
8  
9  
10 200 • MR scanner settings/performance across all four sites is monitored by UK Biobank's  
11  
12 201 full-time in-house MR physicist with continuous quality assurance processes to  
13  
14 202 identify and resolve quality issues that may arise.  
15  
16  
17 203 • All staff are trained to standard operating procedures, and (in the case of the imaging  
18  
19 204 element) compliance/consistency is overseen by an in-house senior radiographer and  
20  
21 205 an in-house MR physicist. The non-imaging aspects are overseen by UK Biobank's  
22  
23 206 dedicated "Training and Monitoring" team.  
24  
25  
26 207 • Systems are already in place to ensure appropriate levels of training for all operational  
27  
28 208 staff, monitored via Clinic Training Assessments/Training Matrices. These will be  
29  
30 209 extended to cover the OCT measures: appropriate training will be provided, training  
31  
32 210 assessments/matrices extended to cover these measures, and performance monitored.  
33  
34  
35 211 • Imaging data are routinely made available to members of the project's expert working  
36  
37 212 group, which is made up of experts in each of the imaging modalities; this group  
38  
39 213 monitors the project progress, periodically provides training interventions and  
40  
41 214 critically, periodically/routinely provides an independent view of performance and  
42  
43 215 data output. A similar approach will be taken regarding the OCT measures with data  
44  
45 216 made available to the Eye Consortium members listed in this application for quality  
46  
47 217 control purposes.  
48  
49  
50

## 51 218 *Recruitment*

52  
53  
54 219 The UK Biobank cohort includes a committed and engaged group of participants who are  
55  
56 220 regularly invited for follow up activities: the typical response rate to online surveys is >50%,  
57  
58 221 and there have been very few withdrawals from the study since recruitment (<0.2%). Regular  
59  
60

1  
2  
3 222 communications with the cohort (via newsletters, participant meetings, study update meetings  
4  
5 223 and the participant section of the UK Biobank website: [www.ukbiobank.ac.uk/explore-your-](http://www.ukbiobank.ac.uk/explore-your-)  
6  
7 [participation](http://www.ukbiobank.ac.uk/explore-your-participation)) help to maintain enthusiasm for and engagement with the study. Direct  
8 224  
9  
10 225 telephone communication with individual participants regarding new sub-studies or general  
11  
12 226 participation questions via a dedicated “Participant Contact Centre” (PCC) provides  
13  
14  
15 227 personalized information and reassurance.

16  
17 228 This study will use the same invitation protocol as the UK Biobank imaging enhancement  
18  
19 229 study (2014-2023)[25]. The planned protocol for this repeat imaging study involves:

- 20  
21 230
- 22 • E-mail/postal explanation of the study and invitation to book an appointment
  - 23 231 • A telephone call to book an appointment and perform safety pre-screening via PRC
  - 24 232 • Assessment at the nearest of four imaging centres across the UK (Stockport,  
25  
26 233 Newcastle, Reading and Bristol) to minimize travel time and maximize participant  
27  
28  
29 234 attendance.

30  
31  
32  
33 235 At the start of the pandemic (lockdown in the UK in March 2020), 50,000 of the target  
34  
35 236 100,000 participants had been imaged. Participant questionnaires on completion of baseline  
36  
37 237 imaging visit indicate >90% would be happy to undertake a repeat imaging visit. Pilot studies  
38  
39 238 involving a few thousand participants have demonstrated ~60% acceptance rates, providing  
40  
41  
42 239 confidence that ~60,000 could be recruited for this repeat imaging study.

#### 43 44 45 240 *Examination procedures*

46  
47  
48 241 The whole-body imaging modalities have been extensively detailed elsewhere[25]; this  
49  
50 242 article only describes the scope of eye and vision measurements in the Repeat Imaging study.  
51  
52 243 The Topcon Triton OCT platform is being used to obtain OCT images in this study. The  
53  
54 244 Triton platform uses ultra-high-speed swept-source (SS) OCT technology with a central  
55  
56 245 wavelength of 1050 microns that penetrates deeper than the retina, allowing visualization of  
57  
58  
59 246 the choroid and the vasculature therein.[26] The platform also takes colour retinal fundus  
60

1  
2  
3 247 photographs immediately after the OCT scans, allowing measurement of the optic disc and  
4  
5 248 retinal vessel metrics (including retinal vessel calibre and tortuosity). The Topcon Triton  
6  
7  
8 249 supports wide-angle 12 mm x 9 mm scans that include the optic disc and macula in a single  
9  
10 250 scan.

11  
12 251 Widefield SS-OCT enables quantitative measurements of several candidate biomarkers,  
13  
14 252 including but not limited to total macular retinal thickness, macular inner retinal sublayer  
15  
16 253 thicknesses, peripapillary retinal nerve fibre layer thickness, choroidal vascularity index,  
17  
18 254 retinal arteriolar and retinal venular calibres, retinal vascular fractal dimension, retinal  
19  
20 255 vascular tortuosity. Details of the candidate biomarkers are summarized in Table 1.  
21  
22

#### 23 24 256 *OCT Image Processing*

25  
26  
27 257 Total retinal thickness and segmented values for retinal sublayer thicknesses for macula and  
28  
29 258 optic nerve scans are generated by the current generation OCT devices, using FDA approved  
30  
31 259 algorithms, during the examination. In contrast to the processing of baseline UK Biobank  
32  
33 260 macular OCT scans[27], they do not generally require the development of new processing  
34  
35 261 pipelines (apart from measures of the choroidal vascular layer, which are now possible thanks  
36  
37 262 to greater depth of imaging than was previously possible with older OCT technology).  
38  
39

40  
41 263 Fundamental to both the challenge and the opportunity that would be provided by UK  
42  
43 264 Biobank OCT imaging is that modern retinal imaging software can measure changes that  
44  
45 265 would be imperceptible to, or missed by, a human grader. In operations featuring large-scale  
46  
47 266 data collection, a small proportion of the imaging is likely to be insufficient quality for  
48  
49 267 automated analysis. Problems may also arise with image acquisition, for instance, due to  
50  
51 268 some study participants presenting with ocular pathology. Thus, the first step in an analysis  
52  
53 269 pipeline is to assess the image quality and discard images that cannot be adequately  
54  
55 270 measured. Subsequent analysis of vasculometrics from retinal photographs would include  
56  
57 271 automated vessel segmentation followed by classification of arterioles and venules (see  
58  
59  
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1  
2  
3 272 below). For OCT, algorithms delineate the borders of the internal limiting membrane (ILM)  
4  
5 273 and the RNFL to give the measurement of RNFL thickness, a biomarker of axonal loss  
6  
7 274 affecting retinal ganglion cells and the optic nerves. The thickness of the RNFL is evaluated  
8  
9  
10 275 using the standard TSNIT (temporal, superior, nasal, inferior, temporal) mapping that  
11  
12 276 subdivides the measurements and colour codes statistical significance compared with a  
13  
14 277 database of normal healthy values. Further delineation of boundaries enables quantitative  
15  
16 278 mapping of the ganglion cell layer (GCL) and inner plexiform layer (IPL) thicknesses, a  
17  
18 279 marker of neuronal somatic loss [13, 28].  
19  
20  
21 280 Although the processing of quantitative retinal vasculometric data is not routinely used in  
22  
23 281 clinical settings, we have developed and validated a fully automated AI-enabled retinal image  
24  
25 282 analysis system (QUARTZ) for extracting vessel maps and quantifying retinal vasculometry  
26  
27 283 (including vessel size and tortuosity), which we will use to create the image processing  
28  
29 284 pipeline. The system overcomes many of the difficulties of earlier vasculometry approaches,  
30  
31 285 particularly by being fully automated.[29, 30] QUARTZ has been demonstrated to be highly  
32  
33 286 robust, capable of processing large datasets with automated image quality assessments,  
34  
35 287 resulting in accurate, reliable and high levels of vessel segmentation. To date, QUARTZ has  
36  
37 288 measured approximately 4 million vessel segments from over 190,000 images from 95,000  
38  
39 289 participants of two very large population-based cohorts (UK Biobank and EPIC-Norfolk).  
40  
41  
42 290 This system has been developed specifically for use on TOPCON macular centred images.  
43  
44 291 In brief, the QUARTZ system distinguishes between right and left eyes, venules and  
45  
46 292 arterioles (with 87% accuracy using AI-enabled deep learning), identifies vessel segments  
47  
48 293 and centreline coordinates and outputs measures of vessel width and tortuosity (based on the  
49  
50 294 mean change in chord length between successive divisions of the vessel).[31, 32] The system  
51  
52 295 obtains 10-20 thousands of measurements of width and tortuosity from the whole retinal  
53  
54 296 image (dependent on image quality), not just selected vessels lying within concentric areas  
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3 297 centred on the disc. Measures are summarized using mean width and tortuosity, weighted by  
4  
5 298 segment length, for arterioles and venules separately for each image. QUARTZ measures in  
6  
7 299 UK Biobank have previously shown that venular width and tortuosity are associated with  
8  
9 300 markers of adiposity[33] and that both arteriolar and venular width and arteriolar tortuosity  
10  
11 301 show strong inverse associations with blood pressure (systolic and diastolic) and arterial  
12  
13 302 stiffness index.[34] More importantly, prognostic models using QUARTZ vasculometry  
14  
15 303 measures perform very well at predicting circulatory mortality and at least as well as  
16  
17 304 established risk scores in the prediction of stroke and myocardial infarction, remarkably  
18  
19 305 without the need for either a blood test or blood pressure measurement.[35] Given the  
20  
21 306 identification of vessel maps, these could be inputted into other systems (i.e., the VAMPIRE  
22  
23 307 system) with additional vasculometry summaries, such as fractal analyses to quantify the  
24  
25 308 complexity of the arteriolar and venular components of the retinal vascular network.  
26  
27 309 Marrying the automated functionality of QUARTZ with VAMPIRE will afford a more in-  
28  
29 310 depth characterization of the vessel complex on an unprecedented scale.  
30  
31 311 The VAMPIRE (Vascular Assessment and Measurement Platform for Images of the REtina)  
32  
33 312 system is an international collaborative project designed to quantify retinal vascular  
34  
35 313 morphometry with large collections of fundus photographs. The system provides automatic  
36  
37 314 detection of retinal landmarks and quantifies some key parameters used frequently in  
38  
39 315 investigative studies - vessel width, vessel branching coefficients, tortuosity, and fractal  
40  
41 316 analyses. Detailed definitions have been reported elsewhere.[36, 37] In general, it computes  
42  
43 317 149 measurements per image, including basic statistics. Thirty-nine are width-related: central  
44  
45 318 retinal arteriolar equivalent (CRAE), central retinal venular equivalent (CRVE), retinal  
46  
47 319 arteriovenous ratio (AVR), basic statistics (mean, median, standard deviation, maximum,  
48  
49 320 minimum), width gradients along vessels, average ratio length-diameter at branching points,  
50  
51 321 by arteries and veins; 104 are tortuosity measurements, computed by different algorithms and  
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3 322 with the statistics listed above; 6 are fractal dimension coefficients. All measures are  
4  
5 323 calculated by vessel type (arteriole or venule) and region (zone, whole image, quadrants).  
6  
7 324 VAMPIRE is a validated software application and has been extensively used in several  
8  
9 325 international studies.[36, 38, 39]  
10  
11  
12

### 13 326 *Patient and public involvement*

14  
15 327 UK Biobank maintains a website to keep participants and researchers up to date on the study  
16  
17 328 (<http://www.ukbiobank.ac.uk/news/>). Eye and vision-related publications resulting from UK  
18  
19 329 Biobank are maintained at (<https://www.ukbiobankeyeconsortium.org.uk/publications>). UK  
20  
21 330 Biobank also holds regular events to inform the participants about the imaging study and the  
22  
23 331 latest research. In addition, UK Biobank has a Twitter feed (@uk\_biobank). The study was  
24  
25 332 set up by the Medical Research Council (MRC), Department of Health (DoH), and Wellcome  
26  
27 333 Trust with input from major patient representative organizations. An annual scientific  
28  
29 334 meeting is recorded and available to the public as a webcast.  
30  
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### 34 335 *Statistical Analysis Plan*

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37 336 Baseline ocular characteristics will be summarized as mean (standard deviation) for  
38  
39 337 continuous variables and number (%) for categorical variables.  
40  
41

42 338 Primary aims would be to examine:

