Retinal age gap as a predictive biomarker for mortality risk

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ABSTRACT

Aim To develop a deep learning (DL) model that predicts age from fundus images (retinal age) and to investigate the association between retinal age gap (retinal age predicted by DL model minus chronological age) and mortality risk.

Methods A total of 80 169 fundus images taken from 46 969 participants in the UK Biobank with reasonable quality were included in this study. Of these, 19 200 fundus images from 11 052 participants without prior medical history at the baseline examination were used to train and validate the DL model for age prediction using fivefold cross-validation. A total of 35 913 of the remaining 35 917 participants had available mortality data and were used to investigate the association between retinal age gap and mortality.

Results The DL model achieved a strong correlation of 0.81 (p<0·001) between retinal age and chronological age, and an overall mean absolute error of 3.55 years. Cox regression models showed that each 1 year increase in the retinal age gap was associated with a 2% increase in risk of all-cause mortality (hazard ratio (HR)=1.02, 95% CI 1.00 to 1.03, p=0.020) and a 3% increase in risk of cause-specific mortality attributable to non-cardiovascular and non-cancer disease (HR=1.03, 95% CI 1.00 to 1.05, p=0.041) after multivariable adjustments. No significant association was identified between retinal age gap and cardiovascular- or cancer-related mortality.

Conclusions Our findings indicate that retinal age gap might be a potential biomarker of ageing that is closely related to risk of mortality, implying the potential of retinal image as a screening tool for risk stratification and delivery of tailored interventions.

INTRODUCTION

Globally, the population aged 60 and over is estimated to reach 2.1 billion in 2050.[1] Ageing populations place tremendous pressure on healthcare systems.[2] Chronological age is a major risk factor for frailty, age-related morbidity and mortality. However, there is great variability in health outcomes among individuals with the same chronological age,[3] implying that the rate of ageing at an individual level is heterogeneous. Biological age rather than chronological age can better represent health status and the ageing process. An accurate quantification of the biological age is significant for risk stratification and the delivery of tailored interventions.[4]

To date, several tissue-, cell-, molecular-, and imaging-based biological ageing markers have been developed, such as DNA-methylation status, brain age and three-dimensional (3D) facial age.[5–8] However, the invasive feature of cellular and molecular ageing biomarkers, high cost and time-consuming nature of neuroimaging and facial ages, and ethical and privacy concerns of facial imaging, have limited their usefulness.

The retina is considered as a window to the whole body,[9–13] which shares similar embryological origins, physiological features and anatomical structures with vital organs such as the heart, the brain and the kidney.[9 10 14] A growing number of studies have suggested that the retinal microvasculature could reliably reflect the systemic circulation in vivo and the retinal neural tissue shared common pathological alterations of neurodegenerative diseases with the brain.[14 15] In addition, the retina is amenable to rapid, non-invasive and cost-effective assessments. The advent of deep learning (DL) has greatly improved the accuracy of image classification and processing. Recent studies have demonstrated successful applications of DL models in the prediction of age using clinical images.[6 7 16] For example, previous studies have used MRI data of the brain and the 3D facial images for age prediction (brain age and facial age).[6–8] The clinical values of biological age gap (such as brain age gap, defined as brain age minus chronological age) in the prediction of neurodegenerative disease and mortality have been verified.[6 8] Taken together, this raises the potential that biological age can be predicted by applying DL to retinal images. For optimal usefulness, viable biomarkers of ageing must also relate to the risk of age-related morbidity and mortality.

We therefore developed a DL model that can predict age from fundus images, known as retinal age. Using a large population-based sample of middle-aged and elderly adults, we investigated the association between retinal age gap, defined as the difference between retinal age and chronological age, and mortality.

METHODS

Study population

The UK Biobank is a large-scale, population-based cohort of more than 500 000 UK residents aged 40–69 years. Participants were recruited between 2006 and 2010, with all participants completing comprehensive healthcare questionnaires, detailed physical measurements, and biological sample

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collections. Health-related events were ascertained via data linkage to hospital admission records and mortality registry. Ophthalmic examinations were introduced in 2009. The overall study protocol and protocols for each test have been described in extensive details elsewhere.[17]

Fundus photography

Paired retinal fundus and optical coherence tomography imaging (Topcon 3D OCT 1000 Mk2, Topcon Corp, Tokyo, Japan) data were collected. A 45 degree non-mydriatic and non-stereo fundus image centred on the macular and including the optic disc was taken for each eye. A total of 131 238 images from 66 500 participants were obtained at the baseline examination from the UK Biobank study, among which 80 169 images from 46 969 participants passed the image quality check. The image quality check process has been described in details elsewhere.[18] In brief, image quality control was based on ground truth manually labelled by two ophthalmologists, who used a three-level quality grading system (good, usable and reject) and identified low-quality indicators (eg, blurring, uneven illumination, low contrast and artefacts). Fundus images with good and usable quality were considered as those with reasonably good image quality.

Deep learning model for age prediction

Consistent with previous studies,[6 8 19–21] chronological age was considered to be equal to biological age in normally ageing individuals. Therefore, in order to set the ground truth of biological age to build and validate the DL model for biological age prediction, participants from the UK Biobank study who did not report any medical history of diseases at the baseline examination were used as the relatively healthy reference dataset. When the ground truth was applied to the test dataset, the difference between predicted biological age and chronological age represented the pathological changes that deviated from normal ageing.

Of the 46 969 participants with reasonable quality fundus images, 11 052 participants did not report any previous diseases as listed in online supplemental table 1. A total of 19 200 fundus images from these relatively healthy individuals were included in the DL model development and validation of the model accuracy using the five-fold cross-validation[8] (relatively healthy dataset). A total of 35 913 of the remaining 35 917 participants had available mortality data and were used to investigate the association between retinal age gap and mortality (analysis dataset). Images from the right eyes were used to calculate the retinal age and were replaced by images from the left eyes if not available.

The development and validation of the DL model for age prediction are outlined in figure 1. Briefly, all fundus images were preprocessed by subtracting average colour,[22] resized to a resolution of 299*299 pixels, and pixel values rescaled to 0∼1 after dividing by 255. After preprocessing, images were fed into a DL model using Xception architecture. During training, data augmentation was performed using random horizontal or vertical flips and the algorithm was optimised using stochastic gradient descent. To prevent overfitting, we implemented a dropout layer with the activation drop rate of 0.5, and carried out early stopping when validation performance did not improve after 10 epochs. The selection of candidate DL models was based on performance in the validation set. The performance of the DL model, including mean absolute error (MAE) and correlation between predicted retinal age and chronological age, was calculated. We then retrieved attention maps from the DL models using guided Grad-CAM,[23] which highlights pixels in the input image based on their contributions to the final evaluation.

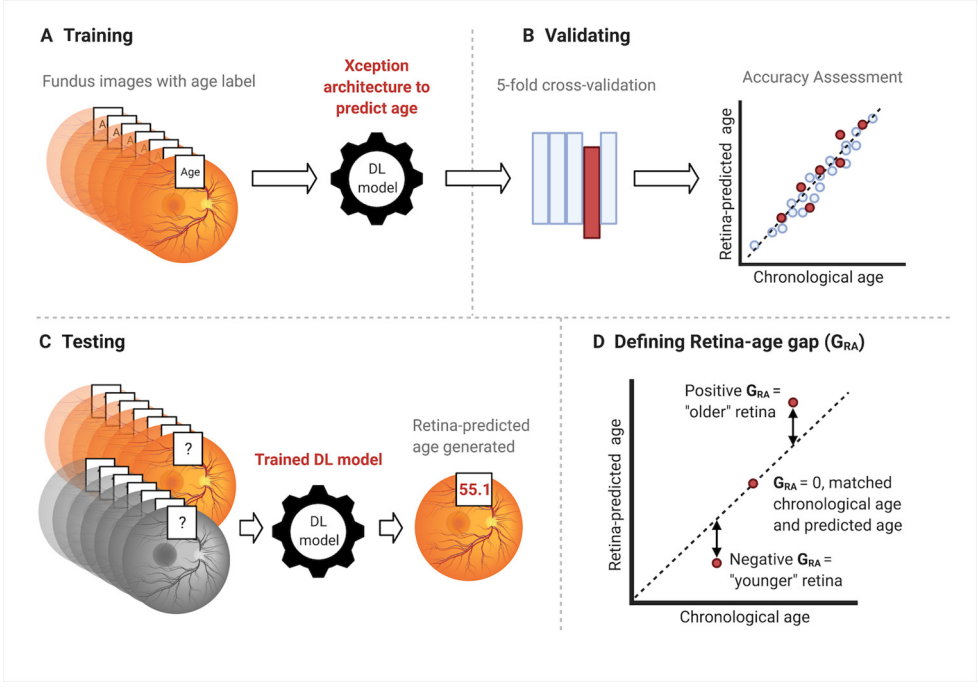

Figure 1 Overview of the study workflow. Figures showing the study workflow used to calculate retinal age gaps from fundus images. Fundus images were preprocessed and fed into the deep learning (DL) model. (A) The Xception architecture was used to train fundus images from the relatively healthy participants, with chronological age as the outcome variable; (B) the selection of DL models was based on fivefold cross-validation; (C) the DL model was then applied to make retinal age predictions from fundus images for participants in the analysis dataset; (D) the difference between predicted retinal age and chronological age was defined as the retinal age gap. A positive retinal age gap indicated an 'older' appearing retina, while a negative retinal age gap indicated a 'younger' appearing retina. This figure was created with BioRender.com.

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Retinal age gap definition

The difference between retinal age predicted by the DL model and chronological age was defined as the retinal age gap. A positive retinal age gap indicated an 'older' appearing retina, while a negative retinal age gap indicated a 'younger' appearing retina.

Mortality ascertainment

Mortality status and date of death were ascertained via data linkage to the National Health Service (NHS) Digital for participants in England and Wales, and the NHS Central Register (NHSCR), for participants in Scotland. Specific cause of death was determined by the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10). Cardiovascular disease (CVD)-related mortality was determined by codes I00 to I09, I11, I13, and I20 to I51 (diseases of heart) and I60 to I69 (cerebrovascular diseases). Cancer-related mortality was determined by codes C00 to C97. Those deaths not attributable to CVD or cancer were considered deaths due to non-CVD/non-cancer mortality. Participants not matched with death certificates were considered alive. Duration of follow-up for each participant (person-year) was calculated as the length of time between baseline age and date of death, loss to follow-up or complete follow-up (28 April 2021), whichever came first.

Covariates

Factors previously known to be associated with mortality[24] were included as potential confounders in the present analyses. These variables included baseline age, sex, ethnicity (recorded as white and non-white), Townsend deprivation indices (an area-based proxy measure for socioeconomic status), education attainment (recorded as college or university degree, and others), smoking status (recorded as current/previous and never), physical activity level (recorded as reaching the moderate/vigorous/walking recommendation and not), general health status (recorded as excellent/good and fair/poor), and comorbidities (obesity, diabetes mellitus, hypertension, history of heart diseases and history of stroke).

Body mass index (BMI) was calculated as body weight in kilograms divided by height squared. Obesity was defined as BMI ≥30 kg/m^2. Diabetes mellitus was defined as self-reported medical history of diabetes mellitus, the use of antihyperglycaemic drugs or insulin, or a glycosylated haemoglobin level of ≥6·5%. Hypertension was defined as self-reported history of hypertension, the use of antihypertensive drugs, an average systolic blood pressure of at least 130 mm Hg or an average diastolic blood pressure of at least 80 mm Hg. Self-reported history of angina and heart attack was used to classify history of heart diseases.

Statistical analyses

Descriptive statistics, including means and standard deviations (SDs), numbers and percentages, were used to report baseline characteristics of study participants. Uupaired t-tests or analysis of variance was used to compare means on continuous variables, and Pearson's χ^2 tests to compare distributions on categorical variables. Cox proportional hazards regression models considering retinal age gap as a continuous linear term were fitted to estimate the effect of a 1 year increase in retinal age gap on mortality risk. We then investigated associations between retinal age gaps at different quantiles with mortality. In addition, a restricted cubic spline analysis of possible non-linear associations between retinal age gap and mortality status was performed, with five knots placed at equal centiles of the retinal age gap, and retinal age gap of zero used as the reference value. We adjusted Cox models for the following covariates: baseline age, sex, ethnicity, and Townsend deprivation indices (model 1); additional educational level, smoking status, physical activity level, general health status, obesity, diabetes mellitus, hypertension, history of heart diseases, and history of stroke (model 2).

For the investigation on the association between retinal age gap and mortality, fundus images from right eyes were selected for primary analyses, while fundus images from left eyes were selected for sensitivity analyses. Subgroup analyses stratified by age group (age <55 years old versus ≥55 years old), smoking status (current/previous smoker vs non-smoker), diabetes mellitus and hypertension were performed.

The proportional hazards assumptions for each variable included in the Cox proportional hazards regression models were graphically assessed. All variables were found to meet the assumption. The multicollinearity for confounding factors included in multivariable Cox models was tested using the variance inflation factor method, and variance inflation factors for all confounders were <2 (mean 1.16). A two-sided p value of <0·05 indicated statistical significance. Analyses were performed using R (version 3.3.0, R Foundation for Statistical Computing, www.R-project.org, Vienna, Austria) and Stata (version 13, StataCorp, Texas, USA).

Standard protocol approvals, registrations, and patient consent

The National Information Governance Board for Health and Social Care and the NHS North West Multicenter Research Ethics Committee approved the UK Biobank study in accordance with the principles of the Declaration of Helsinki, with all participants providing informed consent. Because of the only access to the deidentified data from a public database, the Medical Research Ethics Committee of Guangdong Provincial People's Hospital waived the requirements to obtain ethical approval.

Data availability statement

The UK Biobank is an open-access resource to researchers through registration of proposed research. Our study was approved and registered as study 62525 with the UK Biobank resource.

Code availability statement

The code of this study is available from the corresponding author on request. All models were built using publicly available software and packages.

Role of the funding source

The funders had no role in study design, data collection, data analyses, data interpretation, preparation of the manuscript, and decision to publish. The corresponding author had full access to all data and final responsibility for the decision to submit for publication.

