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Association of retinal image–based, deep learning cardiac BioAge with telomere length and cardiovascular biomarkers

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SIGNIFICANCE: Our retinal image–based deep learning (DL) cardiac biological age (BioAge) model could facilitate fast, accurate, noninvasive screening for cardiovascular disease (CVD) in novel community settings and thus improve outcome with those with limited access to health care services.

PURPOSE: This study aimed to determine whether the results issued by our DL cardiac BioAge model are consistent with the known trends of CVD risk and the biomarker leukocyte telomere length (LTL), in a cohort of individuals from the UK Biobank.

METHODS: A cross-sectional cohort study was conducted using those individuals in the UK Biobank who had LTL data. These individuals were divided by sex, ranked by LTL, and then grouped into deciles. The retinal images were then presented to the DL model, and individual's cardiac BioAge was determined. Individuals within each LTL decile were then ranked by cardiac BioAge, and the mean of the CVD risk biomarkers in the top and bottom quartiles was compared. The relationship between an individual's cardiac BioAge, the CVD biomarkers, and LTL was determined using traditional correlation statistics.

RESULTS: The DL cardiac BioAge model was able to accurately stratify individuals by the traditional CVD risk biomarkers, and for both males and females, those issued with a cardiac BioAge in the top quartile of their chronological peer group had a significantly higher mean systolic blood pressure, hemoglobin A_{1c}, and 10-year Pooled Cohort Equation CVD risk scores compared with those individuals in the bottom quartile ($p<0.001$). Cardiac BioAge was associated with LTL shortening for both males and females (males: −0.22, $r^2 = 0.04$; females: −0.18, $r^2 = 0.03$).

CONCLUSIONS: In this cross-sectional cohort study, increasing CVD risk whether assessed by traditional biomarkers, CVD risk scoring, or our DL cardiac BioAge, CVD risk model, was inversely related to LTL. At a population level, our data support the growing body of evidence that suggests LTL shortening is a surrogate marker for increasing CVD risk and that this risk can be captured by our novel DL cardiac BioAge model.

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Atherosclerotic cardiovascular disease is the commonest cause of hospitalization and premature death in the United States.[1] The risk of an individual experiencing an atherosclerotic cardiovascular disease event includes both nonmodifiable variables, such as age, sex, and race/ethnicity, and modifiable variables, such as diabetes,[2] hypertension,[3] hyperlipidemia,[4] and smoking.[5] Across a population, the risk of experiencing a cardiovascular event varies greatly, and risk-based equations have therefore been developed to identify those who are at greatest risk of a cardiovascular event so that treatments can be instigated appropriate to the individual's risk.[6] The landmark Framingham Heart Study was the first to demonstrate that multivariable equations could identify an individual's risk of a cardiovascular event with far greater accuracy than the existing metrics based solely on blood pressure and cholesterol.[7] Since the Framingham-based equations were first published, other equations have been developed designed to serve different populations with refined accuracy,[8,9] but in all these equations, chronological age remains one of the strongest predictors of atherosclerotic cardiovascular disease risk. However, it is increasingly recognized that biological age (BioAge),[10] the concept that individuals age at different rates, impacts both the risk of an individual developing a chronic disease and the severity to which they are impacted by it. The fact that different individuals age at different rates is not currently captured by traditional regression-based risk equations as they assume all individuals in the population age at the same rate. The traditional equations are therefore insensitive to the variation in individual risk that results from biological aging, and it has therefore been suggested that biological markers such as leukocyte telomere length and DNA methylation rates could be used to refine the prediction of an individual experiencing a cardiovascular event.[11–14]

Currently, leukocyte telomere length testing is impractical for population screening as it is an expensive test that, as a biological specimen, requires careful handling within specialized laboratories. There is then arguably a need to develop other novel techniques that can personalize the atherosclerotic cardiovascular disease risk scores produced by the traditional atherosclerotic cardiovascular disease risk equations. The retina is unique in being the only part of the vascular system that is visible by noninvasive means. It is now recognized that deep learning (DL) can extract data from retinal images to augment the traditional means of estimating atherosclerotic cardiovascular disease risk.[15,16] We have developed a DL model (cardiac BioAge) designed to identify those individuals within a tight chronological age band who are at increased risk of cardiac events. The aim of the study was to determine whether the results issued by our cardiac BioAge model are consistent with the known trends of cardiovascular disease risk, including traditional biomarkers, such as hypertension, hemoglobin A_{1c} (HbA_{1c}), and atherosclerotic cardiovascular disease risk, and the novel biomarker leukocyte telomere length, in a cohort of individuals from the UK BioBank.