- 43  
44 339 1) cross-sectional associations between retinal biomarkers, measures of cognitive  
45  
46 340 performance and brain-volume from MRI imaging
- 47  
48 341 2) the comparative performance of retinal biomarkers for risk stratification, to identify  
49  
50 342 those with cognitive impairment
- 51  
52 343 3) the comparative performance of retinal biomarkers to detect those with longitudinal  
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54 344 decline in cognitive performance  
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3 345 Previous work within UK Biobank examining RNFL measures in relation to mild cognitive  
4  
5 346 impairment, showed that those in the lowest quintile of RNFL thickness were 11% (95%CI:  
6  
7 347 2% to 21%) more likely to fail on at least one of four cognitive tests.[40] This shows that  
8  
9 348 RNFL measures have the potential to identify those at higher risk of cognitive impairment.  
10  
11 349 After vigorous image quality control, the proposed imaging of a further 60,000 participants  
12  
13 350 will provide 45,000-55,000 participants with good-quality retinal images for quantification of  
14  
15 351 individual components of the RNFL and potential to extract detailed retinal vasculometric  
16  
17 352 measures. This large sample size, will have 99% power ( $\alpha = 0.001$ ) to detect at least 0.03  
18  
19 353 standard deviation change in the cognitive score[41] or brain measures[42] per 1 standard  
20  
21 354 deviation increase in any retinal biomarker (RNFL or retinal vasculometric measure). Cross-  
22  
23 355 sectional analyses using multiple linear regression will quantify the dose response  
24  
25 356 relationship between cognitive score with considerable power to evaluate in the region of 30  
26  
27 357 candidate predictors (retinal biomarkers, age, sex, geographical location, height, refraction,  
28  
29 358 intraocular pressure, smoking status, socioeconomic positions and established cardiovascular  
30  
31 359 risk markers).[43] This will allow the independent contribution of retinal biomarkers as a  
32  
33 360 predictor of cognitive performance to be realized with considerable precision,[44] across a  
34  
35 361 spectrum of cognitive scores.[43]  
36  
37 362 Given that UK Biobank has longitudinal data on cognitive change (with repeated measures  
38  
39 363 available from online questionnaires and performed in-person at the imaging assessments),  
40  
41 364 the study would be uniquely placed to assess the determinants of cognitive decline in middle-  
42  
43 365 later life. For prospective evaluation the rates of dementia would also be pivotal in relation to  
44  
45 366 prior cognitive performance. In UK Biobank, the annual incidence of dementia among those  
46  
47 367 aged  $\geq 60$  years old is approximately 2.5 per 1000 person years.[45] Therefore, within 2 years  
48  
49 368 of retinal image capture there would be approximately 250 cases of dementia per 45,000-  
50  
51 369 55,000 participants.  
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3 370 *Existing Data*  
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6 371 Once recruitment was fully under way, additional measures were incorporated into the  
7  
8 372 baseline assessment, including hearing and arterial stiffness tests, a cardiorespiratory fitness  
9  
10 373 test, and various eye and vision measures, including visual acuity on a computerised system  
11  
12 374 designed to observe logMAR principles, and following the British Standard (BS-1968),[46]  
13  
14 375 autorefraction and keratometry, intraocular pressure and corneal biomechanics, and retinal  
15  
16 376 imaging comprising disc/macular digital colour photographs and a 3D macular OCT.[22]  
17  
18 377 After the baseline visit, subsets of participants have supported additional data collection  
19  
20 378 through various enhancements to the study. These have included: a complete repeat of the  
21  
22 379 baseline assessment, collection of physical activity data over 7-days by wearing  
23  
24 380 accelerometers, and regular online questionnaires covering various topics such as diet,  
25  
26 381 cognitive function, occupational history, mental wellbeing, gastrointestinal health and pain.  
27  
28 382 All participants provided consent for their health to be followed-up through linkage to health-  
29  
30 383 related records, which currently includes death, cancer, and hospital inpatient records for the  
31  
32 384 entire cohort. Although UK Biobank is not representative of the entire UK population, the  
33  
34 385 large sample size and variation across all levels of measures nonetheless enable a valid  
35  
36 386 assessment of many exposure-outcome relationships to be made. All publications using UK  
37  
38 387 Biobank data are available on the website ([https://www.ukbiobank.ac.uk/enable-your-](https://www.ukbiobank.ac.uk/enable-your-research/publications)  
39  
40 388 [research/publications](https://www.ukbiobank.ac.uk/enable-your-research/publications)). Eye and vision-related publications resulting from UK Biobank is  
41  
42 389 maintained at (<https://www.ukbiobankeyeconsortium.org.uk/publications>).  
43  
44 390 Baseline characteristics of the study participants were summarized in Table 2. In addition to  
45  
46 391 imaging, UK Biobank has implemented a wide range of cognitive function tests since  
47  
48 392 baseline that are relevant to assessing various aspects of cognitive decline and dementia and  
49  
50 393 will be conducted at the repeat imaging and proposed OCT visit (Table 3).  
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59 394 **FINDINGS TO DATE**  
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3 395 UK Biobank has helped make significant advances in the understanding of risk factors for  
4  
5 396 diseases including cardiovascular diseases, cancer, diabetes, stroke, multiple sclerosis, optic  
6  
7 397 neuritis and dementia.[23, 47-57] Ophthalmic genetics and epidemiology have benefited from  
8  
9  
10 398 the unparalleled combination of very large numbers of participants, very extensive and  
11  
12 399 detailed phenotyping and longitudinal follow-up.[30, 58-62]

13  
14 400 In addition, we have used UK Biobank data to describe the relationship between retinal  
15  
16 401 structures and both cognitive function and brain MR image-derived phenotypes.[40, 42] For  
17  
18 402 example, previous work examining RNFL measures in relation to mild cognitive impairment,  
19  
20 403 showed that those in the lowest quintile of RNFL thickness were 11% (95% CI 2.0% to 2.1%)  
21  
22 404 more likely to fail on at least one of four cognitive tests.[40] This indicates that RNFL thickness  
23  
24 405 measurements have the potential to identify those at higher risk of cognitive impairment. Chua  
25  
26 406 *et al* [42] reported that markers of retinal neurodegeneration are associated with smaller brain  
27  
28 407 volumes – macular ganglion cell-inner plexiform layer (GCIPL) thickness, ganglion cell  
29  
30 408 complex (GCC) thickness and total macular thickness were significantly associated with  
31  
32 409 smaller total brain ( $p < 0.001$ ), grey matter and white matter volume ( $p < 0.01$ ), and grey matter  
33  
34 410 volume in the occipital pole ( $p < 0.05$ ); thinner macular GCC and total macular thicknesses  
35  
36 411 were associated with smaller hippocampal volume ( $p < 0.02$ ).

37  
38 412 In the context of these results, and the findings of other studies (e.g. The Rotterdam  
39  
40 413 Study),[63-65] we proposed supplementing the testing menu in the UK Biobank Whole Body  
41  
42 414 Repeat Imaging Study with measures that support the discovery and quantification of eye and  
43  
44 415 vision variables that are associated with cognitive ageing and decline, and overt dementia.

## 51 52 416 **COLLABORATION**

53  
54 417 UK Biobank aims to provide open access data for healthcare-related research. The data are  
55  
56 418 available to all bona fide researchers from the academic, charity, public and commercial  
57  
58 419 sectors in the UK and internationally, without preferential or exclusive access for any  
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3 420 user.[66] All interested researchers may apply to access the data via an online application.  
4  
5 421 Strict guidelines are in place to help ensure anonymity and confidentiality of participants'  
6  
7 422 data and samples.[67] We have formed the UK Biobank Eye and Vision Consortium, an 80  
8  
9  
10 423 person strong group of researchers with interest and expertise in ophthalmic epidemiology,  
11  
12 424 visual system neurology, and the epidemiology of related diseases such as diabetes and  
13  
14 425 cardiovascular disease (<https://www.ukbiobankeyeconsortium.org.uk/>).

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30  
31

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33 434 This research used data from the UK Biobank Resource, under data access request number  
34  
35 435 2112.  
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41 437 PJF, APK, PJP & ZS had full access to all the data in the study and take responsibility for the  
42  
43 438 integrity and accuracy of the data analysis. Concept and design: PJF, DA, APK, AJL, TM,  
44  
45 439 CGO, PJP, AP, ARR. Data acquisition, analysis, or interpretation: UK Biobank obtained the  
46  
47 440 data. APK performed data analysis. All authors interpreted data. Critical revision of the  
48  
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50  
51 442 Biobank. All authors approved the final manuscript.  
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## 475 REFERENCES

476

- 477 1. Reitz C, Mayeux R: **Alzheimer disease: epidemiology, diagnostic criteria, risk factors**  
478 **and biomarkers.** *Biochemical pharmacology* 2014, **88**(4):640-651.
- 479 2. Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC, Marcus DS, Cairns  
480 NJ, Xie X, Blazey TM: **Clinical and biomarker changes in dominantly inherited**  
481 **Alzheimer's disease.** *N Engl J Med* 2012, **367**:795-804.
- 482 3. Tahami Monfared AA, Byrnes MJ, White LA, Zhang Q: **Alzheimer's Disease:**  
483 **Epidemiology and Clinical Progression.** *Neurol Ther* 2022, **11**(2):553-569.
- 484 4. Kalaria RN, Maestre GE, Arizaga R, Friedland RP, Galasko D, Hall K, Luchsinger JA,  
485 Ogunniyi A, Perry EK, Potocnik F: **Alzheimer's disease and vascular dementia in**  
486 **developing countries: prevalence, management, and risk factors.** *The Lancet*  
487 *Neurology* 2008, **7**(9):812-826.
- 488 5. Collaborators G: **Global, regional, and national burden of Alzheimer's disease and**  
489 **other dementias, 1990-2016: a systematic analysis for the Global Burden of**  
490 **Disease Study 2016.** *Lancet Neurol* 2019, **18**(1):88-106.
- 491 6. Jack Jr CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, Holtzman  
492 DM, Jagust W, Jessen F, Karlawish J: **NIA-AA research framework: toward a**  
493 **biological definition of Alzheimer's disease.** *Alzheimer's & Dementia* 2018,  
494 **14**(4):535-562.
- 495 7. Mehta D, Jackson R, Paul G, Shi J, Sabbagh M: **Why do trials for Alzheimer's disease**  
496 **drugs keep failing? A discontinued drug perspective for 2010-2015.** *Expert opinion*  
497 *on investigational drugs* 2017, **26**(6):735-739.
- 498 8. Gómez-Isla T, Price JL, McKeel Jr DW, Morris JC, Growdon JH, Hyman BT: **Profound**  
499 **loss of layer II entorhinal cortex neurons occurs in very mild Alzheimer's disease.**  
500 *Journal of Neuroscience* 1996, **16**(14):4491-4500.
- 501 9. Long JM, Holtzman DM: **Alzheimer disease: an update on pathobiology and**  
502 **treatment strategies.** *Cell* 2019, **179**(2):312-339.
- 503 10. Dubois B, Villain N, Frisoni GB, Rabinovici GD, Sabbagh M, Cappa S, Bejanin A,  
504 Bombois S, Epelbaum S, Teichmann M: **Clinical diagnosis of Alzheimer's disease:**  
505 **recommendations of the International Working Group.** *The Lancet Neurology* 2021,  
506 **20**(6):484-496.
- 507 11. Cheung CY-I, Ikram MK, Sabanayagam C, Wong TY: **Retinal microvasculature as a**  
508 **model to study the manifestations of hypertension.** *Hypertension* 2012, **60**(5):1094-  
509 1103.
- 510 12. Lesage S, Mosley T, Wong T, Szklo M, Knopman D, Catellier DJ, Cole S, Klein R, Coresh  
511 J, Coker L: **Retinal microvascular abnormalities and cognitive decline: the ARIC 14-**  
512 **year follow-up study.** *Neurology* 2009, **73**(11):862-868.
- 513 13. Petzold A, Balcer LJ, Calabresi PA, Costello F, Frohman TC, Frohman EM, Martinez-  
514 Lapiscina EH, Green AJ, Kardon R, Outteryck O: **Retinal layer segmentation in**  
515 **multiple sclerosis: a systematic review and meta-analysis.** *The Lancet Neurology*  
516 2017, **16**(10):797-812.
- 517 14. O'Bryhim BE, Apte RS, Kung N, Coble D, Van Stavern GP: **Association of preclinical**  
518 **Alzheimer disease with optical coherence tomographic angiography findings.** *JAMA*  
519 *ophthalmology* 2018, **136**(11):1242-1248.