RESULTS

Deep learning model performance for age prediction

The DL model was trained and validated on 11052 relatively healthy participants with a mean age of 52.6±7.97 years; and with 53.7% female. Online supplemental table 2 shows the baseline characteristics of the participants used for DL models development and validation. Figure 2 shows the performance of the DL model in the relatively healthy dataset. Regression dilution was observed, with the overprediction of age at lower

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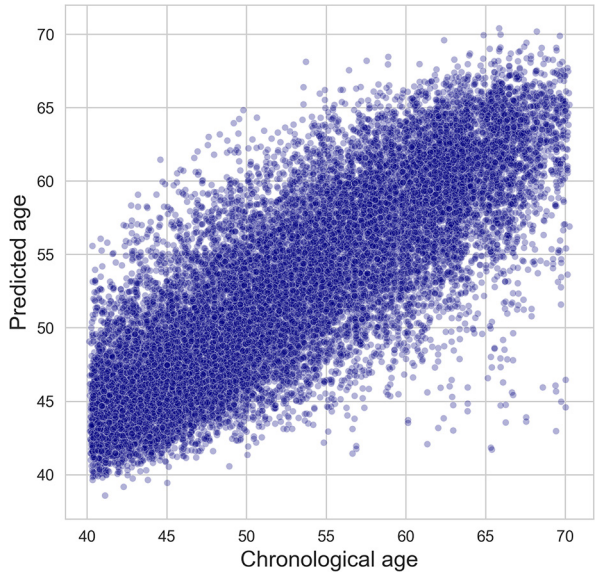

Figure 2 Performance of the deep learning model. Scatterplot depicting correlation of predicted age with chronological age in relatively healthy participants.

chronological age group and underprediction at higher chronological age group. The trained DL model was able to achieve a strong correlation of 0.81 (p<0·001) between predicted retinal age and chronological age, with an overall MAE of 3.55 years. The Bland and Altman plot of difference in years between chronological age and retinal age is shown in online supplemental figure 1. Two representative examples of fundus images with corresponding attention maps for age prediction are shown in figure 3. Regions around retinal vessels are highlighted by the DL model for age prediction.

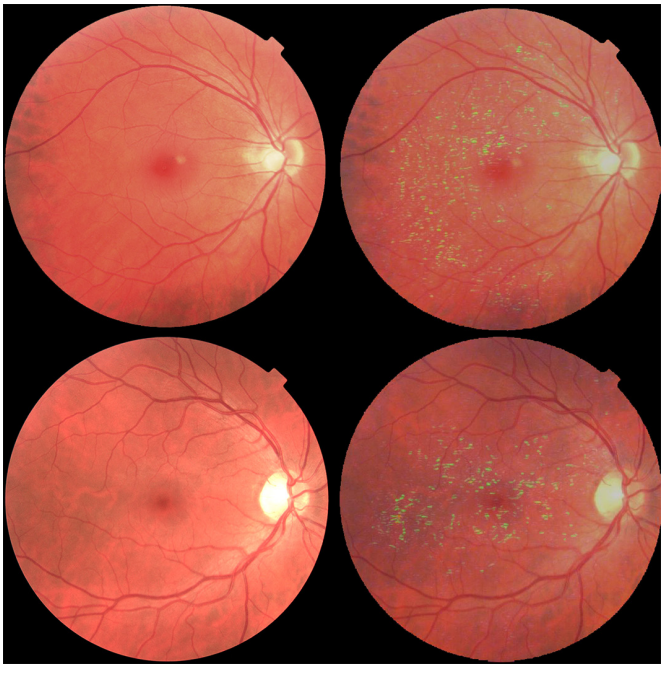

Figure 3 Attention maps for age prediction. Figures showing representative examples of fundus images with corresponding attention maps for age prediction. Regions highlighted with a brighter colour indicate areas that are used by the deep learning model for age prediction. Regions around the retinal vessels are highlighted.

Table 1 Baseline characteristics of study participants in the test dataset

Baseline characteristics	Total
Number	35 913
Age (years) (mean±SD)	56.8±8.04
Female, N (%)	19 999 (55.7)
White ethnicity, N (%)	33 475 (93.2)
Townsend index (mean±SD)	−1.09±2.96
College or university degree, N (%)	12 460 (34.7)
Current/previous smoker, N (%)	15 943 (44.6)
Above physical activity recommendation, N (%)	24 082 (82.0)
Excellent/good health status, N (%)	24 821 (69.5)
Obesity, N (%)	9135 (25.6)
Diabetes mellitus, N (%)	2351 (6.55)
Hypertension, N (%)	27 181 (75.7)
History of heart diseases, N (%)	1534 (4.27)
History of stroke, N (%)	543 (1.51)

SD, Standard Deviation.

Retinal age gap

The baseline characteristics of 35 913 participants included in the investigation of the association between retinal age gap and mortality are described in table 1. The distribution of the retinal age gap in the analysis dataset followed a nearly normal distribution (online supplemental figure 2). The mean (SD) and median (IQR) of the retinal age gap were −1.31 (4.82) and −1.18 (−4.18, 1.79). The proportions of fast agers with retinal age gaps more than 3, 5 and 10 years were 51.0%, 27.6% and 4.34%, respectively.

Baseline characteristics of participants stratified by quantiles of the retinal age gap are shown in online supplemental table 3. There were significant differences in baseline age, gender, ethnicity, Townsend index, educational level, smoking status, physical activity level, health status, obesity, history of hypertension, heart diseases and stroke across the four quantiles of retinal age gap.

Retinal age gap and all-cause mortality

After a median follow-up of 11.0 years (IQR 10.9–11.1 years), a total of 1871 (5.21%) participants died from all causes. The survival curve of participants with retinal age gaps in each quantile is shown in figure 4. Considering linear effects only and following adjustment for all confounding factors, each 1 year increase in retinal age gap was associated with a 2% increase in mortality risk (HR=1.02, 95% CI 1.00 to 1.03, p=0.020; table 2). Compared with participants with retinal age gaps in the lowest quantile, mortality risk was comparable for those in the second quantile (HR=1.05, 95% CI 0.92 to 1.20, p=0.473). Mortality risk was significantly increased for participants with retinal age gaps in the third and fourth quantiles (HR=1.21, 95% CI 1.04 to 1.41, p=0.014; HR=1.35, 95% CI 1.11 to 1.65, p=0.003; respectively; table 2).

Allowing for non-linearity, figure 5 illustrates the estimated association between retinal age gap and mortality risk. Evidence of an overall and non-linear association between retinal age gap and mortality risk was observed ($P_{overall}$ <0.001; $P_{non\text{-}linear}$=0.002). The association between retinal age gaps and mortality is depicted as a J-shaped curve, where positive retinal age gaps were associated with substantially increased risks of mortality.

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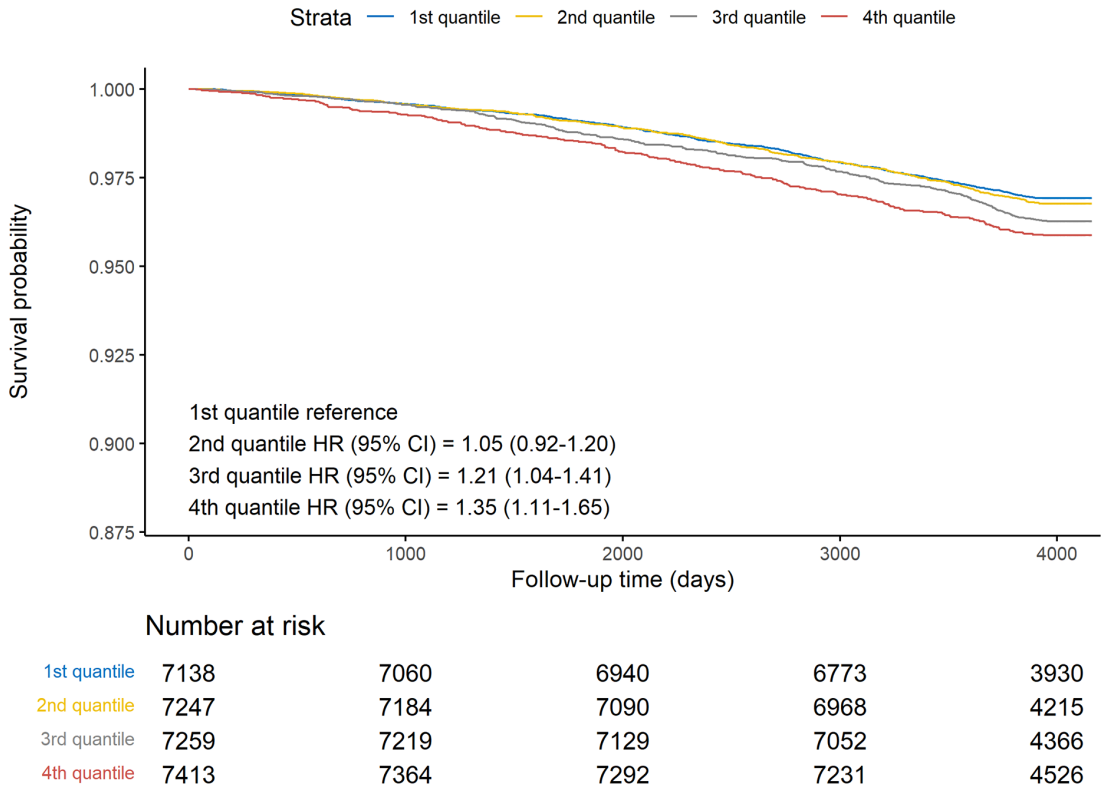

Figure 4 Adjusted survival curves for mortality risk by retinal age gap quantiles. Mortality risk is shown over time for participants in different retinal age gap quantiles. Lower quantiles corresponded to participants who had chronological ages greater than predicted retinal age, whereas higher quantiles corresponded to those with chronological ages lower than predicted retinal age. Plots were based on Cox proportional hazards regression models, adjusted for age, sex, ethnicity, Townsend deprivation indices, educational level, smoking status, physical activity level, general health status, obesity, diabetes mellitus, hypertension, history of heart diseases and history of stroke. Compared with participants with retinal age gaps in the lowest quantile, mortality risk was comparable for those in the second quantile (HR=1.05, 95% CI 0.92 to 1.20, p=0.473). Mortality risk was significantly increased for participants with retinal age gaps in the third and fourth quantiles (HR=1.21, 95% CI 1.04 to 1.41, p=0.014; HR=1.35, 95% CI 1.11 to 1.65, p=0.003, respectively).

Retinal age gap and cause-specific mortality

Among the 1871 participants who died of all causes, 321 (17.2%), 1018 (54.4%) and 532 (28.4%) deaths were attributable to CVD, cancer and others. Cox proportional hazards regression models showed that participants with retinal age gaps in the third and fourth quantiles were significantly associated with 49% to 67% higher risks of mortality not due to CVD or cancer after multiple adjustments (HR=1.49, 95% CI 1.13 to 1.96, p=0.005; HR=1.67, 95% CI 1.17 to 2.39, p=0.005; respectively; table 3). However, we identified no association of retinal age gap with deaths due to CVD or cancer after multivariate adjustments.

Sensitivity analyses

In order to verify the robustness of our findings, fundus images from the left eyes were chosen for the statistical analyses. Similar results were observed for left eyes (online supplemental tables 4 and 5). Another sensitivity analysis was performed to examine the association between retinal age gap with mortality in the full

Table 2 Association between retinal age gap with mortality using Cox proportional hazards regression models.

			Model 1		Model 2	
Retinal age gap	**N**	**Years, mean±SD**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Retinal age gap, per one age (yrs)	35913	−1.31±4.82	1.02 (1.01 to 1.03)	0.001	1.02 (1.00 to 1.03)	0.020
Retinal age gap						
Quantile 1	8979	−7.36±3.44	Reference	–	Reference	–
Quantile 2	8978	−2.63±0.859	1.06 (0.95 to 1.19)	0.313	1.05 (0.92 to 1.20)	0.473
Quantile 3	8978	0.259±0.856	1.22 (1.07 to 1.40)	0.004	1.21 (1.04 to 1.41)	0.014
Quantile 4	8978	4.48±2.35	1.42 (1.19 to 1.69)	<0.001	1.35 (1.11 to 1.65)	0.003
Trending	–	–	1.12 (1.06 to 1.17)	<0.001	1.10 (1.04 to 1.17)	0.001

Model 1 adjusted for age, sex, ethnicity and Townsend deprivation indices.
Model 2 adjusted for covariates in model 1 + educational level, smoking status, physical activity level, general health status, obesity, diabetes mellitus, hypertension, history of heart diseases and history of stroke.
HR, HR ratio; CI, CI interval.

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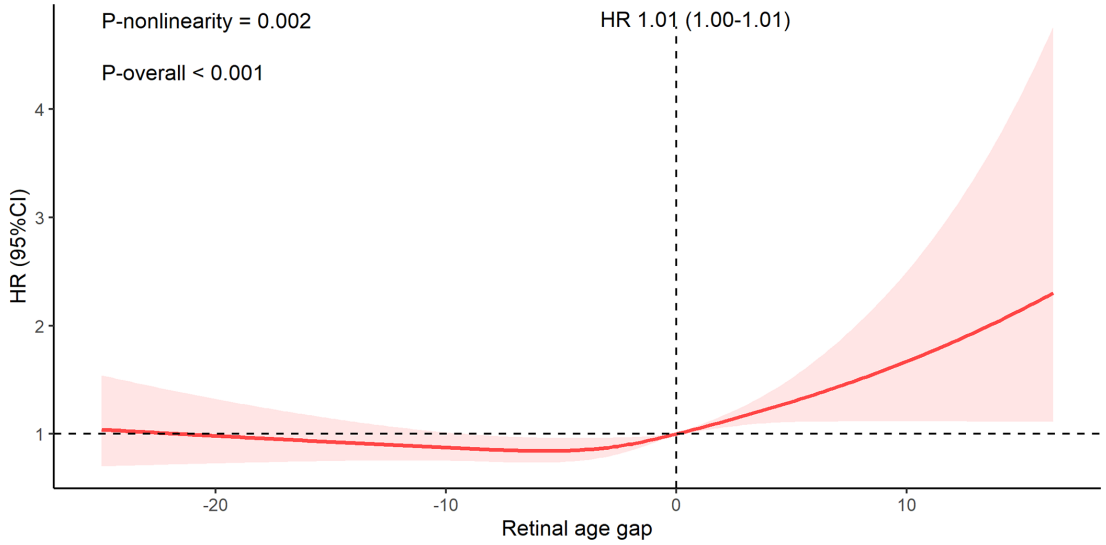

Figure 5 Association between retina age gap and mortality risk, allowing for non-linear effects. The reference retinal age gap for this plot (with hazard ratio (HR) fixed as 1·0) was 0 years. The model was fitted with a restricted cubic spline for retinal age gap (knots placed at equal centiles of retina age gap), adjusted for age, sex, ethnicity, Townsend deprivation indices, educational level, smoking status, physical activity level, general health status, obesity, diabetes mellitus, hypertension, history of heart diseases and history of stroke. Evidence of an overall and non-linear association between retinal age gap and mortality risk was observed ($P_{overall}$ <0.001; $P_{non\text{-}linear}$=0.002). The association between retinal age gaps and mortality is depicted as a J-shaped curve, where positive retinal age gaps were associated with substantially increased risks of mortality.

cohort. Similar results were observed, as shown in online supplemental table 6.