METHODS

This is a cross-sectional cohort study comprising only those individuals in the UK Biobank who had leukocyte telomere length

measurements, fundus images, and relevant cardiovascular biomarker data (systolic blood pressure, total cholesterol, high-density lipoprotein, HbA_{1c}, smoking, and diabetes status), which were used in this study. The data from the UK Biobank can be accessed via a direct request to the UK Biobank (IRB UOA-862 99) and were obtained using approved data management and data transfer protocols. The research presented in this study and the datasets used in it adhered to the principles outlined in the Declaration of Helsinki. Participants in the UK Biobank were recruited from a UK general population, and the composition of the subset of the UK Biobank dataset used in this study is shown in Table 1. Approximately only 5% of the UK Biobank population self-identified as having diabetes diagnosed by a doctor.

Cardiac BioAge model

The cardiac risk assessment DL model, CLAiR, underpinning the cardiac BioAge model, has been described previously.[17] In brief, this model produces a predicted Pooled Cohort Equation–derived atherosclerotic cardiovascular disease risk score[18] and then determines how far that individual's score deviates from that of their chronological peers (Fig. 1). The cardiac BioAge score in effect informs whether the individuals' 10-year atherosclerotic cardiovascular disease risk is greater or less than that of their chronological peers and is derived using the following methodology:

- The degree of similarity of the individual's DL model–predicted atherosclerotic cardiovascular disease risk with the atherosclerotic cardiovascular disease risk score obtained from other similar aged people is determined.
- The average (chronological) age of that individuals' closest neighbors, based on the condition of the retina as expressed by multidimensional features extracted from the
- DL model, is determined.
- The mean expected age for a person with the individual's predicted atherosclerotic cardiovascular disease risk is determined.
- These data are then combined in a probabilistic manner to give a final value for the cardiac BioAge.

The analysis of our data comprised two components:

1. To assess the relationship between leucocyte telomere length with chronological age and the DL model–derived metric cardiac BioAge. The investigators at the UK Biobank recommend that leukocyte telomere length data are represented as the *Z* score log of the leukocyte telomere length T/S ratio, where the T/S ratio is the relative telomere length (T) compared with a polymerase chain reaction product (S) of a reference single copy gene. Individuals were therefore first divided into males and females, and each sex cohort was then ranked by *Z*-adjusted log T/S leukocyte telomere length ratios and grouped into deciles, shortest to longest. The mean chronological age of the individuals in each decile was then derived. Next, the retinal images were presented to the DL model and the individual's cardiac BioAge determined. The mean cardiac BioAge of the individuals in each leukocyte telomere length decile was then also derived. Finally, the correlation between leukocyte telomere length and chronological age and the correlation between leukocyte telomere length and cardiac BioAge were determined using traditional correlation statistics.
2. To determine whether our cardiac BioAge DL model was attributing atherosclerotic cardiovascular disease risk accurately. Individuals within each of the above deciles were secondarily ranked by the cardiac BioAge attributed to them, and the cardiovascular risk profile (as assessed by 10-year atherosclerotic cardiovascular disease risk score, systolic blood pressure, and HbA_{1c}) of these individuals was determined. Next, individuals within each decile were grouped into quartiles based on their cardiac BioAge, and the mean cardiovascular risk profile of those individuals in the lowest quartile across all deciles was compared with the cardiovascular risk profile of those individuals in the highest quartile in all deciles. Finally, the relationship between these cardiovascular risk biomarkers and the *Z*-adjusted log T/S leukocyte telomere lengths across all deciles was determined using traditional correlation statistics.

RESULTS

A total of 33,370 individuals in the UK Biobank had leukocyte telomere length data, retinal images, and relevant biodata. The demographics and the distribution of the *z*-adjusted log T/S leukocyte telomere length ratios of these individuals are shown in Table 1. The chronological age and the cardiac BioAge issued by the DL model of males and females by mean *Z*-adjusted log T/S leukocyte telomere length decile are shown in Table 2.