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- 520 15. Mutlu U, Colijn JM, Ikram MA, Bonnemaier PW, Licher S, Wolters FJ, Tiemeier H,  
521 Koudstaal PJ, Klaver CC, Ikram MK: **Association of retinal neurodegeneration on**  
522 **optical coherence tomography with dementia: a population-based study.** *JAMA*  
523 *neurology* 2018, **75**(10):1256-1263.
- 524 16. Masuzzo A, Dinet V, Cavanagh C, Mascarelli F, Krantic S: **Amyloidosis in retinal**  
525 **neurodegenerative diseases.** *Frontiers in Neurology* 2016, **7**:127.
- 526 17. Reitz C, Brayne C, Mayeux R: **Epidemiology of Alzheimer disease.** *Nature Reviews*  
527 *Neurology* 2011, **7**(3):137-152.
- 528 18. Lambert J-C, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, Jun G,  
529 DeStefano AL, Bis JC, Beecham GW: **Meta-analysis of 74,046 individuals identifies**  
530 **11 new susceptibility loci for Alzheimer's disease.** *Nature genetics* 2013,  
531 **45**(12):1452-1458.
- 532 19. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C: **Potential for primary**  
533 **prevention of Alzheimer's disease: an analysis of population-based data.** *The*  
534 *Lancet Neurology* 2014, **13**(8):788-794.
- 535 20. Larsson SC, Traylor M, Malik R, Dichgans M, Burgess S, Markus HS: **Modifiable**  
536 **pathways in Alzheimer's disease: Mendelian randomisation analysis.** *bmj* 2017,  
537 **359**.
- 538 21. Bowen M, Zutshi H, Cordiner M, Crutch S, Shakespeare T: **Qualitative, exploratory**  
539 **pilot study to investigate how people living with posterior cortical atrophy, their**  
540 **carers and clinicians experience tests used to assess vision.** *BMJ open* 2019,  
541 **9**(3):e020905.
- 542 22. Chua SYL, Thomas D, Allen N, Lotery A, Desai P, Patel P, Muthy Z, Sudlow C, Peto T,  
543 Khaw PT: **Cohort profile: design and methods in the eye and vision consortium of**  
544 **UK Biobank.** *BMJ open* 2019, **9**(2):e025077.
- 545 23. Littlejohns TJ, Sudlow C, Allen NE, Collins R: **UK Biobank: opportunities for**  
546 **cardiovascular research.** *European heart journal* 2019, **40**(14):1158-1166.
- 547 24. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, Motyer A, Vukcevic D,  
548 Delaneau O, O'Connell J: **The UK Biobank resource with deep phenotyping and**  
549 **genomic data.** *Nature* 2018, **562**(7726):203-209.
- 550 25. Littlejohns TJ, Holliday J, Gibson LM, Garratt S, Oesingmann N, Alfaro-Almagro F, Bell  
551 JD, Boultonwood C, Collins R, Conroy MC: **The UK Biobank imaging enhancement of**  
552 **100,000 participants: rationale, data collection, management and future directions.**  
553 *Nature communications* 2020, **11**(1):1-12.
- 554 26. Huber R, Wojtkowski M, Fujimoto JG, Jiang J, Cable A: **Three-dimensional and C-**  
555 **mode OCT imaging with a compact, frequency swept laser source at 1300 nm.**  
556 *Optics express* 2005, **13**(26):10523-10538.
- 557 27. Keane PA, Grossi CM, Foster PJ, Yang Q, Reisman CA, Chan K, Peto T, Thomas D, Patel  
558 PJ, Consortium UBEV: **Optical coherence tomography in the UK biobank study—**  
559 **rapid automated analysis of retinal thickness for large population-based studies.**  
560 *PLoS One* 2016, **11**(10):e0164095.
- 561 28. Cruz-Herranz A, Balk LJ, Oberwahrenbrock T, Saidha S, Martinez-Lapiscina EH,  
562 Lagreze WA, Schuman JS, Villoslada P, Calabresi P, Balcer L: **The APOSTEL**  
563 **recommendations for reporting quantitative optical coherence tomography**  
564 **studies.** *Neurology* 2016, **86**(24):2303-2309.
- 565 29. Welikala R, Fraz M, Habib M, Daniel-Tong S, Yates M, Foster P, Whincup P, Rudnicka  
566 AR, Owen CG, Strachan D: **Automated quantification of retinal vessel morphometry**

- 1  
2  
3 567 **in the UK Biobank Cohort.** In: *2017 Seventh International Conference on Image*  
4 568 *Processing Theory, Tools and Applications (IPTA): 2017*: IEEE; 2017: 1-6.
- 5 569 30. Welikala R, Fraz M, Foster P, Whincup P, Rudnicka AR, Owen CG, Strachan D, Barman  
6 570 **SA: Automated retinal image quality assessment on the UK Biobank dataset for**  
7 571 **epidemiological studies.** *Computers in biology and medicine* 2016, **71**:67-76.
- 8 572 31. Fraz MM, Welikala R, Rudnicka AR, Owen CG, Strachan D, Barman SA: **QUARTZ:**  
9 573 **Quantitative Analysis of Retinal Vessel Topology and size—an automated system for**  
10 574 **quantification of retinal vessels morphology.** *Expert Systems with Applications* 2015,  
11 575 **42**(20):7221-7234.
- 12 576 32. Welikala R, Foster P, Whincup P, Rudnicka AR, Owen CG, Strachan D, Barman S:  
13 577 **Automated arteriole and venule classification using deep learning for retinal**  
14 578 **images from the UK Biobank cohort.** *Computers in biology and medicine* 2017,  
15 579 **90**:23-32.
- 16 580 33. Tapp RJ, Owen CG, Barman SA, Welikala RA, Foster PJ, Whincup PH, Strachan DP,  
17 581 Rudnicka AR, UK Biobank Eye VC: **Retinal vascular tortuosity and diameter**  
18 582 **associations with adiposity and components of body composition.** *Obesity* 2020,  
19 583 **28**(9):1750-1760.
- 20 584 34. Tapp RJ, Owen CG, Barman SA, Welikala RA, Foster PJ, Whincup PH, Strachan DP,  
21 585 Rudnicka AR: **Associations of Retinal Microvascular Diameters and Tortuosity With**  
22 586 **Blood Pressure and Arterial Stiffness: United Kingdom Biobank.** *Hypertension* 2019,  
23 587 **74**(6):1383-1390.
- 24 588 35. Rudnicka AR, Welikala R, Barman S, Foster PJ, Luben R, Hayat S, Khaw KT, Whincup P,  
25 589 Strachan D, Owen CG: **Artificial intelligence-enabled retinal vasculometry for**  
26 590 **prediction of circulatory mortality, myocardial infarction and stroke.** *Br J*  
27 591 *Ophthalmol* 2022.
- 28 592 36. McGrory S, Taylor AM, Pellegrini E, Ballerini L, Kirin M, Doubal FN, Wardlaw JM,  
29 593 Doney AS, Dhillon B, Starr JM: **Towards standardization of quantitative retinal**  
30 594 **vascular parameters: comparison of SIVA and VAMPIRE measurements in the**  
31 595 **Lothian Birth Cohort 1936.** *Translational vision science & technology* 2018, **7**(2):12-  
32 596 12.
- 33 597 37. Perez-Rovira A, MacGillivray T, Trucco E, Chin K, Zutis K, Lupascu C, Tegolo D,  
34 598 Giachetti A, Wilson PJ, Doney A: **VAMPIRE: vessel assessment and measurement**  
35 599 **platform for images of the RETina.** In: *2011 Annual International Conference of the*  
36 600 *IEEE Engineering in Medicine and Biology Society: 2011*: IEEE; 2011: 3391-3394.
- 37 601 38. Remond P, Aptel F, Cunnac P, Labarere J, Palombi K, Pepin J-L, Pollet-Villard F, Hogg  
38 602 S, Wang R, MacGillivray T: **Retinal vessel phenotype in patients with nonarteritic**  
39 603 **anterior ischemic optic neuropathy.** *American journal of ophthalmology* 2019,  
40 604 **208**:178-184.
- 41 605 39. Azanan MS, Chandrasekaran S, Rosli ES, Chua LL, Oh L, Chin TF, Yap TY, Rajagopal R,  
42 606 Rajasuriar R, MacGillivray T: **Retinal Vessel Analysis as a Novel Screening Tool to**  
43 607 **Identify Childhood Acute Lymphoblastic Leukemia Survivors at Risk of**  
44 608 **Cardiovascular Disease.** *Journal of pediatric hematology/oncology* 2020, **42**(6):e394-  
45 609 e400.
- 46 610 40. Ko F, Muthy ZA, Gallacher J, Sudlow C, Rees G, Yang Q, Keane PA, Petzold A, Khaw  
47 611 PT, Reisman C: **Association of retinal nerve fiber layer thinning with current and**  
48 612 **future cognitive decline: a study using optical coherence tomography.** *JAMA*  
49 613 *neurology* 2018, **75**(10):1198-1205.

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2  
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54  
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57  
58  
59  
60

- 614 41. Cornelis MC, Wang Y, Holland T, Agarwal P, Weintraub S, Morris MC: **Age and cognitive decline in the UK Biobank.** *PloS one* 2019, **14**(3):e0213948.
- 615
- 616 42. Chua SY, Lascaratos G, Atan D, Zhang B, Reisman C, Khaw PT, Smith SM, Matthews PM, Petzold A, Strouthidis NG: **Relationships between retinal layer thickness and brain volumes in the UK Biobank cohort.** *European Journal of Neurology* 2021, **28**(5):1490-1498.
- 617
- 618
- 619
- 620 43. Lyall DM, Cullen B, Allerhand M, Smith DJ, Mackay D, Evans J, Anderson J, Fawns-Ritchie C, McIntosh AM, Deary IJ: **Cognitive test scores in UK Biobank: data reduction in 480,416 participants and longitudinal stability in 20,346 participants.** *PloS one* 2016, **11**(4):e0154222.
- 621
- 622
- 623
- 624 44. Riley RD, Snell KI, Ensor J, Burke DL, Harrell Jr FE, Moons KG, Collins GS: **Minimum sample size for developing a multivariable prediction model: PART II-binary and time-to-event outcomes.** *Statistics in medicine* 2019, **38**(7):1276-1296.
- 625
- 626
- 627 45. Petermann-Rocha F, Lyall DM, Gray SR, Esteban-Cornejo I, Quinn TJ, Ho FK, Pell JP, Celis-Morales C: **Associations between physical frailty and dementia incidence: a prospective study from UK Biobank.** *The Lancet Healthy Longevity* 2020, **1**(2):e58-e68.
- 628
- 629
- 630
- 631 46. Standard B: **Test charts for determining distance visual acuity: BS 4274-1968.** *British Standards Institute* 1968.
- 632
- 633 47. Tikkanen E, Gustafsson S, Ingelsson E: **Associations of fitness, physical activity, strength, and genetic risk with cardiovascular disease: longitudinal analyses in the UK Biobank Study.** *Circulation* 2018, **137**(24):2583-2591.
- 634
- 635
- 636 48. Perez-Cornago A, Key TJ, Allen NE, Fensom GK, Bradbury KE, Martin RM, Travis RC: **Prospective investigation of risk factors for prostate cancer in the UK Biobank cohort study.** *British journal of cancer* 2017, **117**(10):1562-1571.
- 637
- 638
- 639 49. Allen NE, Sudlow C, Peakman T, Collins R, biobank U: **UK biobank data: come and get it.** In., vol. 6: American Association for the Advancement of Science; 2014: 224ed224-224ed224.
- 640
- 641
- 642 50. Ntuk UE, Gill JM, Mackay DF, Sattar N, Pell JP: **Ethnic-specific obesity cutoffs for diabetes risk: cross-sectional study of 490,288 UK biobank participants.** *Diabetes care* 2014, **37**(9):2500-2507.
- 643
- 644
- 645 51. Millett ER, Peters SA, Woodward M: **Sex differences in risk factors for myocardial infarction: cohort study of UK Biobank participants.** *bmj* 2018, **363**.
- 646
- 647 52. Gallacher KI, McQueenie R, Nicholl B, Jani BD, Lee D, Mair FS: **Risk factors and mortality associated with multimorbidity in people with stroke or transient ischaemic attack: a study of 8,751 UK Biobank participants.** *Journal of comorbidity* 2018, **8**(1):1-8.
- 648
- 649
- 650
- 651 53. Ma H, Li X, Sun D, Zhou T, Ley SH, Gustat J, Heianza Y, Qi L: **Association of habitual glucosamine use with risk of cardiovascular disease: prospective study in UK Biobank.** *bmj* 2019, **365**.
- 652
- 653
- 654 54. Gao L, Li P, Cui L, Wong PM, Johnson-Akeju O, Lane J, Saxena R, Scheer F, Hu K: **Sleep disturbance and incident Alzheimer's disease: A UK Biobank study of 502,538 middle-aged to older participants: Biomarkers (non-neuroimaging): Alzheimer's disease incidence, risk factors and biomarkers.** *Alzheimer's & Dementia* 2020, **16**:e044575.
- 655
- 656
- 657
- 658
- 659 55. Veronese N, Yang L, Piccio L, Smith L, Firth J, Marx W, Giannelli G, Caruso MG, Cisternino AM, Notarnicola M: **Adherence to a healthy lifestyle and multiple**
- 660