Subgroup analyses

Results from subgroup analyses stratified by age group, smoking status, diabetes mellitus and hypertension are presented in online supplemental tables 7–10. Significant associations between retinal age gap and mortality were noted both in younger and older groups, as well as in participants with and without hypertension. In the analyses stratified by smoking status, retinal age gap was closely related to mortality among the current or previous smoker. Analyses stratified by diabetes mellitus showed a significant association between retinal age gap and mortality in non-diabetic participants, but not in diabetic participants.

DISCUSSION

Using a large population-based sample of middle-aged and elderly adults, we developed a DL model that could predict age from fundus images with high accuracy. Further, we found that the retinal age gap, defined as the difference between predicted retinal age and chronological age, independently predicted the risk of mortality, especially of the non-CVD/non-cancer mortality. Our findings have demonstrated that retinal age gap might be a potential biomarker of ageing that can predict mortality risk.

To the best of our knowledge, this is the first study that has proposed retinal age gap as a biomarker of ageing. Our trained DL model achieved excellent performance with a MAE of 3.5, outperforming most existing biomarkers in the prediction of age. Previous studies have shown MAEs of 3.3–5.2 years for DNA methylation clock,[25 26] 5.5–5.9 years MAEs for blood profiles[27 28] and 6.2–7.8 years MAEs for the transcriptome ageing clock.[29 30] Neuroimaging and 3D facial imaging have achieved accurate performances in age prediction with MAEs between 4.3 and 7.3,[8 31] and 2.8 and 6.4 years,[7 20] respectively. Despite these reasonable accuracies, the invasiveness of cellular and molecular ageing biomarkers, high cost and time-consuming nature of neuroimaging and 3D facial ages, and ethical and privacy concerns of facial age, have limited their usefulness. In addition to excellent performance in age prediction, determining

Table 3 Association between retinal age gap with specific-cause mortality using Cox proportional hazards regression models

	CVD-specific		Cancer-specific		Non-CVD/non-cancer	
Retinal age gap	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Retinal age gap, per one age (yrs)	1.01 (0.97 to 1.04)	0.704	1.01 (1.00 to 1.03)	0.146	1.03 (1.00 to 1.05)	0.041
Retinal age gap						
Quantile 1	Reference	–	Reference	–	Reference	–
Quantile 2	1.11 (0.81 to 1.52)	0.502	1.10 (0.92 to 1.31)	0.309	0.92 (0.71 to 1.19)	0.516
Quantile 3	1.00 (0.68 to 1.48)	0.996	1.14 (0.92 to 1.40)	0.222	1.49 (1.13 to 1.96)	0.005
Quantile 4	1.21 (0.74 to 1.98)	0.450	1.24 (0.95 to 1.63)	0.118	1.67 (1.17 to 2.39)	0.005
Trending	1.04 (0.90 to 1.21)	0.591	1.07 (0.99 to 1.16)	0.099	1.21 (1.08 to 1.35)	0.001

Model 1 adjusted for age, sex, ethnicity, and Townsend deprivation indices.
Model 2 adjusted for covariates in Model I + educational level, smoking status, physical activity level, general health status, obesity, diabetes mellitus, hypertension, history of heart diseases and history of stroke.
CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

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retinal age using fundus images is fast, safe, cost-effective and user-friendly, thus offering great potential for use in a large number of people.

Beyond age prediction, our study has extended the application of retinal age to the prediction of survival. Our novel findings have determined that the retinal age gap is an independent predictor of increased mortality risk, especially of non-CVD/non-cancer mortality. These findings suggest that retinal age may be a clinically significant biomarker of ageing. The relevance of the retinal age gap for general health is intuitive, given that the retina is the only organ that is amenable to in vivo visualisation of the microvasculature and neural tissue. The retina offers a unique, accessible 'window' to evaluate underlying pathological processes of systemic vascular and neurological diseases that are associated with increased risks of mortality. This hypothesis is supported by previous studies, which have suggested that retinal imaging contains information about cardiovascular risk factors,[32] chronic kidney diseases[33] and systemic biomarkers.[34] In addition, this hypothesis is also consistent with previously reported qualitative and quantitative studies that have found that ocular imaging measures (eg, retinal-vessel calibre) and retinal diseases (eg, glaucoma) are significantly associated with mortality.[35 36] The significant association between retinal age gap and non-CVD/non-cancer mortality, together with the growing evidence of the link between eye and brain,[37] may support the notion that the retina is the 'window' of neurological diseases. Nevertheless, the small sample size of deaths due to dementia (n=20) in the present study was underpowered to investigate the association between retinal age gap and dementia-related mortality. Of note, the non-significant association between retinal age gap and CVD-related mortality may be due to the relatively small sample size of the CVD-related deaths and improvement in treatments of fatal CVD.[38] Our pilot study indicated that retinal age gap was an independent predictor for subsequent risk of CVD (defined as the cases from hospital admission dataset and mortality dataset). This body of work supports the hypothesis that the retina plays an important role in the ageing process and is sensitive to the cumulative damages of ageing which increase the mortality risk.

Our findings have several important clinical implications. First, the fast, non-invasive, and cost-effective nature of fundus imaging enables it to be an accessible screening tool to identify individuals at an increased risk of mortality. This risk stratification will assist tailored healthcare decision-making, as well as targeting and monitoring of interventions. Given the rising burden of non-communicable diseases and population ageing globally, the early identification and delivery of personalised healthcare might have tremendous public health benefits. Further, the recent development of smartphone-based retinal cameras, together with the integration of DL algorithms, may in the future provide point-of-care assessments of ageing and improve accessibility to tailored risk assessments. Second, the ability to use fundus images in predicting ageing may improve potential health benefits of eye disease screening, beyond the diagnosis of sight-threatening eye diseases. This may improve the health economic cost-effectiveness of programmes such as diabetic retinopathy screening, thus increasing the impact and access to eye disease screening programmes.

The large-scale sample size, long-term follow-up, standardised protocol in capturing fundus images, validity of mortality data, and adjustment for a wide range of confounding factors in the statistical models of this study support the robustness of our findings. Despite these promising results, our study has several limitations. First, these analyses are limited by retinal images that were captured at a particular cross-section in time, with trajectories in retinal ageing potentially being a better indicator of mortality. Second, participants involved in the UK Biobank study were volunteers, who might not be representative of the population from which they were drawn.[39] Of note, the potential healthy effect might underestimate the retinal age gap in the general population, as individuals with extremely poor health were less likely to participate in this study. Nevertheless, the association between retinal age gap and mortality would not be affected due to the representativeness of the sample.[39] Third, the lack of external datasets might limit the generalisability of our DL algorithms and findings. Lastly, we were unable to fully exclude the possibility of residual confounders between retinal age gap and mortality.

Conclusion

In summary, we have developed a DL algorithm that can detect footprints of ageing in fundus images and predict age with high accuracy. Further, we have been the first to demonstrate that the retinal age gap is significantly associated with an increased risk of mortality. Our findings suggest that the retinal age gap provides novel insights into healthy ageing. Our work calls for future research into applications of the retinal age gap, and whether retinal age can be used to better understand processes underpinning ageing.

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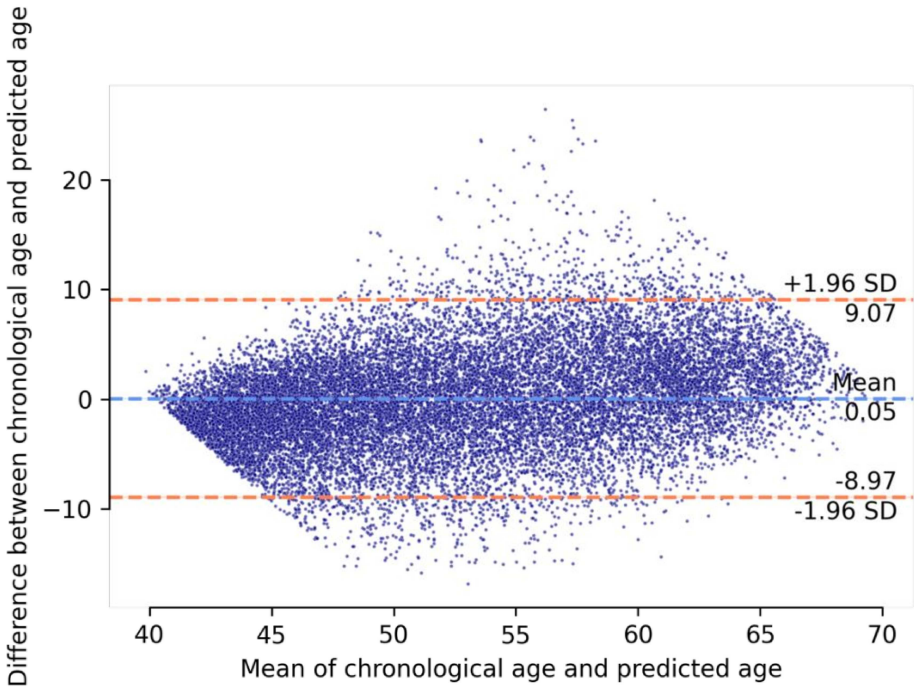
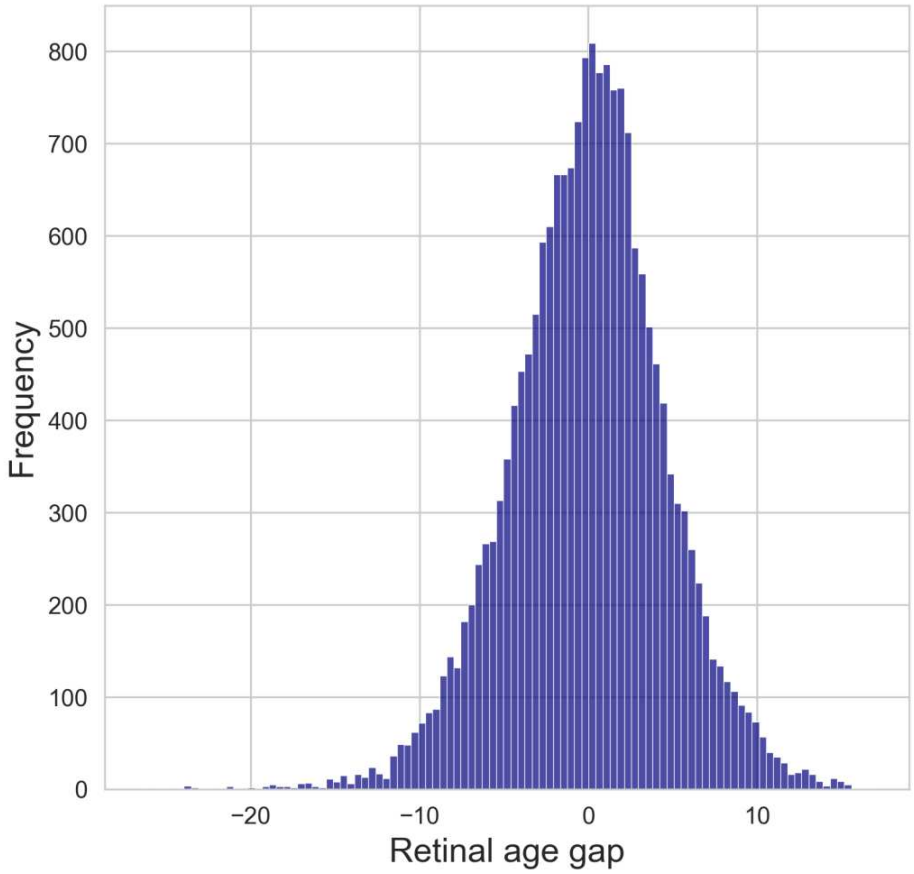
Supplement Figure 1



Supplement Figure 2



Supplement Table 1. Coding for medical history of diseases.

coding	meaning	node_id	parent_id
1065	hypertension	1081	1071
1066	heart/cardiac problem	1082	1071
1067	peripheral vascular disease	1084	1071
1068	venous thromboembolic disease	1085	1071
1072	essential hypertension	1089	1081
1073	gestational hypertension/pre-eclampsia	1090	1081
1074	angina	1091	1082
1075	heart attack/myocardial infarction	1092	1082
1076	heart failure/pulmonary odema	1093	1082
1077	heart arrhythmia	1094	1082
1078	heart valve problem/heart murmur	1095	1082
1079	cardiomyopathy	1096	1082
1080	pericardial problem	1097	1082
1081	stroke	1098	1083
1082	transient ischaemic attack (tia)	1099	1083
1083	subdural haemorrhage/haematoma	1100	1083
1086	subarachnoid haemorrhage	1103	1098
1087	leg claudication/ intermittent claudication	1104	1084
1088	arterial embolism	1105	1084
1093	pulmonary embolism +/- dvt	1111	1085
1094	deep venous thrombosis (dvt)	1112	1085
1111	asthma	1130	1072
1112	chronic obstructive airways disease/copd	1131	1072
1113	emphysema/chronic bronchitis	1132	1072
1114	bronchiectasis	1133	1072
1115	interstitial lung disease	1134	1072
1117	other respiratory problems	1136	1072
1120	asbestosis	1139	1134
1121	pulmonary fibrosis	1140	1134
1122	fibrosing alveolitis/unspecified alveolitis	1141	1134
1123	sleep apnoea	1142	1136
1124	respiratory failure	1143	1136
1125	pleurisy	1144	1136
1126	spontaneous pneumothorax/recurrent pneumothorax	1145	1560
1134	oesophageal disorder	1153	1073
1135	stomach disorder	1154	1073
1136	liver/biliary/pancreas problem	1156	1073