The systolic blood pressure, HbA_{1c}, and 10-year Pooled Cohort Equation–derived atherosclerotic cardiovascular disease risk score of those in individuals issued with a cardiac BioAge score in the top quartile (Q1) and those issued with a cardiac BioAge score in the bottom quartile within each *Z*-adjusted log T/S leukocyte telomere length ratio decile are shown in Table 3 and Fig. 2. When assessed across all *Z*-adjusted log T/S leukocyte telomere length ratio deciles, for both males and females, the mean systolic blood pressure, mean HbA_{1c}, and the mean 10-year Pooled Cohort Equation–derived atherosclerotic cardiovascular disease risk score were all significantly higher in those individuals in the highest quartile of cardiac BioAge compared with those in the lowest quartile of cardiac BioAge ($p<0.001$; Table 3). In both males and females, a worsening biomarker profile, an increased cardiovascular disease

TABLE 1. The demographic and cardiovascular risk profile of individuals in the UK Biobank used in this study

	Mean	Std			Total, n (%)
Age (y)	56	8.3	Sex at birth	Male	15,017 (45)
Systolic blood pressure (mm Hg)	134	18		Female	18,353 (55)
Diastolic blood pressure (mm Hg)	82	10.1	Current smoker	Yes	3971 (11.9)
HbA_{1c} (%)	5.43	0.6		No	29,399 (88.1)
Total cholesterol (mg/dL)	220	43.7	Race/Ethnicity	White	31,001 (92.9)
High-density lipoprotein cholesterol (mg/dL)	57	15.1		Asian	934 (2.8)
BMI (kg/m^2)	27.2	4.7		Black/other	1435 (4.3)

BMI = body mass index; Std = standard deviation.