- 1  
2  
3 661        **sclerosis: a case–control study from the UK Biobank.** *Nutritional neuroscience*  
4 662        2020:1-9.
- 5 663        56.        Petzold A, Chua SY, Khawaja AP, Keane PA, Khaw PT, Reisman C, Dhillon B,  
6 664        Strouthidis NG, Foster PJ, Patel PJ: **Retinal asymmetry in multiple sclerosis.** *Brain*  
7 665        2021, **144**(1):224-235.
- 8 666        57.        Petzold A, Fraser CL, Abegg M, Alroughani R, Alshowaeir D, Alvarenga R, Andris C,  
9 667        Asgari N, Barnett Y, Battistella R: **Diagnosis and classification of optic neuritis.** *The*  
10 668        *Lancet Neurology* 2022.
- 11 669        58.        Cumberland PM, Rahi JS: **Visual function, social position, and health and life**  
12 670        **chances: the UK biobank study.** *JAMA ophthalmology* 2016, **134**(9):959-966.
- 13 671        59.        Chan MP, Grossi CM, Khawaja AP, Yip JL, Khaw K-T, Patel PJ, Khaw PT, Morgan JE,  
14 672        Vernon SA, Foster PJ: **Associations with intraocular pressure in a large cohort:**  
15 673        **results from the UK Biobank.** *Ophthalmology* 2016, **123**(4):771-782.
- 16 674        60.        Shah RL, Guggenheim JA: **Genome-wide association studies for corneal and**  
17 675        **refractive astigmatism in UK Biobank demonstrate a shared role for myopia**  
18 676        **susceptibility loci.** *Human genetics* 2018, **137**(11):881-896.
- 19 677        61.        Wood A, Guggenheim JA: **Refractive error has minimal influence on the risk of age-**  
20 678        **related macular degeneration: a Mendelian randomization study.** *American journal*  
21 679        *of ophthalmology* 2019, **206**:87-93.
- 22 680        62.        Craig JE, Han X, Qassim A, Hassall M, Cooke Bailey JN, Kinzy TG, Khawaja AP, An J,  
23 681        Marshall H, Gharahkhani P: **Multitrait analysis of glaucoma identifies new risk loci**  
24 682        **and enables polygenic prediction of disease susceptibility and progression.** *Nature*  
25 683        *genetics* 2020, **52**(2):160-166.
- 26 684        63.        de Jong FJ, Schrijvers EM, Ikram MK, Koudstaal PJ, de Jong PT, Hofman A, Vingerling  
27 685        JR, Breteler MM: **Retinal vascular caliber and risk of dementia: the Rotterdam**  
28 686        **study.** *Neurology* 2011, **76**(9):816-821.
- 29 687        64.        Mutlu U, Cremers LG, De Groot M, Hofman A, Niessen WJ, Van Der Lugt A, Klaver CC,  
30 688        Ikram MA, Vernooij MW, Ikram MK: **Retinal microvasculature and white matter**  
31 689        **microstructure: the Rotterdam Study.** *Neurology* 2016, **87**(10):1003-1010.
- 32 690        65.        Mutlu U, Bonnemaier PW, Ikram MA, Colijn JM, Cremers LG, Buitendijk GH,  
33 691        Vingerling JR, Niessen WJ, Vernooij MW, Klaver CC: **Retinal neurodegeneration and**  
34 692        **brain MRI markers: the Rotterdam Study.** *Neurobiology of aging* 2017, **60**:183-191.
- 35 693        66.        Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green  
36 694        J, Landray M: **UK biobank: an open access resource for identifying the causes of a**  
37 695        **wide range of complex diseases of middle and old age.** *PLoS medicine* 2015,  
38 696        **12**(3):e1001779.
- 39 697        67.        Biobank U: **UK Biobank ethics and governance framework.** In.; 2015.
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# BMJ Open

## Cohort Profile: Rationale and Methods of UK Biobank Repeat Imaging Study Eye Measures to Study Dementia

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# 1 Cohort Profile: Rationale and Methods of UK Biobank Repeat Imaging Study Eye

## 2 Measures to Study Dementia

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3 35 **ABSTRACT**  
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6 36 **Purpose:** The retina provides biomarkers of neuronal and vascular health that offer  
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8 37 promising insights into cognitive ageing, mild cognitive impairment (MCI) and dementia.  
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10 38 This article described the rationale and methodology of eye and vision assessments with the  
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12 39 aim of supporting the study of dementia in the UK Biobank Repeat Imaging study.  
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15 40 **Participants:** UK Biobank is a large-scale, multicentre, prospective cohort containing in-  
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17 41 depth genetic, lifestyle, environmental and health information from half a million participants  
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19 42 aged 40-69 enrolled in 2006-2010 across the UK. A subset (up to 60,000 participants) of the  
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21 43 cohort will be invited to the UK Biobank Repeat Imaging Study to collect repeated brain,  
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23 44 cardiac and abdominal magnetic resonance imaging (MRI) scans, whole-body DEXA (Dual-  
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25 45 energy x-ray absorptiometry), carotid ultrasound, as well as retinal optical coherence  
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27 46 tomography (OCT) and colour fundus photographs.  
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31 47 **Findings to date:** UK Biobank has helped make significant advances in understanding risk  
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33 48 factors for many common diseases, including for dementia and cognitive decline. Ophthalmic  
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35 49 genetic and epidemiology studies have also benefited from the unparalleled combination of  
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37 50 very large numbers of participants, deep phenotyping, and longitudinal follow-up of the  
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39 51 cohort, with comprehensive health data linkage to disease outcomes. In addition, we have  
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41 52 used UK Biobank data to describe the relationship between retinal structures, cognitive  
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43 53 function and brain MRI-derived phenotypes.  
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47 54 **Future plans:** The collection of eye-related data (e.g., OCT), as part of the UK Biobank  
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49 55 Repeat Imaging study, will take place in 2022-2028. The depth and breadth and longitudinal  
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51 56 nature of this dataset, coupled with its open-access policy, will create a major new resource  
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53 57 for dementia diagnostic discovery and to better understand its association with co-morbid  
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55 58 diseases. Additionally, the broad and diverse data available in this study will support research  
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57 59 into ophthalmic diseases and various other health outcomes beyond dementia.  
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## 60 STRENGTHS AND LIMITATIONS OF THIS STUDY

### 61 *Strengths*

- 62 • World's largest prospective, longitudinal multi-modal imaging cohort with  
63 unprecedented power for analysis of determinants of a wide range of health outcomes.
- 64 • Exceptional added value from the size, depth, and quality of the cross-sectional and  
65 longitudinal MRI data on the eye, brain, body and imaging of heart, carotids, together  
66 with linkage to electronic health records, through which overt dementia and  
67 Alzheimer's disease can be identified.
- 68 • Optimal timing to study cognitive impairment (age distribution: ~80%  $\geq$  60 years and  
69 ~65%  $\geq$  65 years)

### 70 *Limitations*

- 71 ○ Consistency of measurements between imaging devices over time, particularly with  
72 use of different OCT devices.
- 73 ○ Healthier participants compared to the general population.

74

## 75 INTRODUCTION

76 Dementia refers to a heterogeneous group of neurodegenerative disorders affecting  
77 46.8 million people globally.[1-3] Alzheimer's disease (AD) is the commonest, affecting 60-  
78 80% of people with dementia.[4, 5] Usually, a long prodromal period of up to 20 years of  
79 progressive cerebral atrophy is detectable on magnetic resonance imaging (MRI) scans and  
80 using body fluid biomarkers for neurodegeneration before AD is diagnosed.[2] These  
81 observations lead to a biological, rather than a clinical definition of AD.[6] To date, the  
82 majority of candidate drugs for slowing cognitive decline in AD or other dementias have  
83 failed in clinical trials[7], probably because they are used too late in the natural history when  
84 irreversible, advanced degeneration has already set in.[8, 9] Global rollout of screening and  
85 disease progression monitoring strategies for AD based on MRI scans is precluded by their  
86 high cost and frequently limited availability. Body fluid biomarkers might provide ways of  
87 stratifying or diagnosing dementias but will remain complimentary to structural imaging  
88 biomarkers because of their lack of diagnostic specificity and are not recommended as a  
89 screening test.[10]

90 The eye provides insights into the risk or presence of some major systemic diseases,  
91 including hypertension and diabetes, as well as changes associated with cognitive ageing and  
92 neurodegeneration.[11-13] As an alternative to MRI or plasma biomarkers, optical coherence  
93 tomography (OCT) offers a rapid, low-cost and non-invasive method for obtaining high-  
94 resolution (3-5 $\mu$ m) images of the retina at the back of the eye – the only part of the central  
95 nervous system (CNS) that can be visualized directly. The laminated structure of the retina  
96 enables the direct monitoring of neurodegeneration at a near cellular level *in vivo* at a  
97 resolution that is more detailed than for any other non-invasive, *in vivo* imaging modalities.  
98 There is strong evidence that quantitative OCT measurements are associated with concurrent  
99 cognitive impairment and future cognitive decline and dementia.[14, 15] Additionally, OCT

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3 100 methods may directly monitor related vascular pathology: amyloid microangiopathy affects  
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5 101 retinal and choroidal vasculature, as well as that in the cerebrum with AD.[16] Thus, retinal  
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7 102 OCT scans offer the means to identify individuals at high risk of developing AD, providing  
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9 103 them with opportunities to change their lifestyles or enter drug trials to delay or avert the  
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11 104 onset of dementia. OCT scans are also a sensitive way to monitor patients for neurotoxic  
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13 105 side-effects of novel drug treatments. The ability to directly measure specific neuronal layers  
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15 106 and microvascular characteristics in detail may provide a surrogate outcome marker for the  
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17 107 CNS more generally and potentially enhance the power to detect disease much earlier than  
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19 108 methods based on clinical history and genetic factors.

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24 109         Several genetic (e.g. *APOE*), comorbid (e.g. diabetes, hypertension, depression,  
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26 110 obesity), and lifestyle factors (e.g. low educational attainment and smoking) have been  
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28 111 associated with increased AD risk.[17-19] However, observational epidemiological studies  
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30 112 cannot distinguish cause from effect and are vulnerable to bias from reverse causation and  
31  
32 113 confounders. The analyses by Norton and Larsson illustrate how different disease risk factors  
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34 114 can co-exist and are often correlated, but they do not independently increase the risk of  
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36 115 AD.[19, 20] It also highlights the importance of identifying causal risk factors for dementia in  
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38 116 designing upstream public health policies and social policies to reduce disease risk, clinical  
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40 117 trials for new AD drugs and basic science research to understand the underlying mechanisms  
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42 118 of dementia development. The large size of the cohort and the associated healthcare, imaging  
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44 119 and genetic data make UK Biobank uniquely valuable for disambiguation of associations  
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46 120 from causal comorbidities both for patient stratification and for elucidation of underlying  
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48 121 mechanisms.

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53 122         The research gaps, as mentioned earlier, motivated us to develop a major new  
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55 123 resource for dementia diagnostic discovery and to better understand the association with co-  
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57 124 morbid diseases by adding rapid, low-cost OCT to the anticipated UK Biobank Repeat  
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3 125 Imaging study, alongside ancillary testing of autorefraction/keratometry and fragmented letter  
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5 126 test (FLT).[21] The objectives of this article are to describe (1) the process of test selection  
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7 127 (2) the methodology for eye and vision measures in the UK Biobank Repeat Imaging study;  
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9 128 (3) the baseline characteristics of the study population in this study.  
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## 13 129 **COHORT DESCRIPTION**

### 14 15 16 130 *UK Biobank*

17  
18 131 UK Biobank is a large-scale biomedical database and research resource containing in-  
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20 132 depth genetic and health information from over 500,000 participants aged 40-69 enrolled  
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22 133 across the UK between 2006 and 2010. Detailed study protocols are available on the UK  
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24 134 Biobank website (<https://www.ukbiobank.ac.uk/>). It has become the pre-eminent biomedical  
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26 135 research platform for studying the aetiology of common diseases of later life. During the  
27  
28 136 baseline assessment, extensive sociodemographic, lifestyle, and health-related information  
29  
30 137 was collected through a touch screen questionnaire and oral interview, and a wide range of  
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32 138 physical measurements was performed.[22, 23] Participants also provided biological samples  
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34 139 for genotyping, haematological, biochemistry, metabolomics and proteomics assays for the  
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36 140 full cohort.[24]  
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41 141 UK Biobank received approval from the National Information Governance Board for  
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43 142 Health and Social Care and the National Health Service Northwest Centre for Research  
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45 143 Ethics Committee (Ref: 11/NW/0382). UK Biobank is compliant with the previous Data  
46  
47 144 Protection Act and the more recent General Data Protection Regulation (GDPR) implemented  
48  
49 145 in 2018. For the GDPR, participants were contacted by email or post to explain how UK  
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51 146 Biobank meets the requirements of the new regulations (<https://www.ukbiobank.ac.uk/gdpr/>).  
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53 147 At the baseline visit, ophthalmic assessments were performed on a subset of participants  
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55 148 between 2009-2010 at 6 of 22 UK Biobank assessment centres, including visual acuity,  
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57 149 autorefraction, keratometry, intraocular pressure, corneal biomechanics, and retinal imaging  
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3 150 comprising disc/macular digital colour photographs and a 3D macular OCT. Over 110,000  
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5 151 participants have completed the visual acuity, refractive error, and intraocular pressure  
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7 152 measurements; and ~67,000 participants underwent retinal imaging. Detailed information on  
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9 153 the baseline eye and vision measures has been published elsewhere [22].  
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### 13 *The Repeat Imaging Sub-study*