1137	other abdominal problem	1158	1073
1138	gastro-oesophageal reflux (gord) / gastric reflux	1159	1153
1139	oesophagitis/barretts oesophagus	1160	1153
1140	oesophageal stricture	1161	1153
1141	oesophageal varicies	1162	1153
1142	gastric/stomach ulcers	1163	1154
1143	gastritis/gastric erosions	1164	1154
1154	irritable bowel syndrome	1175	1155
1155	hepatitis	1176	1156
1156	infective/viral hepatitis	1177	1176
1157	non-infective hepatitis	1178	1176
1158	liver failure/cirrhosis	1179	1156
1159	bile duct disease	1180	1156
1160	bile duct obstruction/ascending cholangitis	1181	1180
1161	gall bladder disease	1182	1156
1162	cholelithiasis/gall stones	1183	1182
1163	cholecystitis	1184	1182
1164	pancreatic disease	1185	1156
1165	pancreatitis	1186	1185
1190	peritonitis	1211	1158
1191	gastrointestinal bleeding	1212	1158
1192	renal/kidney failure	1213	1074
1193	renal failure requiring dialysis	1214	1213
1194	renal failure not requiring dialysis	1215	1213
1196	urinary tract infection/kidney infection	1217	1074
1197	kidney stone/ureter stone/bladder stone	1218	1074
1200	ureteric obstruction/hydronephrosis	1221	1074
1201	bladder problem (not cancer)	1222	1074
1202	urinary frequency / incontinence	1223	1222
1207	prostate problem (not cancer)	1232	1231
1210	scrotal problem (not cancer)	1235	1231
1214	testicular problems (not cancer)	1239	1231
1220	diabetes	1245	1075
1221	gestational diabetes	1246	1245
1222	type 1 diabetes	1247	1245
1223	type 2 diabetes	1248	1245
1224	thyroid problem (not cancer)	1249	1075
1225	hyperthyroidism/thyrotoxicosis	1250	1249
1226	hypothyroidism/myxoedema	1251	1249
1228	thyroid radioablation therapy	1253	1249
1229	parathyroid gland problem (not cancer)	1254	1075

1230	parathyroid hyperplasia/adenoma	1255	1254
1232	disorder of adrenal gland	1257	1075
1233	adrenal tumour	1258	1257
1234	adrenocortical insufficiency/addison's disease	1259	1257
1235	hyperaldosteronism/conn's syndrome	1260	1257
1236	phaeochromocytoma	1261	1257
1237	disorder or pituitary gland	1262	1075
1238	pituitary adenoma/tumour	1263	1262
1239	cushings syndrome	1264	1075
1240	neurological injury/trauma	1266	1076
1242	eye/eyelid problem	1268	1076
1243	psychological/psychiatric problem	1269	1076
1244	infection of nervous system	1270	1265
1245	brain abscess/intracranial abscess	1271	1270
1246	encephalitis	1272	1270
1247	meningitis	1273	1270
1248	spinal abscess	1274	1270
1249	cranial nerve problem/palsy	1275	1265
1250	bell's palsy/facial nerve palsy	1276	1275
1251	spinal cord disorder	1277	1265
1252	paraplegia	1278	1277
1254	peripheral nerve disorder	1280	1265
1255	peripheral neuropathy	1281	1280
1256	acute infective polyneuritis/guillain-barre syndrome	1282	1280
1257	trapped nerve/compressed nerve	1283	1280
1258	chronic/degenerative neurological problem	1284	1265
1259	motor neurone disease	1285	1284
1260	myasthenia gravis	1286	1284
1261	multiple sclerosis	1287	1284
1262	parkinsons disease	1288	1284
1263	dementia/alzheimers/cognitive impairment	1289	1284
1264	epilepsy	1290	1265
1265	migraine	1291	1265
1266	head injury	1292	1266
1267	spinal injury	1293	1266
1274	eye infection	1300	1268
1275	retinal problem	1301	1268
1276	diabetic eye disease	1302	1268
1277	glaucoma	1303	1268
1278	cataract	1304	1268

1279	eye trauma	1305	1268
1281	retinal detachment	1307	1301
1282	retinal artery/vein occlusion	1308	1301
1286	depression	1312	1269
1287	anxiety/panic attacks	1313	1269
1288	nervous breakdown	1314	1269
1289	schizophrenia	1315	1269
1290	deliberate self-harm/suicide attempt	1316	1269
1291	mania/bipolar disorder/manic depression	1317	1269
1293	bone disorder	1319	1077
1294	back problem	1320	1077
1295	joint disorder	1321	1077
1297	muscle/soft tissue problem	1323	1077
1308	osteomyelitis	1347	1319
1309	osteoporosis	1348	1319
1310	paget's disease	1349	1319
1311	spine arthritis/spondylitis	1350	1320
1312	prolapsed disc/slipped disc	1351	1595
1313	ankylosing spondylitis	1352	1320
1322	myositis/myopathy	1361	1323
1327	low platelets/platelet disorder	1366	1503
1328	haemophilia	1367	1503
1330	iron deficiency anaemia	1369	1504
1331	pernicious anaemia	1370	1504
1332	aplastic anaemia	1371	1504
1339	sickle cell disease	1378	1509
1340	thalassaemia	1379	1509
1344	stevens johnson syndrome	1386	1513
1345	pemphigoid/pemphigus	1387	1513
1348	gynaecological disorder (not cancer)	1390	1079
1349	ovarian cyst or cysts	1391	1614
1350	polycystic ovaries/polycystic ovarian syndrome	1392	1614
1351	uterine fibroids	1393	1615
1352	uterine polyps	1394	1615
1353	vaginal prolapse/uterine prolapse	1395	1615
1364	breast disease (not cancer)	1407	1079
1366	fibrocystic disease	1409	1407
1367	breast cysts	1410	1407
1371	sarcoidosis	1414	1080
1372	vasculitis	1415	1416
1373	connective tissue disorder	1416	1080

1374	allergy/hypersensitivity/anaphylaxis	1417	1080
1376	giant cell/temporal arteritis	1419	1415
1377	polymyalgia rheumatica	1420	1415
1378	wegners granulmatosis	1421	1415
1379	microscopic polyarteritis	1422	1415
1380	polyartertis nodosa	1423	1415
1381	systemic lupus erythematosis/sle	1424	1416
1382	sjogren's syndrome/sicca syndrome	1425	1416
1383	dermatopolymyositis	1426	1416
1384	scleroderma/systemic sclerosis	1427	1416
1385	allergy or anaphylactic reaction to food	1428	1417
1386	allergy or anaphylactic reaction to drug	1429	1417
1387	hayfever/allergic rhinitis	1430	1417
1394	peripheral nerve injury	1438	1266
1396	enlarged prostate	1441	1232
1397	other demyelinating disease (not multiple sclerosis)	1442	1284
1398	pneumonia	1443	1660
1400	peptic ulcer	1445	1158
1402	endometriosis	1451	1615
1403	female infertility	1452	1390
1404	male infertility	1453	1231
1405	other renal/kidney problem	1454	1074
1406	muscle or soft tissue injuries	1457	1323
1407	burns	1458	1077
1408	alcohol dependency	1461	1460
1409	opioid dependency	1462	1460
1410	other substance abuse/dependency	1463	1460
1411	lung abscess	1464	1660
1412	bronchitis	1465	1132
1413	nasal/sinus disorder	1467	1466
1414	throat or larynx disorder	1468	1466
1415	ear/vestibular disorder	1469	1466
1416	chronic sinusitis	1470	1467
1417	nasal polyps	1471	1467
1418	chronic laryngitis	1472	1468
1419	vocal cord polyp	1473	1468
1420	otosclerosis	1474	1469
1421	meniere's disease	1475	1469
1425	cerebral aneurysm	1480	1083
1426	myocarditis	1481	1082

1427	polycystic kidney	1482	1454
1428	thyroiditis	1483	1249
1429	acromegaly	1484	1262
1430	hypopituitarism	1485	1262
1431	hyperprolactinaemia	1486	1262
1432	carcinoid syndrome/tumour	1487	1075
1433	cerebral palsy	1488	1265
1434	other neurological problem	1489	1265
1435	optic neuritis	1490	1268
1436	headaches (not migraine)	1491	1489
1437	myasthenia gravis	1492	1489
1438	polycythaemia vera	1493	1507
1439	hiv/aids	1748	1747
1440	tuberculosis (tb)	1761	1758
1441	malaria	1763	1762
1442	helicobacter pylori	1760	1758
1443	schistosomiasis/bilharzia	1764	1762
1445	clotting disorder/excessive bleeding	1503	1502
1446	anaemia	1504	1502
1447	pancytopenia	1505	1502
1448	neutropenia/lymphopenia	1506	1502
1449	myeloproliferative disorder	1507	1502
1450	monoclonal gammopathy/not myeloma	1508	1502
1451	hereditary/genetic haematological disorder	1509	1502
1452	eczema/dermatitis	1511	1510
1453	psoriasis	1512	1510
1454	blistering/desquamating skin disorder	1513	1510
1455	chronic skin ulcers	1514	1510
1456	malabsorption/coeliac disease	1516	1155
1457	duodenal ulcer	1517	1155
1458	diverticular disease/diverticulitis	1518	1155
1459	colitis/not crohns or ulcerative colitis	1519	1155
1460	rectal or colon adenoma/polyps	1520	1155
1461	inflammatory bowel disease	1521	1155
1462	crohns disease	1522	1521
1463	ulcerative colitis	1523	1521
1464	rheumatoid arthritis	1524	1321
1465	osteoarthritis	1525	1321
1466	gout	1526	1321
1467	other joint disorder	1527	1321
1468	diabetic neuropathy/ulcers	1528	1280

1469	post-traumatic stress disorder	1530	1269
1470	anorexia/bulimia/other eating disorder	1531	1269
1471	atrial fibrillation	1532	1094
1472	emphysema	1534	1132
1473	high cholesterol	1536	1071
1474	hiatus hernia	1537	1153
1475	sclerosing cholangitis	1538	1180
1476	sciatica	1539	1320
1477	psoriatic arthropathy	1540	1321
1478	cervical spondylosis	1541	1608
1479	rheumatic fever	1542	1082
1480	dermatomyositis	1543	1426
1481	polymyositis	1544	1426
1482	chronic fatigue syndrome	1545	1080
1483	atrial flutter	1546	1094
1484	wolff parkinson white / wpw syndrome	1547	1094
1485	irregular heart beat	1548	1094
1486	sick sinus syndrome	1549	1094
1487	svt / supraventricular tachycardia	1550	1094
1488	mitral valve prolapse	1551	1650
1489	mitral stenosis	1552	1650
1490	aortic stenosis	1553	1652
1491	brain haemorrhage	1554	1098
1492	aortic aneurysm	1555	1084
1493	other venous/lymphatic disease	1556	1071
1494	varicose veins	1557	1556
1495	lymphoedema	1558	1556
1496	alpha-1 antitrypsin deficiency	1559	1132
1497	pneumothorax	1560	1136
1498	empyema	1561	1660
1499	labyrinthitis	1562	1469
1500	vertigo	1563	1469
1501	pyloric stenosis	1564	1154
1502	appendicitis	1565	1155
1503	anal problem	1566	1155
1504	anal fissure	1567	1566
1505	haemorrhoids / piles	1568	1566
1506	primary biliary cirrhosis	1569	1179
1507	haemochromatosis	1570	1156
1508	jaundice (unknown cause)	1571	1156
1509	gastroenteritis/dysentry	1572	1158

1510	dyspepsia / indigestion	1573	1158
1511	abdominal hernia	1574	1158
1512	umbilical hernia	1575	1574
1513	inguinal hernia	1576	1574
1514	cystitis	1577	1217
1515	pyelonephritis	1578	1217
1516	bph / benign prostatic hypertrophy	1579	1232
1517	prostatitis	1580	1232
1518	erectile dysfunction / impotence	1581	1231
1519	kidney nephropathy	1582	1454
1520	iga nephropathy	1583	1582
1521	diabetes insipidus	1584	1245
1522	grave's disease	1585	1249
1523	trigemminal neuralgia	1586	1275
1524	spina bifida	1587	1277
1525	benign / essential tremor	1588	1489
1526	polio / poliomyelitis	1589	1489
1527	retinitis pigmentosa	1590	1301
1528	macular degeneration	1591	1301
1529	dry eyes	1592	1268
1530	iritis	1593	1268
1531	post-natal depression	1594	1312
1532	disc problem	1595	1320
1533	disc degeneration	1596	1595
1534	back pain	1597	1320
1535	scoliosis	1598	1320
1536	spinal stenosis	1599	1320
1537	joint pain	1600	1527
1538	arthritis (nos)	1601	1321
1540	plantar fascitis	1603	1323
1541	carpal tunnel syndrome	1604	1323
1542	fibromyalgia	1605	1323
1544	dupuytren's contracture	1607	1323
1545	neck problem/injury	1608	1077
1546	essential thrombocytosis	1609	1503
1548	acne/acne vulgaris	1611	1510
1549	lichen planus	1612	1510
1550	lichen sclerosis	1613	1510
1551	ovarian problem	1614	1390
1552	uterine problem	1615	1390
1553	cervical problem	1616	1390

1554	cervical intra-epithelial neoplasia (cin) / precancerous cells cervix	1617	1616
1555	cervical polyps	1618	1616
1556	menorrhagia (unknown cause)	1619	1390
1557	pelvic inflammatory disease/ pid	1620	1390
1558	ectopic pregnancy	1622	1621
1559	miscarriage	1623	1621
1560	breast fibroadenoma	1624	1407
1561	raynaud's phenomenon/disease	1625	1416
1562	food intolerance	1626	1417
1563	urticaria	1627	1417
1564	antiphospholipid syndrome	1628	1080
1566	mrsa / methicillin resistant staphylococcus aureus	1759	1758
1567	infectious mononucleosis / glandular fever / epstein barr virus (ebv)	1756	1747
1568	measles / morbillivirus	1750	1747
1569	mumps / epidemic parotitis	1757	1747
1570	rubella / german measles	1751	1747
1571	chickenpox	1753	1752
1572	whooping cough / pertussis	1769	1758
1573	shingles	1754	1752
1574	diphtheria	1768	1758
1575	herpes simplex	1755	1747
1576	dengue fever	1765	1762
1577	typhoid fever	1766	1762
1578	hepatitis a	1642	1177
1579	hepatitis b	1643	1177
1580	hepatitis c	1644	1177
1581	hepatitis d	1645	1177
1582	hepatitis e	1646	1177
1583	ischaemic stroke	1649	1098
1584	mitral valve disease	1650	1095
1585	mitral regurgitation / incompetence	1651	1650
1586	aortic valve disease	1652	1095
1587	aortic regurgitation / incompetence	1653	1652
1588	hypertrophic cardiomyopathy (hcm / hocm)	1654	1096
1589	pericarditis	1655	1097
1590	pericardial effusion	1656	1097
1591	aortic aneurysm rupture	1657	1555
1592	aortic dissection	1658	1555
1593	varicose ulcer	1659	1556