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15 155 In 2014, UK Biobank launched the world's largest multimodal imaging study,  
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17 156 intending to include baseline magnetic resonance imaging (MRI) of the brain, heart and  
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19 157 abdomen, whole-body DEXA (Dual-energy x-ray absorptiometry) and carotid Doppler  
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21 158 ultrasound on up to 100,000 participants. Detailed methods of the UK Biobank imaging  
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23 159 enhancement were published elsewhere.[25] Although imaging 100,000 participants is a  
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25 160 unique and powerful enhancement to the UKB resource, many valuable insights could only  
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27 161 be gained from observing the change in imaging phenotypes over time. Recognising the  
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29 162 importance of serial measurements, up to 60,000 of those in the imaging enhancement study  
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31 163 will be invited to undergo repeat multimodal imaging between 2019-2028. As part of the  
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33 164 repeat imaging study, data collection of the eye measures (e.g., OCT) is anticipated to take  
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35 165 place from 2022-2028. The specific study design is as follows:  
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- 40  
41 166 • All UK Biobank participants who have previously attended a baseline brain and body  
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43 167 imaging visit will be invited to attend a repeat imaging visit (the invitation will  
44  
45 168 specify the same imaging centre as their baseline imaging visit to minimize  
46  
47 169 measurement error caused by differences between scanners at different centres).  
48  
49 170 • Appointment slots are planned in groups of 3 to minimize equipment downtime and to  
50  
51 171 maximize participant throughput and data quality.  
52  
53 172 • On arrival, those who accept will be asked to consent to the study, and each  
54  
55 173 participant will then undergo a pre-screening safety assessment.  
56  
57 174 • The 3 participants would then progress to the imaging modalities as follows:  
58  
59  
60

- 1  
2  
3 175           ○ Participant #1 => Brain MRI  
4  
5 176           ○ Participant #2 => Abdomen and heart MRI  
6  
7 177           ○ Participant #3 => DeXA, ultrasound and OCT  
8  
9  
10 178       • Each imaging modality “group” takes approximately 40 minutes, after which the  
11  
12 179           participants will move to the next modality, then switch again after 40 minutes so that  
13  
14 180           each member of the group of 3 has visited all three imaging measurement stations  
15  
16  
17 181           over a 2-hour period.  
18  
19 182       • The participants then all progress to the non-imaging parts of the visit where they will  
20  
21 183           complete questionnaires, have physical measures, and give biological samples, which  
22  
23 184           mirrors much of the initial (2006-2010) baseline visit.  
24  
25  
26 185       • As one group of 3 participants exits the imaging part of the visit, the next group of 3  
27  
28 186           are ready to enter, thus ensuring that the imaging part of the visit is fully utilized.  
29  
30  
31 187       • This process will repeat for five groups of 3 people (15 total) on 7 days per week at  
32  
33 188           each of UK Biobank’s 4 dedicated imaging centres.  
34  
35

### 36 189 *Study location*

37  
38 190           This multisite study will be run from four dedicated UK Biobank Imaging Centres  
39  
40  
41 191           across the UK (Newcastle upon Tyne, Stockport, Reading and Bristol). These 4 centres help  
42  
43 192           ensure most participants are within a reasonable distance to attend a scanning visit. As far as  
44  
45 193           is reasonably practical, maintaining the same instruments and software/firmware across the  
46  
47 194           sites and all phases of the UK Biobank project will ensure consistency and comparability of  
48  
49 195           results from the start of the baseline imaging project to the end of the repeat imaging  
50  
51 196           program. UK Biobank built the following strategies to reduce variability across the different  
52  
53 197           sites:  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 198 • The sites are each populated with the same equipment (same manufacturer, same  
4  
5 199 model, same software/firmware etc.) configured with the same protocols and the same  
6  
7 200 settings.  
8  
9  
10 201 • MR scanner settings/performance across all four sites is monitored by UK Biobank's  
11  
12 202 full-time in-house MR physicist with continuous quality assurance processes to  
13  
14 203 identify and resolve quality issues that may arise.  
15  
16  
17 204 • All staff are trained to standard operating procedures, and (in the case of the imaging  
18  
19 205 element) compliance/consistency is overseen by an in-house senior radiographer and  
20  
21 206 an in-house MR physicist. The non-imaging aspects are overseen by UK Biobank's  
22  
23 207 dedicated "Training and Monitoring" team.  
24  
25  
26 208 • Systems are already in place to ensure appropriate levels of training for all operational  
27  
28 209 staff, monitored via Clinic Training Assessments/Training Matrices. These will be  
29  
30 210 extended to cover the OCT measures: appropriate training will be provided, training  
31  
32 211 assessments/matrices extended to cover these measures, and performance monitored.  
33  
34  
35 212 • Imaging data are routinely made available to members of the project's expert working  
36  
37 213 group, which is made up of experts in each of the imaging modalities; this group  
38  
39 214 monitors the project progress, periodically provides training interventions and  
40  
41 215 critically, periodically/routinely provides an independent view of performance and  
42  
43 216 data output. A similar approach will be taken regarding the OCT measures with data  
44  
45 217 made available to the Eye Consortium members listed in this application for quality  
46  
47 218 control purposes.  
48  
49  
50

### 51 219 *Recruitment*

52 220 The UK Biobank cohort includes a committed and engaged group of participants who  
53  
54 221 are regularly invited for follow up activities: the typical response rate to online surveys  
55  
56 222 is >50%, and there have been very few withdrawals from the study since recruitment  
57  
58  
59  
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1  
2  
3 223 (<0.2%). Regular communications with the cohort (via newsletters, participant meetings,  
4  
5 224 study update meetings and the participant section of the UK Biobank website:  
6  
7  
8 225 [www.ukbiobank.ac.uk/explore-your-participation](http://www.ukbiobank.ac.uk/explore-your-participation)) help to maintain enthusiasm for and  
9  
10 226 engagement with the study. Direct telephone communication with individual participants  
11  
12 227 regarding new sub-studies or general participation questions via a dedicated “Participant  
13  
14 228 Contact Centre” (PCC) provides personalized information and reassurance.

15  
16  
17 229 This study will use the same invitation protocol as the UK Biobank imaging enhancement  
18  
19 230 study (2014-2023)[25]. The planned protocol for this repeat imaging study involves:

- 20  
21 231
- 22 • E-mail/postal explanation of the study and invitation to book an appointment.
  - 23 232
  - 24 • A telephone call to book an appointment and perform safety pre-screening via  
25  
26 233 Participant Resource Centre (PRC).
  - 27  
28 234
  - 29 • Assessment at the nearest of four imaging centres across the UK (Stockport,  
30  
31 235 Newcastle, Reading and Bristol) to minimize travel time and maximize participant  
32  
33 236 attendance.

34  
35 237 At the start of the pandemic (lockdown in the UK in March 2020), 50,000 of the target  
36  
37 238 100,000 participants had been imaged. Participant questionnaires on completion of baseline  
38  
39 239 imaging visit indicate >90% would be happy to undertake a repeat imaging visit. Pilot studies  
40  
41 240 involving a few thousand participants have demonstrated ~60% acceptance rates, providing  
42  
43 241 confidence that ~60,000 could be recruited for this repeat imaging study.

#### 44 242 *Examination procedures*

45  
46  
47 243 The whole-body imaging modalities have been extensively detailed elsewhere[25];  
48  
49 244 this article only describes the scope of eye and vision measurements in the Repeat Imaging  
50  
51 245 study. The Topcon Triton OCT platform is being used to obtain OCT images in this study.  
52  
53 246 The Triton platform uses ultra-high-speed swept-source (SS) OCT technology with a central  
54  
55 247 wavelength of 1050 microns that penetrates deeper than the retina, allowing visualization of  
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57  
58  
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1  
2  
3 248 the choroid and the vasculature therein.[26] The platform also takes colour retinal fundus  
4  
5 249 photographs immediately after the OCT scans, allowing measurement of the optic disc and  
6  
7  
8 250 retinal vessel metrics (including retinal vessel calibre and tortuosity). The Topcon Triton  
9  
10 251 supports wide-angle 12 mm x 9 mm scans that include the optic disc and macula in a single  
11  
12 252 scan.

13  
14 253 Widefield SS-OCT enables quantitative measurements of several candidate biomarkers,  
15  
16 254 including but not limited to total macular retinal thickness, macular inner retinal sublayer  
17  
18 255 thicknesses, peripapillary retinal nerve fibre layer thickness, choroidal vascularity index,  
19  
20 256 retinal arteriolar and retinal venular calibres, retinal vascular fractal dimension, retinal  
21  
22 257 vascular tortuosity. Details of the candidate biomarkers are summarized in Table 1.

#### 23 24 25 26 258 *OCT Image Processing*

27  
28  
29 259 Total retinal thickness and segmented values for retinal sublayer thicknesses for  
30  
31 260 macula and optic nerve scans are generated by the current generation OCT devices, using  
32  
33 261 FDA approved algorithms, during the examination. In contrast to the processing of baseline  
34  
35 262 UK Biobank macular OCT scans[27], they do not generally require the development of new  
36  
37 263 processing pipelines (apart from measures of the choroidal vascular layer, which are now  
38  
39 264 possible thanks to greater depth of imaging than was previously possible with older OCT  
40  
41 265 technology). Fundamental to both the challenge and the opportunity that would be provided  
42  
43 266 by UK Biobank OCT imaging is that modern retinal imaging software can measure changes  
44  
45 267 that would be imperceptible to, or missed by, a human grader. In operations featuring large-  
46  
47 268 scale data collection, a small proportion of the imaging is likely to be insufficient quality for  
48  
49 269 automated analysis. Problems may also arise with image acquisition, for instance, due to  
50  
51 270 some study participants presenting with ocular pathology. Thus, the first step in an analysis  
52  
53 271 pipeline is to assess the image quality and discard images that cannot be adequately  
54  
55 272 measured. Subsequent analysis of vasculometrics from retinal photographs would include  
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57  
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1  
2  
3 273 automated vessel segmentation followed by classification of arterioles and venules (see  
4  
5 274 below). For OCT, algorithms delineate the borders of the internal limiting membrane (ILM)  
6  
7  
8 275 and the RNFL to give the measurement of RNFL thickness, a biomarker of axonal loss  
9  
10 276 affecting retinal ganglion cells and the optic nerves. The thickness of the RNFL is evaluated  
11  
12 277 using the standard TSNIT (temporal, superior, nasal, inferior, temporal) mapping that  
13  
14 278 subdivides the measurements and colour codes statistical significance compared with a  
15  
16  
17 279 database of normal healthy values. Further delineation of boundaries enables quantitative  
18  
19 280 mapping of the ganglion cell layer (GCL) and inner plexiform layer (IPL) thicknesses, a  
20  
21 281 marker of neuronal somatic loss [13, 28].  
22

23  
24 282 Although the processing of quantitative retinal vasculometric data is not routinely  
25  
26 283 used in clinical settings, we have developed and validated a fully automated AI-enabled  
27  
28 284 retinal image analysis system (QUARTZ) for extracting vessel maps and quantifying retinal  
29  
30 285 vasculometry (including vessel size and tortuosity), which we will use to create the image  
31  
32  
33 286 processing pipeline. The system overcomes many of the difficulties of earlier vasculometry  
34  
35 287 approaches, particularly by being fully automated.[29, 30] QUARTZ has been demonstrated  
36  
37 288 to be highly robust, capable of processing large datasets with automated image quality  
38  
39  
40 289 assessments, resulting in accurate, reliable and high levels of vessel segmentation. To date,  
41  
42 290 QUARTZ has measured approximately 4 million vessel segments from over 190,000 images  
43  
44 291 from 95,000 participants of two very large population-based cohorts (UK Biobank and EPIC-  
45  
46  
47 292 Norfolk). This system has been developed specifically for use on TOPCON macular centred  
48  
49 293 images.  
50

51 294 In brief, the QUARTZ system distinguishes between right and left eyes, venules and  
52  
53 295 arterioles (with 87% accuracy using AI-enabled deep learning), identifies vessel segments  
54  
55  
56 296 and centreline coordinates and outputs measures of vessel width and tortuosity (based on the  
57  
58 297 mean change in chord length between successive divisions of the vessel).[31, 32] The system  
59  
60

1  
2  
3 298 obtains 10-20 thousands of measurements of width and tortuosity from the whole retinal  
4  
5 299 image (dependent on image quality), not just selected vessels lying within concentric areas  
6  
7  
8 300 centred on the disc. Measures are summarized using mean width and tortuosity, weighted by  
9  
10 301 segment length, for arterioles and venules separately for each image. QUARTZ measures in  
11  
12 302 UK Biobank have previously shown that venular width and tortuosity are associated with  
13  
14 303 markers of adiposity[33] and that both arteriolar and venular width and arteriolar tortuosity  
15  
16 304 show strong inverse associations with blood pressure (systolic and diastolic) and arterial  
17  
18 305 stiffness index.[34] More importantly, prognostic models using QUARTZ vasculometry  
19  
20 306 measures perform very well at predicting circulatory mortality and at least as well as  
21  
22 307 established risk scores in the prediction of stroke and myocardial infarction, remarkably  
23  
24 308 without the need for either a blood test or blood pressure measurement.[35] Given the  
25  
26 309 identification of vessel maps, these could be inputted into other systems (i.e., the VAMPIRE  
27  
28 310 system) with additional vasculometry summaries, such as fractal analyses to quantify the  
29  
30 311 complexity of the arteriolar and venular components of the retinal vascular network.  
31  
32 312 Marrying the automated functionality of QUARTZ with VAMPIRE will afford a more in-  
33  
34 313 depth characterization of the vessel complex on an unprecedented scale.  
35  
36  
37  
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39