1594	respiratory infection	1660	1072
1595	pleural plaques (not known asbestosis)	1662	1136
1596	pleural effusion	1663	1136
1597	tinnitus / tiniitis	1664	1469
1598	tonsiltis	1665	1468
1599	constipation	1666	1155
1600	bowel / intestinal perforation	1667	1155
1601	bowel / intestinal infarction	1668	1155
1602	bowel / intestinal obstruction	1670	1155
1603	rectal prolapse	1671	1155
1604	alcoholic liver disease / alcoholic cirrhosis	1672	1179
1605	femoral hernia	1673	1574
1606	incisional hernia	1674	1574
1607	diabetic nephropathy	1675	1582
1608	nephritis	1676	1454
1609	glomerulnephritis	1677	1676
1610	thyroid goitre	1678	1249
1611	hyperparathyroidism	1679	1254
1613	blepharitis / eyelid infection	1681	1268
1614	stress	1682	1269
1615	obsessive compulsive disorder (ocd)	1683	1269
1616	insomnia	1684	1269
1617	osteopenia	1685	1319
1618	soft tissue inflammation	1686	1323
1619	tendonitis / tendinitis / tenosynovitis	1687	1686
1620	bursitis	1688	1686
1621	synovitis	1689	1686
1622	epicondylitis	1690	1686
1623	tennis elbow / lateral epicondylitis	1691	1690
1624	housemaid's knee (prepatellar bursitis)	1692	1688
1625	cellulitis	1693	1510
1626	fracture skull / head	1697	1696
1627	fracture jaw	1698	1696
1628	fracture nose	1699	1696
1629	fracture face / orbit / eye socket	1700	1696
1630	fracture neck / cervical fracture	1701	1696
1631	fracture clavicle / collar bone	1703	1702
1632	fracture shoulder / scapula	1704	1702
1633	fracture upper arm / humerus / elbow	1705	1702
1634	fracture forearm / wrist	1706	1702
1635	fracture radius	1707	1706

1636	fracture ulna	1708	1706
1637	fracture wrist / colles fracture	1709	1706
1638	fracture hand	1710	1702
1639	fracture finger	1711	1702
1640	fracture thumb	1712	1702
1644	fracture rib	1717	1713
1645	fracture sternum	1718	1713
1646	fracture vertebra / crush fracture / vertebral collapse	1719	1713
1647	fracture pelvis	1721	1720
1648	fracture neck of femur / hip	1722	1720
1649	fracture shaft of femur	1723	1720
1650	fracture patella / knee	1724	1720
1651	fracture lower leg / ankle	1725	1720
1652	fracture tibia	1726	1725
1653	fracture fibula	1727	1725
1654	fracture foot	1728	1720
1655	fracture metatarsal	1729	1728
1656	fracture toe	1730	1728
1657	septicaemia / sepsis	1731	1495
1658	myelofibrosis	1732	1507
1659	meningioma / benign meningeal tumour	1733	1489
1660	rosacea	1734	1510
1661	vitiligo	1735	1510
1662	cervical erosion	1736	1616
1663	abnormal smear (cervix)	1737	1617
1664	dysmenorrhoea / dysmenorrhea	1738	1390
1665	menopausal symptoms / menopause	1739	1390
1666	benign breast lump	1740	1407
1667	alopecia / hair loss	1741	1510
1668	allergy to house dust mite	1742	1417
1669	contact dermatitis	1743	1417
1670	allergy to elastoplast	1744	1743
1671	allergy to nickel	1745	1743
1674	varicella zoster virus	1752	1747
1675	giardia / giardiasis	1767	1762
1676	yellow fever	1770	1762
1677	scarlet fever / scarlatina	1771	1758
1678	chlamydia	1772	1758
1679	undescended testicle	1773	1231
1680	bowen's disease	1776	1510

1681	hydatiform mole	1777	1391
1682	benign insulinoma	1778	1075
1683	benign neuroma	1779	1489
1001	lung cancer	1003	1095
1002	breast cancer	1007	0
1003	skin cancer	1010	0
1004	cancer of lip/mouth/pharynx/oral cavity	1012	1001
1005	salivary gland cancer	1013	1012
1006	larynx/throat cancer	1014	1095
1007	nasal cavity cancer	1015	1001
1008	ear cancer	1016	1095
1009	sinus cancer	1017	1001
1010	lip cancer	1018	1012
1011	tongue cancer	1019	1012
1012	gum cancer	1020	1012
1015	parotid gland cancer	1023	1013
1016	other salivary gland cancer	1024	1013
1017	oesophageal cancer	1025	1002
1018	stomach cancer	1026	1002
1019	small intestine/small bowel cancer	1027	1002
1020	large bowel cancer/colorectal cancer	1028	1002
1021	anal cancer	1029	1002
1022	colon cancer/sigmoid cancer	1030	1028
1023	rectal cancer	1031	1028
1024	liver/hepatocellular cancer	1032	1002
1025	gallbladder/bile duct cancer	1033	1002
1026	pancreas cancer	1034	1002
1027	small cell lung cancer	1035	1003
1028	non-small cell lung cancer	1036	1003
1029	peripheral nerve/autonomic nerve cancer	1037	1005
1030	eye and/or adnexal cancer	1038	1005
1031	meningeal cancer / malignant meningioma	1039	1005
1032	brain cancer / primary malignant brain tumour	1040	1005
1033	spinal cord or cranial nerve cancer	1041	1005
1034	kidney/renal cell cancer	1042	1006
1035	bladder cancer	1043	1006
1036	other cancer of urinary tract	1044	1006
1037	female genital tract cancer	1045	1008
1038	male genital tract cancer	1046	1008
1039	ovarian cancer	1047	1045
1040	uterine/endometrial cancer	1048	1045

1041	cervical cancer	1049	1045
1042	vaginal cancer	1050	1045
1043	vulval cancer	1051	1045
1044	prostate cancer	1052	1046
1045	testicular cancer	1053	1046
1046	penis cancer	1054	1046
1047	lymphoma	1055	1009
1048	leukaemia	1056	1009
1050	multiple myeloma	1058	1009
1051	myelofibrosis or myelodysplasia	1059	1009
1052	hodgkins lymphoma / hodgkins disease	1060	1055
1053	non-hodgkins lymphoma	1061	1055
1055	chronic lymphocytic	1063	1056
1056	chronic myeloid	1064	1056
1058	other haematological malignancy	1066	1009
1059	malignant melanoma	1067	1010
1060	non-melanoma skin cancer	1068	1010
1061	basal cell carcinoma	1069	1068
1062	squamous cell carcinoma	1070	1068
1063	primary bone cancer	1071	1011
1064	mesothelioma	1072	1011
1065	thyroid cancer	1073	1011
1066	parathyroid cancer	1074	1011
1067	adrenal cancer	1075	1011
1068	sarcoma/fibrosarcoma	1076	1011
1070	malignant lymph node, unspecified	1078	1011
1071	metastatic cancer (unknown primary)	1079	1011
1072	cin/pre-cancer cells cervix	1080	1049
1073	rodent ulcer	1081	1069
1074	acute myeloid leukaemia	1082	1056
1075	retinoblastoma	1083	1038
1076	kaposis sarcoma	1084	1011
1077	mouth cancer	1087	1012
1078	tonsil cancer	1088	1012
1079	oropharynx / oropharyngeal cancer	1089	1012
1080	trachea cancer	1091	1095
1081	thymus cancer / malignant thymoma	1092	1095
1082	heart / mediastinum cancer	1093	1095
1084	respiratory / intrathoracic cancer	1095	0
1085	bone metastases / bony secondaries	1097	1079
1086	appendix cancer	1098	1030

1087	fallopian tube cancer	1099	1045
1088	malignant insulinoma	1100	1034

Supplement Table 2. Baseline characteristics of relatively healthy participants included in the development and validation of the deep learning models.

Baseline Characteristics	**Total**
N	11,052
Mean age (mean±SD, yrs)	52.6±7.97
Female, N (%)	5,932(53.7)
White ethnicity, N (%)	10,008(90.6)
Townsend index (mean±SD)	-1.06±2.94
College or university degree, N (%)	4,576(41.4)

Supplement Table 3. Baseline characteristics of study participants stratified by quartiles of retinal age gap.

Baseline Characteristics	Retinal Age Gap				P value
	Q1	Q2	Q3	Q4	
N	8,979	8,978	8,978	8,978	-
Mean age (mean±SD, yrs)	63.1±4.80	59.3±6.43	54.7±7.35	49.9±6.43	**<0.001**
Female, N (%)	4,751(50.9)	5,008(55.8)	5,167(57.6)	5,253(58.5)	**<0.001**
White ethnicity, N (%)	8,474(94.4)	8,430(93.9)	8,316(92.6)	8,255(92.0)	**<0.001**
Townsend index (mean±SD)	-1.45(2.79)	-1.22(2.88)	-0.989(3.02)	-0.695(3.08)	**<0.001**
College or university degree, N (%)	2,723(30.3)	2,975(35.5)	3,185(35.5)	3,577(39.8)	**<0.001**
Current/previous smoker, N (%)	4,057(45.5)	4,081(45.7)	4,056(45.4)	3,749(42.0)	**<0.001**
Above physical activity recommendation, N (%)	6,095(84.3)	6,039(82.6)	5.961(81.2)	5,987(79.8)	**<0.001**
Excellent/good health status, N (%)	6,465(72.3)	6,304(70.5)	6,150(68.9)	5,902(66.3)	**<0.001**
Obesity, N (%)	2,143(24.0)	2,282(25.5)	2,310(25.9)	2,400(26.9)	**<0.001**
Diabetes mellitus, N (%)	583(6.49)	589(6.56)	553(6.16)	626(6.97)	0.179
Hypertension, N (%)	7,429(82.7)	7,047(78.5)	6,604(73.6)	6,101(68.0)	**<0.001**
History of heart diseases, N (%)	580(6.46)	432(4.81)	313(3.49)	209(2.33)	**<0.001**
History of stroke, N (%)	187(2.08)	145(1.62)	115(1.28)	96(1.07)	**<0.001**

Supplement Table 4. Association between retinal age gap based on fundus images from left eyes with mortality using Cox proportional hazards regression models.

			Model I		Model II	
Retinal age gap	**N**	**Mean±SD (yrs)**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Retinal age gap, per one age (yrs)	32,035	-1.27±4.77	1.02 (1.00, 1.03)	**0.008**	1.01 (1.00, 1.03)	0.105
Retinal age gap						
Quantile 1	8,009	-7.26±3.36	Reference	-	Reference	-
Quantile 2	8,009	-2.57±0.86	1.07(0.95, 1.21)	0.264	1.04(0.91, 1.20)	0.570
Quantile 3	8,009	0.31±0.85	1.16(1.00, 1.34)	**0.048**	1.14(0.97, 1.35)	0.114
Quantile 4	8,008	4.47±2.33	1.42(1.18, 1.71)	**<0.001**	1.31(1.06, 1.62)	**0.012**
Trending	-	-	1.11 (1.05, 1.17)	**<0.001**	1.09 (1.02, 1.16)	**0.013**

HR = hazard ratio; CI = confidence interval.

Model I adjusted for age, sex, ethnicity, and Townsend deprivation indices.

Model II adjusted for covariates in Model I + educational level, obesity, smoking status, physical activity level, diabetes mellitus, hypertension, general health status, history of heart diseases, and history of stroke.

Supplement Table 5. Association between retinal age gap based on fundus images from left eyes with specific-cause mortality using Cox proportional hazards regression models.

	CVD-Specific		Cancer-Specific		Non-CVD/Non-cancer	
Retinal age gap	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Retinal age gap, per one age (yrs)	1.00(0.965, 1.04)	0.975	1.01(0.994, 1.03)	0.180	1.02(0.989, 1.04)	0.238
Retinal age gap						
Quantile 1	Reference	-	Reference	-	Reference	-
Quantile 2	1.20(0.86, 1.68)	0.292	1.07(0.89, 1.30)	0.476	0.90(0.69, 1.18)	0.442
Quantile 3	0.92(0.59, 1.42)	0.697	1.11(0.89, 1.39)	0.365	1.33(0.99, 1.79)	0.060
Quantile 4	1.21(0.71, 2.05)	0.485	1.22(0.92, 1.63)	0.172	1.53(1.05, 2.23)	**0.028**
Trending	1.03(0.87, 1.21)	0.736	1.06(0.97, 1.16)	0.170	1.16(1.03, 1.30)	**0.015**

HR = hazard ratio; CI = confidence interval.

Model I adjusted for age, sex, ethnicity, and Townsend deprivation indices.

Model II adjusted for covariates in Model I + educational level, obesity, smoking status, physical activity level, diabetes mellitus, hypertension, general health status, history of heart diseases, and history of stroke.

Supplement Table 6. Association between retinal age gap with mortality in the full cohort.

			Model I		Model II	
Retinal age gap	**N**	**Mean±SD (yrs)**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Retinal age gap, per one age (yrs)	46,965	-1.02±4.80	1.02(1.01, 1.03)	**<0.001**	1.02(1.01, 1.03)	**0.004**
Retinal age gap						
Quantile 1	11,742	-7.06±3.31	Reference	-	Reference	-
Quantile 2	11,741	-2.33±0.869	1.14(1.02, 1.27)	**0.019**	1.10(0.97, 1.24)	0.144
Quantile 3	11,741	0.561±0.843	1.22(1.08, 1.39)	**0.002**	1.20(1.04, 1.39)	**0.015**
Quantile 4	11,741	4.77±2.38	1.54(1.31, 1.81)	**<0.001**	1.44(1.20, 1.73)	**<0.001**
Trending	-	-	1.14(1.08, 1.20)	**<0.001**	1.12(1.06, 1.18)	**<0.001**

HR = hazard ratio; CI = confidence interval.

Model I adjusted for age, sex, ethnicity, and Townsend deprivation indices.

Model II adjusted for covariates in Model I + educational level, obesity, smoking status, physical activity level, diabetes mellitus, hypertension, general health status, history of heart diseases, and history of stroke.

Supplement Table 7. Association between retinal age gap with mortality stratified by age group.