40 314 The VAMPIRE (Vascular Assessment and Measurement Platform for Images of the  
41  
42 315 REtina) system is an international collaborative project designed to quantify retinal vascular  
43  
44 316 morphometry with large collections of fundus photographs. The system provides automatic  
45  
46 317 detection of retinal landmarks and quantifies some key parameters used frequently in  
47  
48 318 investigative studies - vessel width, vessel branching coefficients, tortuosity, and fractal  
49  
50 319 analyses. Detailed definitions have been reported elsewhere.[36, 37] In general, it computes  
51  
52 320 149 measurements per image, including basic statistics. Thirty-nine are width-related: central  
53  
54 321 retinal arteriolar equivalent (CRAE), central retinal venular equivalent (CRVE), retinal  
55  
56 322 arteriovenous ratio (AVR), basic statistics (mean, median, standard deviation, maximum,  
57  
58  
59  
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3 323 minimum), width gradients along vessels, average ratio length-diameter at branching points,  
4  
5 324 by arteries and veins; 104 are tortuosity measurements, computed by different algorithms and  
6  
7 325 with the statistics listed above; 6 are fractal dimension coefficients. All measures are  
8  
9 326 calculated by vessel type (arteriole or venule) and region (zone, whole image, quadrants).  
10  
11 327 VAMPIRE is a validated software application and has been extensively used in several  
12  
13 328 international studies.[36, 38, 39]  
14  
15

### 16 17 329 *Patient and public involvement*

18  
19  
20 330 UK Biobank maintains a website to keep participants and researchers up to date on  
21  
22 331 the study (<http://www.ukbiobank.ac.uk/news/>). Eye and vision-related publications resulting  
23  
24 332 from UK Biobank are maintained at  
25  
26 333 (<https://www.ukbiobankeyeconsortium.org.uk/publications>). UK Biobank also holds regular  
27  
28 334 events to inform the participants about the imaging study and the latest research. In addition,  
29  
30 335 UK Biobank has a Twitter feed (@uk\_biobank). The study was set up by the Medical  
31  
32 336 Research Council (MRC), Department of Health (DoH), and Wellcome Trust with input from  
33  
34 337 major patient representative organizations. An annual scientific meeting is recorded and  
35  
36 338 available to the public as a webcast.  
37  
38  
39

### 40 41 339 *Statistical Analysis Plan*

42  
43  
44 340 Baseline ocular characteristics will be summarized as mean (standard deviation) for  
45  
46 341 continuous variables and number (%) for categorical variables.

47  
48  
49 342 Primary aims would be to examine:

- 50  
51 343 1) cross-sectional associations between retinal biomarkers, measures of cognitive  
52  
53 344 performance and brain-volume from MRI imaging  
54  
55 345 2) the comparative performance of retinal biomarkers for risk stratification, to identify  
56  
57 346 those with cognitive impairment.  
58  
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3 347 3) the comparative performance of retinal biomarkers to detect those with longitudinal  
4  
5 348 decline in cognitive performance.

6  
7 349 Previous work within UK Biobank examining RNFL measures in relation to mild  
8  
9  
10 350 cognitive impairment, showed that those in the lowest quintile of RNFL thickness were 11%  
11  
12 351 (95% CI: 2% to 21%) more likely to fail on at least one of four cognitive tests.[40] This  
13  
14 352 shows that RNFL measures have the potential to identify those at higher risk of cognitive  
15  
16 353 impairment. After vigorous image quality control, the proposed imaging of a further 60,000  
17  
18 354 participants will provide 45,000-55,000 participants with good-quality retinal images for  
19  
20 355 quantification of individual components of the RNFL and potential to extract detailed retinal  
21  
22 356 vasculometric measures. This large sample size, will have 99% power ( $\alpha = 0.001$ ) to  
23  
24 357 detect at least 0.03 standard deviation change in the cognitive score[41] or brain  
25  
26 358 measures[42] (based on F-tests of linear regression coefficients from cross-sectional  
27  
28 359 analyses) per 1 standard deviation increase in any retinal biomarker (RNFL or retinal  
29  
30 360 vasculometric measure). Cross-sectional analyses using multiple linear regression will  
31  
32 361 quantify the dose response relationship between cognitive score with considerable power to  
33  
34 362 evaluate in the region of 30 candidate predictors (retinal biomarkers, age, sex, geographical  
35  
36 363 location, height, refraction, intraocular pressure, smoking status, socioeconomic positions and  
37  
38 364 established cardiovascular risk markers).[43] This will allow the independent contribution of  
39  
40 365 retinal biomarkers as a predictor of cognitive performance to be realized with considerable  
41  
42 366 precision,[44] across a spectrum of cognitive scores.[43]

43  
44 367 Given that UK Biobank has longitudinal data on cognitive change (with repeated  
45  
46 368 measures available from online questionnaires and performed in-person at the imaging  
47  
48 369 assessments), the study would be uniquely placed to assess the determinants of cognitive  
49  
50 370 decline in middle-later life. For prospective evaluation the rates of dementia would also be  
51  
52 371 pivotal in relation to prior cognitive performance. In UK Biobank, the annual incidence of  
53  
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3 372 dementia among those aged  $\geq 60$  years old is approximately 2.5 per 1000 person years.[45]  
4  
5 373 Therefore, within 2 years of retinal image capture there would be approximately 250 cases of  
6  
7 374 dementia per 45,000-55,000 participants. The longitudinal nature of the data will allow  
8  
9 375 models to be developed for incident cognitive outcomes / neurodegenerative events using  
10  
11 376 multivariable Cox proportional hazards models with relevant eye measures (i.e., OCT, retinal  
12  
13 377 vasculometry derived measures) as continuous predictors both with and without inclusion of  
14  
15 378 other parameters, including age at cognitive decline / neurodegenerative onset, sex, ethnicity  
16  
17 379 (although the cohort is largely of white European ancestry), smoking status (current, former  
18  
19 380 and never), alcohol consumption, body mass index, blood pressure, blood biochemistry  
20  
21 381 measures, social deprivation (by postcode), physical activity / sedentary behaviour, and  
22  
23 382 relevant family history where available.  
24  
25  
26  
27  
28

### 29 383 *Existing Data*

30  
31 384       Once recruitment was fully under way, additional measures were incorporated into the  
32  
33 385 baseline assessment, including hearing and arterial stiffness tests, a cardiorespiratory fitness  
34  
35 386 test, and various eye and vision measures, including visual acuity on a computerised system  
36  
37 387 designed to observe logarithm of the minimum angle of resolution (logMAR) principles, and  
38  
39 388 following the British Standard (BS-1968),[46] autorefraction and keratometry, intraocular  
40  
41 389 pressure and corneal biomechanics, and retinal imaging comprising disc/macular digital  
42  
43 390 colour photographs and a 3D macular OCT.[22] After the baseline visit, subsets of  
44  
45 391 participants have supported additional data collection through various enhancements to the  
46  
47 392 study. These have included: a complete repeat of the baseline assessment, collection of  
48  
49 393 physical activity data over 7-days by wearing accelerometers, and regular online  
50  
51 394 questionnaires covering various topics such as diet, cognitive function, occupational history,  
52  
53 395 mental wellbeing, gastrointestinal health and pain. All participants provided consent for their  
54  
55 396 health to be followed-up through linkage to health-related records, which currently includes  
56  
57  
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59  
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1  
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3 397 death, cancer, and hospital inpatient records for the entire cohort. Although UK Biobank is  
4  
5 398 not representative of the entire UK population, the large sample size and variation across all  
6  
7 399 levels of measures nonetheless enable a valid assessment of many exposure-outcome  
8  
9 400 relationships to be made. All publications using UK Biobank data are available on the  
10  
11 401 website (<https://www.ukbiobank.ac.uk/enable-your-research/publications>). Eye and vision-  
12  
13 402 related publications resulting from UK Biobank is maintained at  
14  
15 403 (<https://www.ukbiobankeyeconsortium.org.uk/publications>).

16  
17 404 In brief, based on data from UK Biobank participants attending the baseline imaging  
18  
19 405 assessment to date (N=48,998), the mean (standard deviation) age was 55.2 (7.6) years; 52%  
20  
21 406 (N=25,290) of them were female. A subset of 13,732 (28%) participants had undergone  
22  
23 407 retinal imaging. As there is a policy for the UK Biobank Repeat Imaging Study to over-  
24  
25 408 sample participants with baseline retinal imaging, the estimated numbers of participants with  
26  
27 409 overlapping retinal imaging and whole-body imaging data in the repeat imaging visit will be  
28  
29 410 more than 16,800. Detailed cognitive scores, APOE genotypes, self-reported comorbidities  
30  
31 411 and medication use are provided in Table 2. In addition to imaging, UK Biobank has  
32  
33 412 implemented a wide range of cognitive function tests since baseline that are relevant to  
34  
35 413 assessing various aspects of cognitive decline and dementia and will be conducted at the  
36  
37 414 repeat imaging and proposed OCT visit (Table 3).

## 45 **FINDINGS TO DATE**

46  
47 416 UK Biobank has helped make significant advances in the understanding of risk factors  
48  
49 417 for diseases including cardiovascular diseases, cancer, diabetes, stroke, multiple sclerosis,  
50  
51 418 optic neuritis and dementia.[23, 47-57] Ophthalmic genetics and epidemiology have  
52  
53 419 benefited from the unparalleled combination of very large numbers of participants, very  
54  
55 420 extensive and detailed phenotyping and longitudinal follow-up.[30, 58-62]

1  
2  
3 421 In addition, we have used UK Biobank data to describe the relationship between retinal  
4  
5 422 structures and both cognitive function and brain MR image-derived phenotypes.[40, 42] For  
6  
7 423 example, previous work examining RNFL measures in relation to mild cognitive impairment,  
8  
9 424 showed that those in the lowest quintile of RNFL thickness were 11% (95% CI 2.0% to 2.1%)  
10  
11 425 more likely to fail on at least one of four cognitive tests.[40] This indicates that RNFL thickness  
12  
13 426 measurements have the potential to identify those at higher risk of cognitive impairment. Chua  
14  
15 427 *et al* [42] reported that markers of retinal neurodegeneration are associated with smaller brain  
16  
17 428 volumes – macular ganglion cell-inner plexiform layer (GCIPL) thickness, ganglion cell  
18  
19 429 complex (GCC) thickness and total macular thickness were significantly associated with  
20  
21 430 smaller total brain ( $p < 0.001$ ), grey matter and white matter volume ( $p < 0.01$ ), and grey matter  
22  
23 431 volume in the occipital pole ( $p < 0.05$ ); thinner macular GCC and total macular thicknesses  
24  
25 432 were associated with smaller hippocampal volume ( $p < 0.02$ ).

26  
27 433 In the context of these results, and the findings of other studies (e.g. The Rotterdam  
28  
29 434 Study),[63-65] we proposed supplementing the testing menu in the UK Biobank Whole Body  
30  
31 435 Repeat Imaging Study with measures that support the discovery and quantification of eye and  
32  
33 436 vision variables that are associated with cognitive ageing and decline, and overt dementia.

## 40 437 **COLLABORATION**

41  
42  
43 438 UK Biobank aims to provide open access data for healthcare-related research. The  
44  
45 439 data are available to all bona fide researchers from the academic, charity, public and  
46  
47 440 commercial sectors in the UK and internationally, without preferential or exclusive access for  
48  
49 441 any user.[66] All interested researchers may apply to access the data via an online  
50  
51 442 application. Strict guidelines are in place to help ensure anonymity and confidentiality of  
52  
53 443 participants' data and samples.[67] We have formed the UK Biobank Eye and Vision  
54  
55 444 Consortium, an 80 person strong group of researchers with interest and expertise in  
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57  
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2  
3 445 ophthalmic epidemiology, visual system neurology, and the epidemiology of related diseases  
4  
5 446 such as diabetes and cardiovascular disease (<https://www.ukbiobankeyeconsortium.org.uk/>).  
6  
7

8 447 **FURTHER DETAILS**  
9

10  
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16  
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18  
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20  
21 453 participants of UK Biobank for their vital contribution to the resource.  
22  
23

24  
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26

27 455 This research used data from the UK Biobank Resource, under data access request number  
28  
29 456 2112.  
30

31  
32 457 ***Contributorship statement:***  
33

34 458 PJF, APK, PJP & ZS had full access to all the data in the study and take responsibility for the  
35  
36 459 integrity and accuracy of the data analysis. Concept and design: PJF, DA, APK, AJL, TM,  
37  
38 460 CGO, PJP, AP, ARR. Data acquisition, analysis, or interpretation: UK Biobank obtained the  
39  
40 461 data. APK performed data analysis. All authors interpreted data. Critical revision of the  
41  
42 462 manuscript for important intellectual content: all authors. Obtained funding: NA, SS, UK  
43  
44 463 Biobank. All authors approved the final manuscript.  
45  
46

47  
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49

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51  
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60

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2  
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8  
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496 **Table 1. Description of the candidate biomarkers**

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Biomarkers	View	Description
Total macular retinal thickness	cross-section	distance between the inner boundary of ILM to the lower boundary to RPE
Macular inner retinal sublayer thicknesses		
RNFL thickness	cross-section	distance between ILM to the outer boundary of RNFL
GC-IPL thickness	cross-section	distance between the inner boundary of GCL to the outer boundary of IPL
GCC thickness	cross-section	GC-IPL+ RNFL
Peripapillary RNFL thickness	cross-section	distance between ILM to the outer boundary of RNFL
Choroidal vascularity index	cross-section/ <i>en face</i>	ratio of vascular luminal area to the total choroidal area
Retinal arteriolar calibres	<i>en face</i>	evaluates generalized arteriolar narrowing
Retinal venular calibres	<i>en face</i>	evaluates generalized arteriolar narrowing
Retinal vascular fractal dimension	<i>en face</i>	measure the vascular pattern complexity
Retinal vascular tortuosity	<i>en face</i>	characterized by an abnormal curvature of the vessels, evincing a non-smooth appearance, presenting turns and twists throughout their course.