	Age < 55 yrs		Age ≥ 55 yrs	
Retinal age gap	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Retinal age gap, per one age (yrs)	1.07(1.03, 1.11)	**0.001**	1.01(1.00, 1.02)	0.200
Retinal age gap				
Quantile 1	Reference	-	Reference	-
Quantile 2	1.12(0.53, 2.36)	0.760	1.05(0.92, 1.21)	0.455
Quantile 3	1.27(0.62, 2.60)	0.510	1.23(1.05, 1.45)	**0.012**
Quantile 4	1.62(0.81, 3.25)	0.175	1.27(1.00, 1.61)	**0.048**
Trending	1.19(1.01, 1.41)	**0.034**	1.09(1.02, 1.17)	**0.008**

HR = hazard ratio; CI = confidence interval.

Model adjusted for age, sex, ethnicity, Townsend deprivation indices, educational level, obesity, smoking status, physical activity level, diabetes mellitus, hypertension, general health status, history of heart diseases, and history of stroke.

Supplement Table 8. Association between retinal age gap with mortality stratified by smoking status.

	Current/previous smoker		Non-smoker	
Retinal age gap	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Retinal age gap, per one age (yrs)	1.02(1.00, 1.04)	**0.013**	1.01(0.99, 1.03)	0.720
Retinal age gap				
Quantile 1	Reference	-	Reference	-
Quantile 2	1.09(0.91, 1.30)	0.346	0.99(0.82, 1.21)	0.952
Quantile 3	1.43(1.17, 1.74)	**<0.001**	0.96(0.75, 1.22)	0.737
Quantile 4	1.53(1.18, 1.99)	**0.002**	1.15(0.85, 1.55)	0.357
Trending	1.17(1.08, 1.27)	**<0.001**	1.02(0.93, 1.12)	0.621

HR = hazard ratio; CI = confidence interval.

Model adjusted for age, sex, ethnicity, Townsend deprivation indices, educational level, obesity, smoking status, physical activity level, diabetes mellitus, hypertension, general health status, history of heart diseases, and history of stroke.

Supplement Table 9. Association between retinal age gap with mortality stratified by diabetes mellitus.

	Diabetes mellitus		Non-diabetes mellitus	
Retinal age gap	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Retinal age gap, per one age (yrs)	1.00(0.96, 1.03)	0.766	1.02(1.01, 1.04)	**0.009**
Retinal age gap				
Quantile 1	Reference	-	Reference	-
Quantile 2	0.84(0.58, 1.21)	0.340	1.09(0.94, 1.25)	0.244
Quantile 3	1.01(0.66, 1.52)	0.987	1.25(1.06, 1.47)	**0.008**
Quantile 4	1.18(0.70, 1.97)	0.541	1.38(1.12, 1.72)	**0.003**
Trending	1.04(0.88, 1.23)	0.635	1.12(1.05, 1.19)	**0.001**

HR = hazard ratio; CI = confidence interval.

Model adjusted for age, sex, ethnicity, Townsend deprivation indices, educational level, obesity, smoking status, physical activity level, diabetes mellitus, hypertension, general health status, history of heart diseases, and history of stroke.

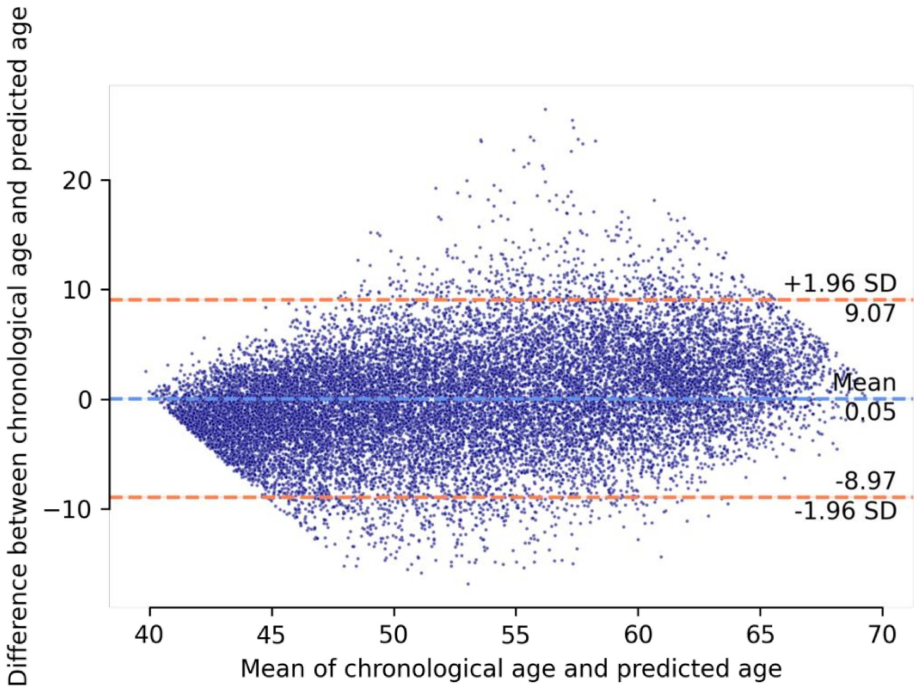
Supplement Table 10. Association between retinal age gap with mortality stratified by hypertension.

	Hypertension		Non-hypertension	
Retinal age gap	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Retinal age gap, per one age (yrs)	1.01(1.00, 1.03)	0.054	1.03(0.99, 1.06)	0.170
Retinal age gap				
Quantile 1	Reference	-	Reference	-
Quantile 2	1.04(0.90, 1.20)	0.617	1.14(0.79, 1.64)	0.494
Quantile 3	1.20(1.01, 1.41)	**0.033**	1.13(0.86, 1.97)	0.213
Quantile 4	1.26(1.01, 1.56)	**0.040**	1.91(1.18, 3.07)	**0.008**
Trending	1.08(1.02, 1.16)	**0.015**	1.22(1.04, 1.42)	**0.013**

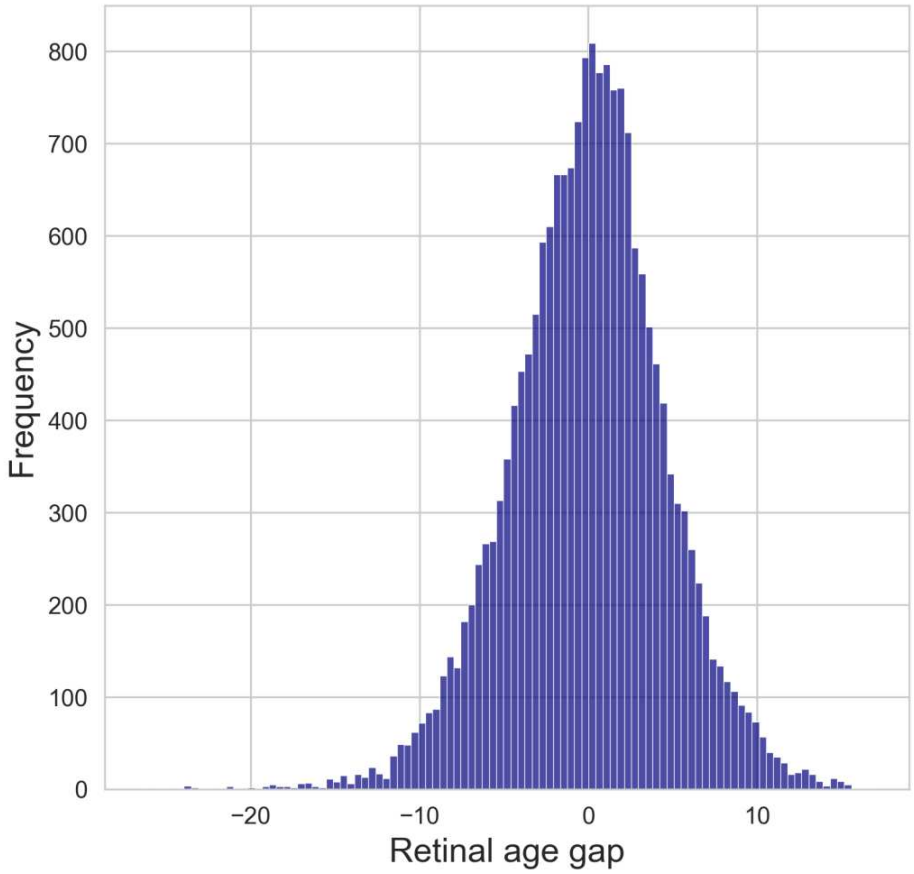
HR = hazard ratio; CI = confidence interval.

Model adjusted for age, sex, ethnicity, Townsend deprivation indices, educational level, obesity, smoking status, physical activity level, diabetes mellitus, hypertension, general health status, history of heart diseases, and history of stroke.

Supplement Figure 1



Supplement Figure 2



Supplement Table 1. Coding for medical history of diseases.

coding	meaning	node_id	parent_id
1065	hypertension	1081	1071
1066	heart/cardiac problem	1082	1071
1067	peripheral vascular disease	1084	1071
1068	venous thromboembolic disease	1085	1071
1072	essential hypertension	1089	1081
1073	gestational hypertension/pre-eclampsia	1090	1081
1074	angina	1091	1082
1075	heart attack/myocardial infarction	1092	1082
1076	heart failure/pulmonary odema	1093	1082
1077	heart arrhythmia	1094	1082
1078	heart valve problem/heart murmur	1095	1082
1079	cardiomyopathy	1096	1082
1080	pericardial problem	1097	1082
1081	stroke	1098	1083
1082	transient ischaemic attack (tia)	1099	1083
1083	subdural haemorrhage/haematoma	1100	1083
1086	subarachnoid haemorrhage	1103	1098
1087	leg claudication/ intermittent claudication	1104	1084
1088	arterial embolism	1105	1084
1093	pulmonary embolism +/- dvt	1111	1085
1094	deep venous thrombosis (dvt)	1112	1085
1111	asthma	1130	1072
1112	chronic obstructive airways disease/copd	1131	1072
1113	emphysema/chronic bronchitis	1132	1072
1114	bronchiectasis	1133	1072
1115	interstitial lung disease	1134	1072
1117	other respiratory problems	1136	1072
1120	asbestosis	1139	1134
1121	pulmonary fibrosis	1140	1134
1122	fibrosing alveolitis/unspecified alveolitis	1141	1134
1123	sleep apnoea	1142	1136
1124	respiratory failure	1143	1136
1125	pleurisy	1144	1136
1126	spontaneous pneumothorax/recurrent pneumothorax	1145	1560
1134	oesophageal disorder	1153	1073
1135	stomach disorder	1154	1073
1136	liver/biliary/pancreas problem	1156	1073

1137	other abdominal problem	1158	1073
1138	gastro-oesophageal reflux (gord) / gastric reflux	1159	1153
1139	oesophagitis/barretts oesophagus	1160	1153
1140	oesophageal stricture	1161	1153
1141	oesophageal varicies	1162	1153
1142	gastric/stomach ulcers	1163	1154
1143	gastritis/gastric erosions	1164	1154
1154	irritable bowel syndrome	1175	1155
1155	hepatitis	1176	1156
1156	infective/viral hepatitis	1177	1176
1157	non-infective hepatitis	1178	1176
1158	liver failure/cirrhosis	1179	1156
1159	bile duct disease	1180	1156
1160	bile duct obstruction/ascending cholangitis	1181	1180
1161	gall bladder disease	1182	1156
1162	cholelithiasis/gall stones	1183	1182
1163	cholecystitis	1184	1182
1164	pancreatic disease	1185	1156
1165	pancreatitis	1186	1185
1190	peritonitis	1211	1158
1191	gastrointestinal bleeding	1212	1158
1192	renal/kidney failure	1213	1074
1193	renal failure requiring dialysis	1214	1213
1194	renal failure not requiring dialysis	1215	1213
1196	urinary tract infection/kidney infection	1217	1074
1197	kidney stone/ureter stone/bladder stone	1218	1074
1200	ureteric obstruction/hydronephrosis	1221	1074
1201	bladder problem (not cancer)	1222	1074
1202	urinary frequency / incontinence	1223	1222
1207	prostate problem (not cancer)	1232	1231
1210	scrotal problem (not cancer)	1235	1231
1214	testicular problems (not cancer)	1239	1231
1220	diabetes	1245	1075
1221	gestational diabetes	1246	1245
1222	type 1 diabetes	1247	1245
1223	type 2 diabetes	1248	1245
1224	thyroid problem (not cancer)	1249	1075
1225	hyperthyroidism/thyrotoxicosis	1250	1249
1226	hypothyroidism/myxoedema	1251	1249
1228	thyroid radioablation therapy	1253	1249
1229	parathyroid gland problem (not cancer)	1254	1075

1230	parathyroid hyperplasia/adenoma	1255	1254
1232	disorder of adrenal gland	1257	1075
1233	adrenal tumour	1258	1257
1234	adrenocortical insufficiency/addison's disease	1259	1257
1235	hyperaldosteronism/conn's syndrome	1260	1257
1236	phaeochromocytoma	1261	1257
1237	disorder or pituitary gland	1262	1075
1238	pituitary adenoma/tumour	1263	1262
1239	cushings syndrome	1264	1075
1240	neurological injury/trauma	1266	1076
1242	eye/eyelid problem	1268	1076
1243	psychological/psychiatric problem	1269	1076
1244	infection of nervous system	1270	1265
1245	brain abscess/intracranial abscess	1271	1270
1246	encephalitis	1272	1270
1247	meningitis	1273	1270
1248	spinal abscess	1274	1270
1249	cranial nerve problem/palsy	1275	1265
1250	bell's palsy/facial nerve palsy	1276	1275
1251	spinal cord disorder	1277	1265
1252	paraplegia	1278	1277
1254	peripheral nerve disorder	1280	1265
1255	peripheral neuropathy	1281	1280
1256	acute infective polyneuritis/guillain-barre syndrome	1282	1280
1257	trapped nerve/compressed nerve	1283	1280
1258	chronic/degenerative neurological problem	1284	1265
1259	motor neurone disease	1285	1284
1260	myasthenia gravis	1286	1284
1261	multiple sclerosis	1287	1284
1262	parkinsons disease	1288	1284
1263	dementia/alzheimers/cognitive impairment	1289	1284
1264	epilepsy	1290	1265
1265	migraine	1291	1265
1266	head injury	1292	1266
1267	spinal injury	1293	1266
1274	eye infection	1300	1268
1275	retinal problem	1301	1268
1276	diabetic eye disease	1302	1268
1277	glaucoma	1303	1268
1278	cataract	1304	1268