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*RNFL=retinal nerve fibre layer; GCIPL=ganglion cell-inner plexiform layer; GCL=ganglion cell layer; ILM=inner limiting membrane; IPL=inner plexiform layer; m=macular.*

502 **Table 2. Demographics, cognitive scores, APOE genotype, self-reported comorbidities,**  
 503 **medication use and availability of eye imaging factors for UK Biobank participants**  
 504 **attending the baseline imaging assessment to-date (N = 48,998).**  
 505

Characteristics	n (%) or mean (SD)
Age (years)	55.2 (7.6)
Sex	
Female	25,290 (52%)
Male	23,708 (48%)
Cognitive scores at baseline assessment	
Numeric memory: maximum digits remembered correctly (n=4,911)	6.97 (1.25)
Fluid intelligence score (n=16,427)	6.68 (2.04)
Prospective memory test (n=16,544)	1.10 (0.36)
Snap game: mean time to correctly identify matches (ms) (n=48,858)	539.2 (101.3)
Pairs matching: number of incorrect matches in round (n=24,988)	0.66 (1.24)
APOE genotype	
ε3ε3	28,297 (59%)
ε3ε4	11,063 (23%)
ε2ε3	5,892 (12%)
ε2ε4	1,128 (2%)
ε4ε4	1,065 (2%)
ε2ε2	277 (1%)
Comorbidities	
Hypertension	13,666 (28%)
Diabetes	2,008 (4%)
Ischemic heart disease	2,649 (5%)
Stroke	719 (1%)
Chronic obstructive pulmonary disease	1,016 (2%)
Asthma	6,689 (14%)
Obesity (BMI > 30 kg/m <sup>2</sup> )	8,918 (18%)
Parkinson's disease	136 (<1%)
Alzheimer's disease	34 (<1%)
Multiple sclerosis	202 (<1%)
Medication use	
Anti-hypertensive	9,769 (20%)
Statin	8,750 (18%)
Eye imaging available	13,732 (28%)

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508 *Mean (SD) is presented for continuous variables and count (%) for categorical variables. All variables are*  
 509 *presented for the full sample except for APOE genotype (1276 missing) and for cognitive scores (numbers*  
 510 *of participants for each test at ANY PHASE of UK Biobank examinations are presented in the table).*  
 511 *BMI=body mass index; SD=standard deviation; ms=microsecond; APOE=Apolipoprotein E.*  
 512

513 **Table 3. Cognitive function measures currently available in UK Biobank at different**  
 514 **time points.**

(variable ID)	Study phase (n)				
	Baseline (n) (2006-2010)	Repeat Assessment (2012-2013)	Online (2015)	Imaging study (2014-now)	Repeat Imaging (2019-2020)
Fluid IQ ( <a href="#">100027</a> )	165,500	20,100	123,500	39,600	800
Pairs matching ( <a href="#">100030</a> )	497,900	20,300	118,500	40,400	800
Prospective memory ( <a href="#">100031</a> )	171,600	20,300	0	40,400	800
Reaction time ( <a href="#">100032</a> )	496,700	20,300	0	40,200	800
Numeric memory ( <a href="#">100029</a> )	51,800	0	111,000	28,7000	800
Matrix ( <a href="#">501</a> )	0	0	0	27,600	800
Symbol digit substitution ( <a href="#">502</a> )	0	0	118,500	27,600	800
Tower test ( <a href="#">503</a> )	0	0	0	27,300	800
Picture vocabulary ( <a href="#">504</a> )	0	0	0	27,500	800
Trail making ( <a href="#">505</a> )	0	0	120,500	27,900	800
Paired associate learning ( <a href="#">506</a> )	0	0	0	27,900	800

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## 516 REFERENCES

- 517 1. Reitz C, Mayeux R: **Alzheimer disease: epidemiology, diagnostic criteria, risk factors**  
518 **and biomarkers.** *Biochemical pharmacology* 2014, **88**(4):640-651.
- 519 2. Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC, Marcus DS, Cairns  
520 NJ, Xie X, Blazey TM: **Clinical and biomarker changes in dominantly inherited**  
521 **Alzheimer's disease.** *N Engl J Med* 2012, **367**:795-804.
- 522 3. Tahami Monfared AA, Byrnes MJ, White LA, Zhang Q: **Alzheimer's Disease:**  
523 **Epidemiology and Clinical Progression.** *Neurol Ther* 2022, **11**(2):553-569.
- 524 4. Kalaria RN, Maestre GE, Arizaga R, Friedland RP, Galasko D, Hall K, Luchsinger JA,  
525 Ogunniyi A, Perry EK, Potocnik F: **Alzheimer's disease and vascular dementia in**  
526 **developing countries: prevalence, management, and risk factors.** *The Lancet*  
527 *Neurology* 2008, **7**(9):812-826.
- 528 5. Collaborators G: **Global, regional, and national burden of Alzheimer's disease and**  
529 **other dementias, 1990-2016: a systematic analysis for the Global Burden of**  
530 **Disease Study 2016.** *Lancet Neurol* 2019, **18**(1):88-106.
- 531 6. Jack Jr CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, Holtzman  
532 DM, Jagust W, Jessen F, Karlawish J: **NIA-AA research framework: toward a**  
533 **biological definition of Alzheimer's disease.** *Alzheimer's & Dementia* 2018,  
534 **14**(4):535-562.
- 535 7. Mehta D, Jackson R, Paul G, Shi J, Sabbagh M: **Why do trials for Alzheimer's disease**  
536 **drugs keep failing? A discontinued drug perspective for 2010-2015.** *Expert opinion*  
537 *on investigational drugs* 2017, **26**(6):735-739.
- 538 8. Gómez-Isla T, Price JL, McKeel Jr DW, Morris JC, Growdon JH, Hyman BT: **Profound**  
539 **loss of layer II entorhinal cortex neurons occurs in very mild Alzheimer's disease.**  
540 *Journal of Neuroscience* 1996, **16**(14):4491-4500.
- 541 9. Long JM, Holtzman DM: **Alzheimer disease: an update on pathobiology and**  
542 **treatment strategies.** *Cell* 2019, **179**(2):312-339.
- 543 10. Dubois B, Villain N, Frisoni GB, Rabinovici GD, Sabbagh M, Cappa S, Bejanin A,  
544 Bombois S, Epelbaum S, Teichmann M: **Clinical diagnosis of Alzheimer's disease:**  
545 **recommendations of the International Working Group.** *The Lancet Neurology* 2021,  
546 **20**(6):484-496.
- 547 11. Cheung CY-I, Ikram MK, Sabanayagam C, Wong TY: **Retinal microvasculature as a**  
548 **model to study the manifestations of hypertension.** *Hypertension* 2012, **60**(5):1094-  
549 1103.
- 550 12. Lesage S, Mosley T, Wong T, Szklo M, Knopman D, Catellier DJ, Cole S, Klein R, Coresh  
551 J, Coker L: **Retinal microvascular abnormalities and cognitive decline: the ARIC 14-**  
552 **year follow-up study.** *Neurology* 2009, **73**(11):862-868.
- 553 13. Petzold A, Balcer LJ, Calabresi PA, Costello F, Frohman TC, Frohman EM, Martinez-  
554 Lapiscina EH, Green AJ, Kardon R, Outteryck O: **Retinal layer segmentation in**  
555 **multiple sclerosis: a systematic review and meta-analysis.** *The Lancet Neurology*  
556 2017, **16**(10):797-812.
- 557 14. O'Bryhim BE, Apte RS, Kung N, Coble D, Van Stavern GP: **Association of preclinical**  
558 **Alzheimer disease with optical coherence tomographic angiography findings.** *JAMA*  
559 *ophthalmology* 2018, **136**(11):1242-1248.
- 560 15. Mutlu U, Colijn JM, Ikram MA, Bonnemaijer PW, Licher S, Wolters FJ, Tiemeier H,  
561 Koudstaal PJ, Klaver CC, Ikram MK: **Association of retinal neurodegeneration on**

1  
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56  
57  
58  
59  
60

- 562 **optical coherence tomography with dementia: a population-based study.** *JAMA*  
563 *neurology* 2018, **75**(10):1256-1263.
- 564 16. Masuzzo A, Dinet V, Cavanagh C, Mascarelli F, Krantic S: **Amyloidosis in retinal**  
565 **neurodegenerative diseases.** *Frontiers in Neurology* 2016, **7**:127.
- 566 17. Reitz C, Brayne C, Mayeux R: **Epidemiology of Alzheimer disease.** *Nature Reviews*  
567 *Neurology* 2011, **7**(3):137-152.
- 568 18. Lambert J-C, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, Jun G,  
569 DeStefano AL, Bis JC, Beecham GW: **Meta-analysis of 74,046 individuals identifies**  
570 **11 new susceptibility loci for Alzheimer's disease.** *Nature genetics* 2013,  
571 **45**(12):1452-1458.
- 572 19. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C: **Potential for primary**  
573 **prevention of Alzheimer's disease: an analysis of population-based data.** *The*  
574 *Lancet Neurology* 2014, **13**(8):788-794.
- 575 20. Larsson SC, Traylor M, Malik R, Dichgans M, Burgess S, Markus HS: **Modifiable**  
576 **pathways in Alzheimer's disease: Mendelian randomisation analysis.** *bmj* 2017,  
577 **359**.
- 578 21. Bowen M, Zutshi H, Cordiner M, Crutch S, Shakespeare T: **Qualitative, exploratory**  
579 **pilot study to investigate how people living with posterior cortical atrophy, their**  
580 **carers and clinicians experience tests used to assess vision.** *BMJ open* 2019,  
581 **9**(3):e020905.
- 582 22. Chua SYL, Thomas D, Allen N, Lotery A, Desai P, Patel P, Muthy Z, Sudlow C, Peto T,  
583 Khaw PT: **Cohort profile: design and methods in the eye and vision consortium of**  
584 **UK Biobank.** *BMJ open* 2019, **9**(2):e025077.
- 585 23. Littlejohns TJ, Sudlow C, Allen NE, Collins R: **UK Biobank: opportunities for**  
586 **cardiovascular research.** *European heart journal* 2019, **40**(14):1158-1166.
- 587 24. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, Motyer A, Vukcevic D,  
588 Delaneau O, O'Connell J: **The UK Biobank resource with deep phenotyping and**  
589 **genomic data.** *Nature* 2018, **562**(7726):203-209.
- 590 25. Littlejohns TJ, Holliday J, Gibson LM, Garratt S, Oesingmann N, Alfaro-Almagro F, Bell  
591 JD, Boultonwood C, Collins R, Conroy MC: **The UK Biobank imaging enhancement of**  
592 **100,000 participants: rationale, data collection, management and future directions.**  
593 *Nature communications* 2020, **11**(1):1-12.
- 594 26. Huber R, Wojtkowski M, Fujimoto JG, Jiang J, Cable A: **Three-dimensional and C-**  
595 **mode OCT imaging with a compact, frequency swept laser source at 1300 nm.**  
596 *Optics express* 2005, **13**(26):10523-10538.
- 597 27. Keane PA, Grossi CM, Foster PJ, Yang Q, Reisman CA, Chan K, Peto T, Thomas D, Patel  
598 PJ, Consortium UBEV: **Optical coherence tomography in the UK biobank study—**  
599 **rapid automated analysis of retinal thickness for large population-based studies.**  
600 *PLoS One* 2016, **11**(10):e0164095.
- 601 28. Cruz-Herranz A, Balk LJ, Oberwahrenbrock T, Saidha S, Martinez-Lapiscina EH,  
602 Lagreze WA, Schuman JS, Villoslada P, Calabresi P, Balcer L: **The APOSTEL**  
603 **recommendations for reporting quantitative optical coherence tomography**  
604 **studies.** *Neurology* 2016, **86**(24):2303-2309.
- 605 29. Welikala R, Fraz M, Habib M, Daniel-Tong S, Yates M, Foster P, Whincup P, Rudnicka  
606 AR, Owen CG, Strachan D: **Automated quantification of retinal vessel morphometry**  
607 **in the UK Biobank Cohort.** In: *2017 Seventh International Conference on Image*  
608 *Processing Theory, Tools and Applications (IPTA): 2017: IEEE; 2017: 1-6.*