1279	eye trauma	1305	1268
1281	retinal detachment	1307	1301
1282	retinal artery/vein occlusion	1308	1301
1286	depression	1312	1269
1287	anxiety/panic attacks	1313	1269
1288	nervous breakdown	1314	1269
1289	schizophrenia	1315	1269
1290	deliberate self-harm/suicide attempt	1316	1269
1291	mania/bipolar disorder/manic depression	1317	1269
1293	bone disorder	1319	1077
1294	back problem	1320	1077
1295	joint disorder	1321	1077
1297	muscle/soft tissue problem	1323	1077
1308	osteomyelitis	1347	1319
1309	osteoporosis	1348	1319
1310	paget's disease	1349	1319
1311	spine arthritis/spondylitis	1350	1320
1312	prolapsed disc/slipped disc	1351	1595
1313	ankylosing spondylitis	1352	1320
1322	myositis/myopathy	1361	1323
1327	low platelets/platelet disorder	1366	1503
1328	haemophilia	1367	1503
1330	iron deficiency anaemia	1369	1504
1331	pernicious anaemia	1370	1504
1332	aplastic anaemia	1371	1504
1339	sickle cell disease	1378	1509
1340	thalassaemia	1379	1509
1344	stevens johnson syndrome	1386	1513
1345	pemphigoid/pemphigus	1387	1513
1348	gynaecological disorder (not cancer)	1390	1079
1349	ovarian cyst or cysts	1391	1614
1350	polycystic ovaries/polycystic ovarian syndrome	1392	1614
1351	uterine fibroids	1393	1615
1352	uterine polyps	1394	1615
1353	vaginal prolapse/uterine prolapse	1395	1615
1364	breast disease (not cancer)	1407	1079
1366	fibrocystic disease	1409	1407
1367	breast cysts	1410	1407
1371	sarcoidosis	1414	1080
1372	vasculitis	1415	1416
1373	connective tissue disorder	1416	1080

1374	allergy/hypersensitivity/anaphylaxis	1417	1080
1376	giant cell/temporal arteritis	1419	1415
1377	polymyalgia rheumatica	1420	1415
1378	wegners granulmatosis	1421	1415
1379	microscopic polyarteritis	1422	1415
1380	polyartertis nodosa	1423	1415
1381	systemic lupus erythematosis/sle	1424	1416
1382	sjogren's syndrome/sicca syndrome	1425	1416
1383	dermatopolymyositis	1426	1416
1384	scleroderma/systemic sclerosis	1427	1416
1385	allergy or anaphylactic reaction to food	1428	1417
1386	allergy or anaphylactic reaction to drug	1429	1417
1387	hayfever/allergic rhinitis	1430	1417
1394	peripheral nerve injury	1438	1266
1396	enlarged prostate	1441	1232
1397	other demyelinating disease (not multiple sclerosis)	1442	1284
1398	pneumonia	1443	1660
1400	peptic ulcer	1445	1158
1402	endometriosis	1451	1615
1403	female infertility	1452	1390
1404	male infertility	1453	1231
1405	other renal/kidney problem	1454	1074
1406	muscle or soft tissue injuries	1457	1323
1407	burns	1458	1077
1408	alcohol dependency	1461	1460
1409	opioid dependency	1462	1460
1410	other substance abuse/dependency	1463	1460
1411	lung abscess	1464	1660
1412	bronchitis	1465	1132
1413	nasal/sinus disorder	1467	1466
1414	throat or larynx disorder	1468	1466
1415	ear/vestibular disorder	1469	1466
1416	chronic sinusitis	1470	1467
1417	nasal polyps	1471	1467
1418	chronic laryngitis	1472	1468
1419	vocal cord polyp	1473	1468
1420	otosclerosis	1474	1469
1421	meniere's disease	1475	1469
1425	cerebral aneurysm	1480	1083
1426	myocarditis	1481	1082

1427	polycystic kidney	1482	1454
1428	thyroiditis	1483	1249
1429	acromegaly	1484	1262
1430	hypopituitarism	1485	1262
1431	hyperprolactinaemia	1486	1262
1432	carcinoid syndrome/tumour	1487	1075
1433	cerebral palsy	1488	1265
1434	other neurological problem	1489	1265
1435	optic neuritis	1490	1268
1436	headaches (not migraine)	1491	1489
1437	myasthenia gravis	1492	1489
1438	polycythaemia vera	1493	1507
1439	hiv/aids	1748	1747
1440	tuberculosis (tb)	1761	1758
1441	malaria	1763	1762
1442	helicobacter pylori	1760	1758
1443	schistosomiasis/bilharzia	1764	1762
1445	clotting disorder/excessive bleeding	1503	1502
1446	anaemia	1504	1502
1447	pancytopenia	1505	1502
1448	neutropenia/lymphopenia	1506	1502
1449	myeloproliferative disorder	1507	1502
1450	monoclonal gammopathy/not myeloma	1508	1502
1451	hereditary/genetic haematological disorder	1509	1502
1452	eczema/dermatitis	1511	1510
1453	psoriasis	1512	1510
1454	blistering/desquamating skin disorder	1513	1510
1455	chronic skin ulcers	1514	1510
1456	malabsorption/coeliac disease	1516	1155
1457	duodenal ulcer	1517	1155
1458	diverticular disease/diverticulitis	1518	1155
1459	colitis/not crohns or ulcerative colitis	1519	1155
1460	rectal or colon adenoma/polyps	1520	1155
1461	inflammatory bowel disease	1521	1155
1462	crohns disease	1522	1521
1463	ulcerative colitis	1523	1521
1464	rheumatoid arthritis	1524	1321
1465	osteoarthritis	1525	1321
1466	gout	1526	1321
1467	other joint disorder	1527	1321
1468	diabetic neuropathy/ulcers	1528	1280

1469	post-traumatic stress disorder	1530	1269
1470	anorexia/bulimia/other eating disorder	1531	1269
1471	atrial fibrillation	1532	1094
1472	emphysema	1534	1132
1473	high cholesterol	1536	1071
1474	hiatus hernia	1537	1153
1475	sclerosing cholangitis	1538	1180
1476	sciatica	1539	1320
1477	psoriatic arthropathy	1540	1321
1478	cervical spondylosis	1541	1608
1479	rheumatic fever	1542	1082
1480	dermatomyositis	1543	1426
1481	polymyositis	1544	1426
1482	chronic fatigue syndrome	1545	1080
1483	atrial flutter	1546	1094
1484	wolff parkinson white / wpw syndrome	1547	1094
1485	irregular heart beat	1548	1094
1486	sick sinus syndrome	1549	1094
1487	svt / supraventricular tachycardia	1550	1094
1488	mitral valve prolapse	1551	1650
1489	mitral stenosis	1552	1650
1490	aortic stenosis	1553	1652
1491	brain haemorrhage	1554	1098
1492	aortic aneurysm	1555	1084
1493	other venous/lymphatic disease	1556	1071
1494	varicose veins	1557	1556
1495	lymphoedema	1558	1556
1496	alpha-1 antitrypsin deficiency	1559	1132
1497	pneumothorax	1560	1136
1498	empyema	1561	1660
1499	labyrinthitis	1562	1469
1500	vertigo	1563	1469
1501	pyloric stenosis	1564	1154
1502	appendicitis	1565	1155
1503	anal problem	1566	1155
1504	anal fissure	1567	1566
1505	haemorrhoids / piles	1568	1566
1506	primary biliary cirrhosis	1569	1179
1507	haemochromatosis	1570	1156
1508	jaundice (unknown cause)	1571	1156
1509	gastroenteritis/dysentry	1572	1158

1510	dyspepsia / indigestion	1573	1158
1511	abdominal hernia	1574	1158
1512	umbilical hernia	1575	1574
1513	inguinal hernia	1576	1574
1514	cystitis	1577	1217
1515	pyelonephritis	1578	1217
1516	bph / benign prostatic hypertrophy	1579	1232
1517	prostatitis	1580	1232
1518	erectile dysfunction / impotence	1581	1231
1519	kidney nephropathy	1582	1454
1520	iga nephropathy	1583	1582
1521	diabetes insipidus	1584	1245
1522	grave's disease	1585	1249
1523	trigemminal neuralgia	1586	1275
1524	spina bifida	1587	1277
1525	benign / essential tremor	1588	1489
1526	polio / poliomyelitis	1589	1489
1527	retinitis pigmentosa	1590	1301
1528	macular degeneration	1591	1301
1529	dry eyes	1592	1268
1530	iritis	1593	1268
1531	post-natal depression	1594	1312
1532	disc problem	1595	1320
1533	disc degeneration	1596	1595
1534	back pain	1597	1320
1535	scoliosis	1598	1320
1536	spinal stenosis	1599	1320
1537	joint pain	1600	1527
1538	arthritis (nos)	1601	1321
1540	plantar fascitis	1603	1323
1541	carpal tunnel syndrome	1604	1323
1542	fibromyalgia	1605	1323
1544	dupuytren's contracture	1607	1323
1545	neck problem/injury	1608	1077
1546	essential thrombocytosis	1609	1503
1548	acne/acne vulgaris	1611	1510
1549	lichen planus	1612	1510
1550	lichen sclerosis	1613	1510
1551	ovarian problem	1614	1390
1552	uterine problem	1615	1390
1553	cervical problem	1616	1390

1554	cervical intra-epithelial neoplasia (cin) / precancerous cells cervix	1617	1616
1555	cervical polyps	1618	1616
1556	menorrhagia (unknown cause)	1619	1390
1557	pelvic inflammatory disease/ pid	1620	1390
1558	ectopic pregnancy	1622	1621
1559	miscarriage	1623	1621
1560	breast fibroadenoma	1624	1407
1561	raynaud's phenomenon/disease	1625	1416
1562	food intolerance	1626	1417
1563	urticaria	1627	1417
1564	antiphospholipid syndrome	1628	1080
1566	mrsa / methicillin resistant staphylococcus aureus	1759	1758
1567	infectious mononucleosis / glandular fever / epstein barr virus (ebv)	1756	1747
1568	measles / morbillivirus	1750	1747
1569	mumps / epidemic parotitis	1757	1747
1570	rubella / german measles	1751	1747
1571	chickenpox	1753	1752
1572	whooping cough / pertussis	1769	1758
1573	shingles	1754	1752
1574	diphtheria	1768	1758
1575	herpes simplex	1755	1747
1576	dengue fever	1765	1762
1577	typhoid fever	1766	1762
1578	hepatitis a	1642	1177
1579	hepatitis b	1643	1177
1580	hepatitis c	1644	1177
1581	hepatitis d	1645	1177
1582	hepatitis e	1646	1177
1583	ischaemic stroke	1649	1098
1584	mitral valve disease	1650	1095
1585	mitral regurgitation / incompetence	1651	1650
1586	aortic valve disease	1652	1095
1587	aortic regurgitation / incompetence	1653	1652
1588	hypertrophic cardiomyopathy (hcm / hocm)	1654	1096
1589	pericarditis	1655	1097
1590	pericardial effusion	1656	1097
1591	aortic aneurysm rupture	1657	1555
1592	aortic dissection	1658	1555
1593	varicose ulcer	1659	1556

1594	respiratory infection	1660	1072
1595	pleural plaques (not known asbestosis)	1662	1136
1596	pleural effusion	1663	1136
1597	tinnitus / tiniitis	1664	1469
1598	tonsiltis	1665	1468
1599	constipation	1666	1155
1600	bowel / intestinal perforation	1667	1155
1601	bowel / intestinal infarction	1668	1155
1602	bowel / intestinal obstruction	1670	1155
1603	rectal prolapse	1671	1155
1604	alcoholic liver disease / alcoholic cirrhosis	1672	1179
1605	femoral hernia	1673	1574
1606	incisional hernia	1674	1574
1607	diabetic nephropathy	1675	1582
1608	nephritis	1676	1454
1609	glomerulnephritis	1677	1676
1610	thyroid goitre	1678	1249
1611	hyperparathyroidism	1679	1254
1613	blepharitis / eyelid infection	1681	1268
1614	stress	1682	1269
1615	obsessive compulsive disorder (ocd)	1683	1269
1616	insomnia	1684	1269
1617	osteopenia	1685	1319
1618	soft tissue inflammation	1686	1323
1619	tendonitis / tendinitis / tenosynovitis	1687	1686
1620	bursitis	1688	1686
1621	synovitis	1689	1686
1622	epicondylitis	1690	1686
1623	tennis elbow / lateral epicondylitis	1691	1690
1624	housemaid's knee (prepatellar bursitis)	1692	1688
1625	cellulitis	1693	1510
1626	fracture skull / head	1697	1696
1627	fracture jaw	1698	1696
1628	fracture nose	1699	1696
1629	fracture face / orbit / eye socket	1700	1696
1630	fracture neck / cervical fracture	1701	1696
1631	fracture clavicle / collar bone	1703	1702
1632	fracture shoulder / scapula	1704	1702
1633	fracture upper arm / humerus / elbow	1705	1702
1634	fracture forearm / wrist	1706	1702
1635	fracture radius	1707	1706

1636	fracture ulna	1708	1706
1637	fracture wrist / colles fracture	1709	1706
1638	fracture hand	1710	1702
1639	fracture finger	1711	1702
1640	fracture thumb	1712	1702
1644	fracture rib	1717	1713
1645	fracture sternum	1718	1713
1646	fracture vertebra / crush fracture / vertebral collapse	1719	1713
1647	fracture pelvis	1721	1720
1648	fracture neck of femur / hip	1722	1720
1649	fracture shaft of femur	1723	1720
1650	fracture patella / knee	1724	1720
1651	fracture lower leg / ankle	1725	1720
1652	fracture tibia	1726	1725
1653	fracture fibula	1727	1725
1654	fracture foot	1728	1720
1655	fracture metatarsal	1729	1728
1656	fracture toe	1730	1728
1657	septicaemia / sepsis	1731	1495
1658	myelofibrosis	1732	1507
1659	meningioma / benign meningeal tumour	1733	1489
1660	rosacea	1734	1510
1661	vitiligo	1735	1510
1662	cervical erosion	1736	1616
1663	abnormal smear (cervix)	1737	1617
1664	dysmenorrhoea / dysmenorrhea	1738	1390
1665	menopausal symptoms / menopause	1739	1390
1666	benign breast lump	1740	1407
1667	alopecia / hair loss	1741	1510
1668	allergy to house dust mite	1742	1417
1669	contact dermatitis	1743	1417
1670	allergy to elastoplast	1744	1743
1671	allergy to nickel	1745	1743
1674	varicella zoster virus	1752	1747
1675	giardia / giardiasis	1767	1762
1676	yellow fever	1770	1762
1677	scarlet fever / scarlatina	1771	1758
1678	chlamydia	1772	1758
1679	undescended testicle	1773	1231
1680	bowen's disease	1776	1510

1681	hydatiform mole	1777	1391
1682	benign insulinoma	1778	1075
1683	benign neuroma	1779	1489
1001	lung cancer	1003	1095
1002	breast cancer	1007	0
1003	skin cancer	1010	0
1004	cancer of lip/mouth/pharynx/oral cavity	1012	1001
1005	salivary gland cancer	1013	1012
1006	larynx/throat cancer	1014	1095
1007	nasal cavity cancer	1015	1001
1008	ear cancer	1016	1095
1009	sinus cancer	1017	1001
1010	lip cancer	1018	1012
1011	tongue cancer	1019	1012
1012	gum cancer	1020	1012
1015	parotid gland cancer	1023	1013
1016	other salivary gland cancer	1024	1013
1017	oesophageal cancer	1025	1002
1018	stomach cancer	1026	1002
1019	small intestine/small bowel cancer	1027	1002
1020	large bowel cancer/colorectal cancer	1028	1002
1021	anal cancer	1029	1002
1022	colon cancer/sigmoid cancer	1030	1028
1023	rectal cancer	1031	1028
1024	liver/hepatocellular cancer	1032	1002
1025	gallbladder/bile duct cancer	1033	1002
1026	pancreas cancer	1034	1002
1027	small cell lung cancer	1035	1003
1028	non-small cell lung cancer	1036	1003
1029	peripheral nerve/autonomic nerve cancer	1037	1005
1030	eye and/or adnexal cancer	1038	1005
1031	meningeal cancer / malignant meningioma	1039	1005
1032	brain cancer / primary malignant brain tumour	1040	1005
1033	spinal cord or cranial nerve cancer	1041	1005
1034	kidney/renal cell cancer	1042	1006
1035	bladder cancer	1043	1006
1036	other cancer of urinary tract	1044	1006
1037	female genital tract cancer	1045	1008
1038	male genital tract cancer	1046	1008
1039	ovarian cancer	1047	1045
1040	uterine/endometrial cancer	1048	1045

1041	cervical cancer	1049	1045
1042	vaginal cancer	1050	1045
1043	vulval cancer	1051	1045
1044	prostate cancer	1052	1046
1045	testicular cancer	1053	1046
1046	penis cancer	1054	1046
1047	lymphoma	1055	1009
1048	leukaemia	1056	1009
1050	multiple myeloma	1058	1009
1051	myelofibrosis or myelodysplasia	1059	1009
1052	hodgkins lymphoma / hodgkins disease	1060	1055
1053	non-hodgkins lymphoma	1061	1055
1055	chronic lymphocytic	1063	1056
1056	chronic myeloid	1064	1056
1058	other haematological malignancy	1066	1009
1059	malignant melanoma	1067	1010
1060	non-melanoma skin cancer	1068	1010
1061	basal cell carcinoma	1069	1068
1062	squamous cell carcinoma	1070	1068
1063	primary bone cancer	1071	1011
1064	mesothelioma	1072	1011
1065	thyroid cancer	1073	1011
1066	parathyroid cancer	1074	1011
1067	adrenal cancer	1075	1011
1068	sarcoma/fibrosarcoma	1076	1011
1070	malignant lymph node, unspecified	1078	1011
1071	metastatic cancer (unknown primary)	1079	1011
1072	cin/pre-cancer cells cervix	1080	1049
1073	rodent ulcer	1081	1069
1074	acute myeloid leukaemia	1082	1056
1075	retinoblastoma	1083	1038
1076	kaposis sarcoma	1084	1011
1077	mouth cancer	1087	1012
1078	tonsil cancer	1088	1012
1079	oropharynx / oropharyngeal cancer	1089	1012
1080	trachea cancer	1091	1095
1081	thymus cancer / malignant thymoma	1092	1095
1082	heart / mediastinum cancer	1093	1095
1084	respiratory / intrathoracic cancer	1095	0
1085	bone metastases / bony secondaries	1097	1079
1086	appendix cancer	1098	1030

1087	fallopian tube cancer	1099	1045
1088	malignant insulinoma	1100	1034

Supplement Table 2. Baseline characteristics of relatively healthy participants included in the development and validation of the deep learning models.

Baseline Characteristics	**Total**
N	11,052
Mean age (mean±SD, yrs)	52.6±7.97
Female, N (%)	5,932(53.7)
White ethnicity, N (%)	10,008(90.6)
Townsend index (mean±SD)	-1.06±2.94
College or university degree, N (%)	4,576(41.4)

Supplement Table 3. Baseline characteristics of study participants stratified by quartiles of retinal age gap.

Baseline Characteristics	Retinal Age Gap				P value
	Q1	Q2	Q3	Q4	
N	8,979	8,978	8,978	8,978	-
Mean age (mean±SD, yrs)	63.1±4.80	59.3±6.43	54.7±7.35	49.9±6.43	**<0.001**
Female, N (%)	4,751(50.9)	5,008(55.8)	5,167(57.6)	5,253(58.5)	**<0.001**
White ethnicity, N (%)	8,474(94.4)	8,430(93.9)	8,316(92.6)	8,255(92.0)	**<0.001**
Townsend index (mean±SD)	-1.45(2.79)	-1.22(2.88)	-0.989(3.02)	-0.695(3.08)	**<0.001**
College or university degree, N (%)	2,723(30.3)	2,975(35.5)	3,185(35.5)	3,577(39.8)	**<0.001**
Current/previous smoker, N (%)	4,057(45.5)	4,081(45.7)	4,056(45.4)	3,749(42.0)	**<0.001**
Above physical activity recommendation, N (%)	6,095(84.3)	6,039(82.6)	5.961(81.2)	5,987(79.8)	**<0.001**
Excellent/good health status, N (%)	6,465(72.3)	6,304(70.5)	6,150(68.9)	5,902(66.3)	**<0.001**
Obesity, N (%)	2,143(24.0)	2,282(25.5)	2,310(25.9)	2,400(26.9)	**<0.001**
Diabetes mellitus, N (%)	583(6.49)	589(6.56)	553(6.16)	626(6.97)	0.179
Hypertension, N (%)	7,429(82.7)	7,047(78.5)	6,604(73.6)	6,101(68.0)	**<0.001**
History of heart diseases, N (%)	580(6.46)	432(4.81)	313(3.49)	209(2.33)	**<0.001**
History of stroke, N (%)	187(2.08)	145(1.62)	115(1.28)	96(1.07)	**<0.001**

Supplement Table 4. Association between retinal age gap based on fundus images from left eyes with mortality using Cox proportional hazards regression models.

			Model I		Model II	
Retinal age gap	**N**	**Mean±SD (yrs)**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Retinal age gap, per one age (yrs)	32,035	-1.27±4.77	1.02 (1.00, 1.03)	**0.008**	1.01 (1.00, 1.03)	0.105
Retinal age gap						
Quantile 1	8,009	-7.26±3.36	Reference	-	Reference	-
Quantile 2	8,009	-2.57±0.86	1.07(0.95, 1.21)	0.264	1.04(0.91, 1.20)	0.570
Quantile 3	8,009	0.31±0.85	1.16(1.00, 1.34)	**0.048**	1.14(0.97, 1.35)	0.114
Quantile 4	8,008	4.47±2.33	1.42(1.18, 1.71)	**<0.001**	1.31(1.06, 1.62)	**0.012**
Trending	-	-	1.11 (1.05, 1.17)	**<0.001**	1.09 (1.02, 1.16)	**0.013**

HR = hazard ratio; CI = confidence interval.

Model I adjusted for age, sex, ethnicity, and Townsend deprivation indices.

Model II adjusted for covariates in Model I + educational level, obesity, smoking status, physical activity level, diabetes mellitus, hypertension, general health status, history of heart diseases, and history of stroke.

Supplement Table 5. Association between retinal age gap based on fundus images from left eyes with specific-cause mortality using Cox proportional hazards regression models.

	CVD-Specific		Cancer-Specific		Non-CVD/Non-cancer	
Retinal age gap	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Retinal age gap, per one age (yrs)	1.00(0.965, 1.04)	0.975	1.01(0.994, 1.03)	0.180	1.02(0.989, 1.04)	0.238
Retinal age gap						
Quantile 1	Reference	-	Reference	-	Reference	-
Quantile 2	1.20(0.86, 1.68)	0.292	1.07(0.89, 1.30)	0.476	0.90(0.69, 1.18)	0.442
Quantile 3	0.92(0.59, 1.42)	0.697	1.11(0.89, 1.39)	0.365	1.33(0.99, 1.79)	0.060
Quantile 4	1.21(0.71, 2.05)	0.485	1.22(0.92, 1.63)	0.172	1.53(1.05, 2.23)	**0.028**
Trending	1.03(0.87, 1.21)	0.736	1.06(0.97, 1.16)	0.170	1.16(1.03, 1.30)	**0.015**

HR = hazard ratio; CI = confidence interval.

Model I adjusted for age, sex, ethnicity, and Townsend deprivation indices.

Model II adjusted for covariates in Model I + educational level, obesity, smoking status, physical activity level, diabetes mellitus, hypertension, general health status, history of heart diseases, and history of stroke.

Supplement Table 6. Association between retinal age gap with mortality in the full cohort.

			Model I		Model II	
Retinal age gap	**N**	**Mean±SD (yrs)**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Retinal age gap, per one age (yrs)	46,965	-1.02±4.80	1.02(1.01, 1.03)	**<0.001**	1.02(1.01, 1.03)	**0.004**
Retinal age gap						
Quantile 1	11,742	-7.06±3.31	Reference	-	Reference	-
Quantile 2	11,741	-2.33±0.869	1.14(1.02, 1.27)	**0.019**	1.10(0.97, 1.24)	0.144
Quantile 3	11,741	0.561±0.843	1.22(1.08, 1.39)	**0.002**	1.20(1.04, 1.39)	**0.015**
Quantile 4	11,741	4.77±2.38	1.54(1.31, 1.81)	**<0.001**	1.44(1.20, 1.73)	**<0.001**
Trending	-	-	1.14(1.08, 1.20)	**<0.001**	1.12(1.06, 1.18)	**<0.001**

HR = hazard ratio; CI = confidence interval.

Model I adjusted for age, sex, ethnicity, and Townsend deprivation indices.

Model II adjusted for covariates in Model I + educational level, obesity, smoking status, physical activity level, diabetes mellitus, hypertension, general health status, history of heart diseases, and history of stroke.

Supplement Table 7. Association between retinal age gap with mortality stratified by age group.

	Age < 55 yrs		Age ≥ 55 yrs	
Retinal age gap	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Retinal age gap, per one age (yrs)	1.07(1.03, 1.11)	**0.001**	1.01(1.00, 1.02)	0.200
Retinal age gap				
Quantile 1	Reference	-	Reference	-
Quantile 2	1.12(0.53, 2.36)	0.760	1.05(0.92, 1.21)	0.455
Quantile 3	1.27(0.62, 2.60)	0.510	1.23(1.05, 1.45)	**0.012**
Quantile 4	1.62(0.81, 3.25)	0.175	1.27(1.00, 1.61)	**0.048**
Trending	1.19(1.01, 1.41)	**0.034**	1.09(1.02, 1.17)	**0.008**

HR = hazard ratio; CI = confidence interval.

Model adjusted for age, sex, ethnicity, Townsend deprivation indices, educational level, obesity, smoking status, physical activity level, diabetes mellitus, hypertension, general health status, history of heart diseases, and history of stroke.

Supplement Table 8. Association between retinal age gap with mortality stratified by smoking status.

	Current/previous smoker		Non-smoker	
Retinal age gap	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Retinal age gap, per one age (yrs)	1.02(1.00, 1.04)	**0.013**	1.01(0.99, 1.03)	0.720
Retinal age gap				
Quantile 1	Reference	-	Reference	-
Quantile 2	1.09(0.91, 1.30)	0.346	0.99(0.82, 1.21)	0.952
Quantile 3	1.43(1.17, 1.74)	**<0.001**	0.96(0.75, 1.22)	0.737
Quantile 4	1.53(1.18, 1.99)	**0.002**	1.15(0.85, 1.55)	0.357
Trending	1.17(1.08, 1.27)	**<0.001**	1.02(0.93, 1.12)	0.621

HR = hazard ratio; CI = confidence interval.

Model adjusted for age, sex, ethnicity, Townsend deprivation indices, educational level, obesity, smoking status, physical activity level, diabetes mellitus, hypertension, general health status, history of heart diseases, and history of stroke.

Supplement Table 9. Association between retinal age gap with mortality stratified by diabetes mellitus.

	Diabetes mellitus		Non-diabetes mellitus	
Retinal age gap	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Retinal age gap, per one age (yrs)	1.00(0.96, 1.03)	0.766	1.02(1.01, 1.04)	**0.009**
Retinal age gap				
Quantile 1	Reference	-	Reference	-
Quantile 2	0.84(0.58, 1.21)	0.340	1.09(0.94, 1.25)	0.244
Quantile 3	1.01(0.66, 1.52)	0.987	1.25(1.06, 1.47)	**0.008**
Quantile 4	1.18(0.70, 1.97)	0.541	1.38(1.12, 1.72)	**0.003**
Trending	1.04(0.88, 1.23)	0.635	1.12(1.05, 1.19)	**0.001**

HR = hazard ratio; CI = confidence interval.

Model adjusted for age, sex, ethnicity, Townsend deprivation indices, educational level, obesity, smoking status, physical activity level, diabetes mellitus, hypertension, general health status, history of heart diseases, and history of stroke.

Supplement Table 10. Association between retinal age gap with mortality stratified by hypertension.

	Hypertension		**Non-hypertension**	
Retinal age gap	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Retinal age gap, per one age (yrs)	1.01(1.00, 1.03)	0.054	1.03(0.99, 1.06)	0.170
Retinal age gap				
Quantile 1	Reference	-	Reference	-
Quantile 2	1.04(0.90, 1.20)	0.617	1.14(0.79, 1.64)	0.494
Quantile 3	1.20(1.01, 1.41)	**0.033**	1.13(0.86, 1.97)	0.213
Quantile 4	1.26(1.01, 1.56)	**0.040**	1.91(1.18, 3.07)	**0.008**
Trending	1.08(1.02, 1.16)	**0.015**	1.22(1.04, 1.42)	**0.013**

HR = hazard ratio; CI = confidence interval.

Model adjusted for age, sex, ethnicity, Townsend deprivation indices, educational level, obesity, smoking status, physical activity level, diabetes mellitus, hypertension, general health status, history of heart diseases, and history of stroke.