- 1  
2  
3 609 30. Welikala R, Fraz M, Foster P, Whincup P, Rudnicka AR, Owen CG, Strachan D, Barman  
4 610 SA: **Automated retinal image quality assessment on the UK Biobank dataset for**  
5 611 **epidemiological studies.** *Computers in biology and medicine* 2016, **71**:67-76.
- 6 612 31. Fraz MM, Welikala R, Rudnicka AR, Owen CG, Strachan D, Barman SA: **QUARTZ:**  
7 613 **Quantitative Analysis of Retinal Vessel Topology and size—an automated system for**  
8 614 **quantification of retinal vessels morphology.** *Expert Systems with Applications* 2015,  
9 615 **42(20)**:7221-7234.
- 10 616 32. Welikala R, Foster P, Whincup P, Rudnicka AR, Owen CG, Strachan D, Barman S:  
11 617 **Automated arteriole and venule classification using deep learning for retinal**  
12 618 **images from the UK Biobank cohort.** *Computers in biology and medicine* 2017,  
13 619 **90**:23-32.
- 14 620 33. Tapp RJ, Owen CG, Barman SA, Welikala RA, Foster PJ, Whincup PH, Strachan DP,  
15 621 Rudnicka AR, UK Biobank Eye VC: **Retinal vascular tortuosity and diameter**  
16 622 **associations with adiposity and components of body composition.** *Obesity* 2020,  
17 623 **28(9)**:1750-1760.
- 18 624 34. Tapp RJ, Owen CG, Barman SA, Welikala RA, Foster PJ, Whincup PH, Strachan DP,  
19 625 Rudnicka AR: **Associations of Retinal Microvascular Diameters and Tortuosity With**  
20 626 **Blood Pressure and Arterial Stiffness: United Kingdom Biobank.** *Hypertension* 2019,  
21 627 **74(6)**:1383-1390.
- 22 628 35. Rudnicka AR, Welikala R, Barman S, Foster PJ, Luben R, Hayat S, Khaw KT, Whincup P,  
23 629 Strachan D, Owen CG: **Artificial intelligence-enabled retinal vasculometry for**  
24 630 **prediction of circulatory mortality, myocardial infarction and stroke.** *Br J*  
25 631 *Ophthalmol* 2022.
- 26 632 36. McGrory S, Taylor AM, Pellegrini E, Ballerini L, Kirin M, Doubal FN, Wardlaw JM,  
27 633 Doney AS, Dhillon B, Starr JM: **Towards standardization of quantitative retinal**  
28 634 **vascular parameters: comparison of SIVA and VAMPIRE measurements in the**  
29 635 **Lothian Birth Cohort 1936.** *Translational vision science & technology* 2018, **7(2)**:12-  
30 636 12.
- 31 637 37. Perez-Rovira A, MacGillivray T, Trucco E, Chin K, Zutis K, Lupascu C, Tegolo D,  
32 638 Giachetti A, Wilson PJ, Doney A: **VAMPIRE: vessel assessment and measurement**  
33 639 **platform for images of the RETina.** In: *2011 Annual International Conference of the*  
34 640 *IEEE Engineering in Medicine and Biology Society: 2011: IEEE; 2011: 3391-3394.*
- 35 641 38. Remond P, Aptel F, Cunnac P, Labarere J, Palombi K, Pepin J-L, Pollet-Villard F, Hogg  
36 642 S, Wang R, MacGillivray T: **Retinal vessel phenotype in patients with nonarteritic**  
37 643 **anterior ischemic optic neuropathy.** *American journal of ophthalmology* 2019,  
38 644 **208**:178-184.
- 39 645 39. Azanan MS, Chandrasekaran S, Rosli ES, Chua LL, Oh L, Chin TF, Yap TY, Rajagopal R,  
40 646 Rajasuriar R, MacGillivray T: **Retinal Vessel Analysis as a Novel Screening Tool to**  
41 647 **Identify Childhood Acute Lymphoblastic Leukemia Survivors at Risk of**  
42 648 **Cardiovascular Disease.** *Journal of pediatric hematology/oncology* 2020, **42(6)**:e394-  
43 649 e400.
- 44 650 40. Ko F, Muthy ZA, Gallacher J, Sudlow C, Rees G, Yang Q, Keane PA, Petzold A, Khaw  
45 651 PT, Reisman C: **Association of retinal nerve fiber layer thinning with current and**  
46 652 **future cognitive decline: a study using optical coherence tomography.** *JAMA*  
47 653 *neurology* 2018, **75(10)**:1198-1205.
- 48 654 41. Cornelis MC, Wang Y, Holland T, Agarwal P, Weintraub S, Morris MC: **Age and**  
49 655 **cognitive decline in the UK Biobank.** *PLoS one* 2019, **14(3)**:e0213948.

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51  
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53  
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55  
56  
57  
58  
59  
60

- 656 42. Chua SY, Lascaratos G, Atan D, Zhang B, Reisman C, Khaw PT, Smith SM, Matthews  
657 PM, Petzold A, Strouthidis NG: **Relationships between retinal layer thickness and**  
658 **brain volumes in the UK Biobank cohort.** *European Journal of Neurology* 2021,  
659 **28(5):1490-1498.**
- 660 43. Lyall DM, Cullen B, Allerhand M, Smith DJ, Mackay D, Evans J, Anderson J, Fawns-  
661 Ritchie C, McIntosh AM, Deary IJ: **Cognitive test scores in UK Biobank: data**  
662 **reduction in 480,416 participants and longitudinal stability in 20,346 participants.**  
663 *PloS one* 2016, **11(4):e0154222.**
- 664 44. Riley RD, Snell KI, Ensor J, Burke DL, Harrell Jr FE, Moons KG, Collins GS: **Minimum**  
665 **sample size for developing a multivariable prediction model: PART II-binary and**  
666 **time-to-event outcomes.** *Statistics in medicine* 2019, **38(7):1276-1296.**
- 667 45. Petermann-Rocha F, Lyall DM, Gray SR, Esteban-Cornejo I, Quinn TJ, Ho FK, Pell JP,  
668 Celis-Morales C: **Associations between physical frailty and dementia incidence: a**  
669 **prospective study from UK Biobank.** *The Lancet Healthy Longevity* 2020, **1(2):e58-**  
670 **e68.**
- 671 46. Standard B: **Test charts for determining distance visual acuity: BS 4274-1968.** *British*  
672 *Standards Institute* 1968.
- 673 47. Tikkanen E, Gustafsson S, Ingelsson E: **Associations of fitness, physical activity,**  
674 **strength, and genetic risk with cardiovascular disease: longitudinal analyses in the**  
675 **UK Biobank Study.** *Circulation* 2018, **137(24):2583-2591.**
- 676 48. Perez-Cornago A, Key TJ, Allen NE, Fensom GK, Bradbury KE, Martin RM, Travis RC:  
677 **Prospective investigation of risk factors for prostate cancer in the UK Biobank**  
678 **cohort study.** *British journal of cancer* 2017, **117(10):1562-1571.**
- 679 49. Allen NE, Sudlow C, Peakman T, Collins R, biobank U: **UK biobank data: come and get**  
680 **it.** In., vol. 6: American Association for the Advancement of Science; 2014: 224ed224-  
681 224ed224.
- 682 50. Ntuk UE, Gill JM, Mackay DF, Sattar N, Pell JP: **Ethnic-specific obesity cutoffs for**  
683 **diabetes risk: cross-sectional study of 490,288 UK biobank participants.** *Diabetes*  
684 *care* 2014, **37(9):2500-2507.**
- 685 51. Millett ER, Peters SA, Woodward M: **Sex differences in risk factors for myocardial**  
686 **infarction: cohort study of UK Biobank participants.** *bmj* 2018, **363.**
- 687 52. Gallacher KI, McQueenie R, Nicholl B, Jani BD, Lee D, Mair FS: **Risk factors and**  
688 **mortality associated with multimorbidity in people with stroke or transient**  
689 **ischaemic attack: a study of 8,751 UK Biobank participants.** *Journal of comorbidity*  
690 2018, **8(1):1-8.**
- 691 53. Ma H, Li X, Sun D, Zhou T, Ley SH, Gustat J, Heianza Y, Qi L: **Association of habitual**  
692 **glucosamine use with risk of cardiovascular disease: prospective study in UK**  
693 **Biobank.** *bmj* 2019, **365.**
- 694 54. Gao L, Li P, Cui L, Wong PM, Johnson-Akeju O, Lane J, Saxena R, Scheer F, Hu K: **Sleep**  
695 **disturbance and incident Alzheimer's disease: A UK Biobank study of 502,538**  
696 **middle-aged to older participants: Biomarkers (non-neuroimaging): Alzheimer's**  
697 **disease incidence, risk factors and biomarkers.** *Alzheimer's & Dementia* 2020,  
698 **16:e044575.**
- 699 55. Veronese N, Yang L, Piccio L, Smith L, Firth J, Marx W, Giannelli G, Caruso MG,  
700 Cisternino AM, Notarnicola M: **Adherence to a healthy lifestyle and multiple**  
701 **sclerosis: a case-control study from the UK Biobank.** *Nutritional neuroscience*  
702 2020:1-9.

- 1  
2  
3 703 56. Petzold A, Chua SY, Khawaja AP, Keane PA, Khaw PT, Reisman C, Dhillon B,  
4 704 Strouthidis NG, Foster PJ, Patel PJ: **Retinal asymmetry in multiple sclerosis.** *Brain*  
5 705 2021, **144**(1):224-235.
- 6  
7 706 57. Petzold A, Fraser CL, Abegg M, Alroughani R, Alshowaier D, Alvarenga R, Andris C,  
8 707 Asgari N, Barnett Y, Battistella R: **Diagnosis and classification of optic neuritis.** *The*  
9 708 *Lancet Neurology* 2022.
- 10 709 58. Cumberland PM, Rahi JS: **Visual function, social position, and health and life**  
11 710 **chances: the UK biobank study.** *JAMA ophthalmology* 2016, **134**(9):959-966.
- 12 711 59. Chan MP, Grossi CM, Khawaja AP, Yip JL, Khaw K-T, Patel PJ, Khaw PT, Morgan JE,  
13 712 Vernon SA, Foster PJ: **Associations with intraocular pressure in a large cohort:**  
14 713 **results from the UK Biobank.** *Ophthalmology* 2016, **123**(4):771-782.
- 15 714 60. Shah RL, Guggenheim JA: **Genome-wide association studies for corneal and**  
16 715 **refractive astigmatism in UK Biobank demonstrate a shared role for myopia**  
17 716 **susceptibility loci.** *Human genetics* 2018, **137**(11):881-896.
- 18 717 61. Wood A, Guggenheim JA: **Refractive error has minimal influence on the risk of age-**  
19 718 **related macular degeneration: a Mendelian randomization study.** *American journal*  
20 719 *of ophthalmology* 2019, **206**:87-93.
- 21 720 62. Craig JE, Han X, Qassim A, Hassall M, Cooke Bailey JN, Kinzy TG, Khawaja AP, An J,  
22 721 Marshall H, Gharahkhani P: **Multitrait analysis of glaucoma identifies new risk loci**  
23 722 **and enables polygenic prediction of disease susceptibility and progression.** *Nature*  
24 723 *genetics* 2020, **52**(2):160-166.
- 25 724 63. de Jong FJ, Schrijvers EM, Ikram MK, Koudstaal PJ, de Jong PT, Hofman A, Vingerling  
26 725 JR, Breteler MM: **Retinal vascular caliber and risk of dementia: the Rotterdam**  
27 726 **study.** *Neurology* 2011, **76**(9):816-821.
- 28 727 64. Mutlu U, Cremers LG, De Groot M, Hofman A, Niessen WJ, Van Der Lugt A, Klaver CC,  
29 728 Ikram MA, Vernooij MW, Ikram MK: **Retinal microvasculature and white matter**  
30 729 **microstructure: the Rotterdam Study.** *Neurology* 2016, **87**(10):1003-1010.
- 31 730 65. Mutlu U, Bonnemaier PW, Ikram MA, Colijn JM, Cremers LG, Buitendijk GH,  
32 731 Vingerling JR, Niessen WJ, Vernooij MW, Klaver CC: **Retinal neurodegeneration and**  
33 732 **brain MRI markers: the Rotterdam Study.** *Neurobiology of aging* 2017, **60**:183-191.
- 34 733 66. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green  
35 734 J, Landray M: **UK biobank: an open access resource for identifying the causes of a**  
36 735 **wide range of complex diseases of middle and old age.** *PLoS medicine* 2015,  
37 736 **12**(3):e1001779.
- 38 737 67. Biobank U: **UK Biobank ethics and governance framework.** In.; 2015.  
39 738  
40  
41  
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43  
44  
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46  
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48  
49  
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52  
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