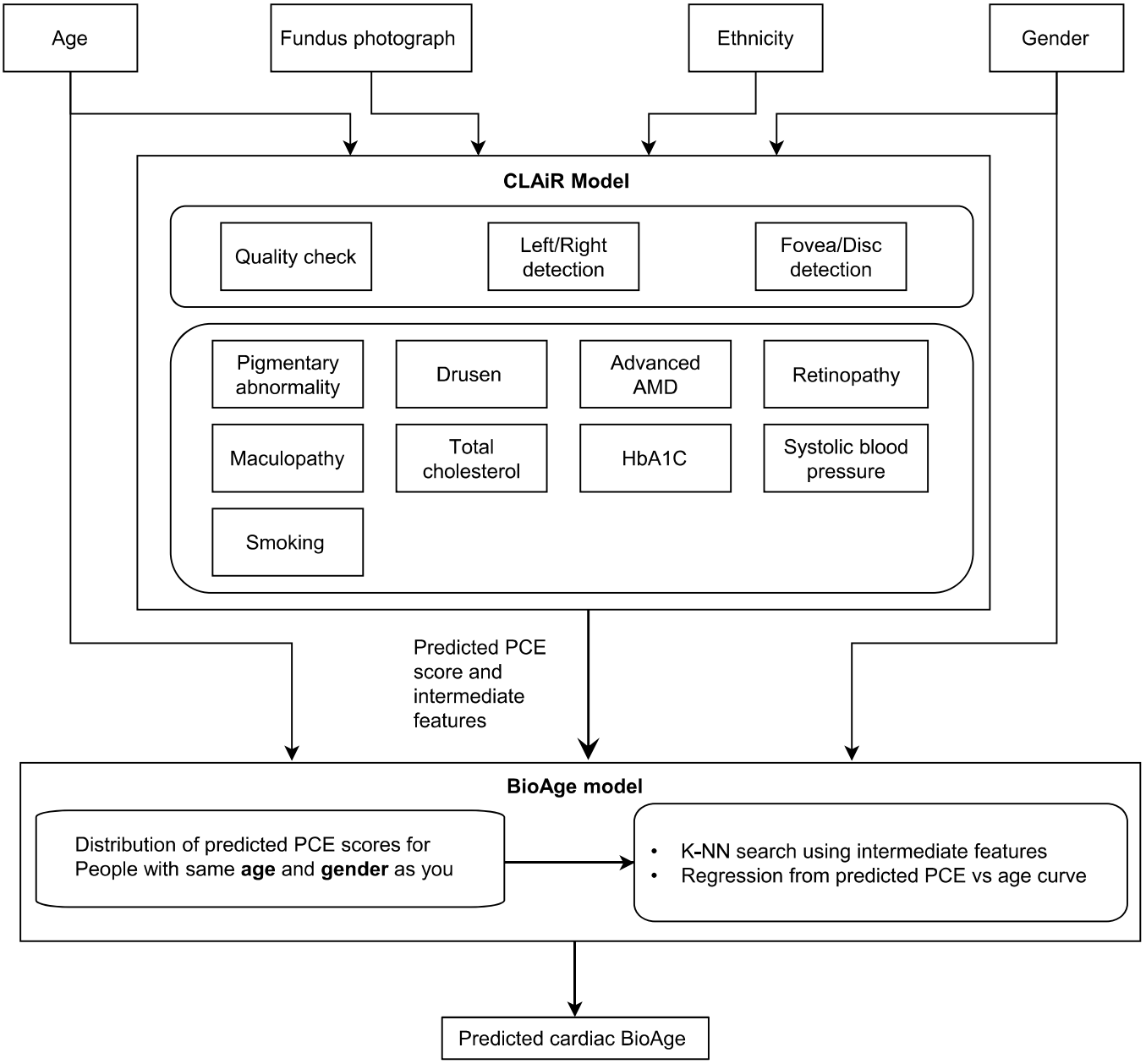

FIGURE 1. Diagrammatic representation of how the deep learning model and aggregation models are integrated to produce an individual's cardiac BioAge. *CLAiR[17] is the deep learning model that produces the baseline cardiovascular risk score and comprises a series of deep learning models that first identifies which eye is being assessed, before analyzing the retina for a variety of biomarkers as described. *K-NN = K-nearest neighbors method. BioAge = biological age.

risk, and increasing cardiac BioAge were inversely correlated with telomere length (Table 2, Fig. 2).

The correlation between relevant biomarker and *Z*-adjusted log T/S leukocyte telomere length was determined: systolic blood pressure of −0.05 ($r^2 = 0.004$), HbA_{1c} −0.05 ($r^2 = 0.003$), and 10-year atherosclerotic cardiovascular disease–derived Pooled Cohort Equation risk score of −0.14 ($r^2 = 0.02$) for males and systolic blood pressure of −0.06 ($r^2 = 0.004$), HbA_{1c} of −0.05 ($r^2 = 0.002$), and 10-year atherosclerotic cardiovascular disease–derived Pooled Cohort Equation risk score of −0.12 ($r^2 = 0.013$) for females.

DISCUSSION

In this cross-sectional study using a subset of individuals drawn from the UK Biobank, we found that our DL cardiac BioAge model was able to accurately stratify individuals by the traditional cardiovascular disease risk biomarkers, and that for both males and females, an elevated cardiac BioAge score was associated with leukocyte telomere length shortening. In line with traditional cardiovascular disease assessment models, both males and females who were issued with a cardiac BioAge in the top quartile of their

TABLE 2. Chronological and cardiac BioAge, categorized by mean *Z*-adjusted log T/S LTL ratio deciles for males and females

	Males			Female		
***Z*-adjusted log T/S LTL ratio decile**	**Mean *Z*-adjusted log T/S LTL ratio***	**Mean chronological age (y)**	**Mean cardiac BioAge (y)**	**Mean *Z*-adjusted log T/S LTL ratio***	**Mean chronological age (y)**	**Mean cardiac BioAge (y)**
0	−0.4242	68.1	67.7	−0.2337	68.0	67.8
10	−0.3501	65.5	65.0	−0.1416	65.5	64.9
20	−0.2431	63.4	62.9	−0.0828	63.4	62.9
30	−0.1647	61.5	60.6	−0.0108	61.5	60.5
40	−0.1536	59.1	57.8	0.0655	59.0	57.7
50	−0.0236	56.0	54.6	0.0594	56.0	54.7
60	0.0333	53.0	51.7	0.1200	53.0	51.6
70	0.0549	49.9	48.8	0.1927	50.0	48.8
80	0.1209	46.5	45.6	0.2710	46.5	45.9
90	0.2559	42.2	41.8	0.3568	42.2	41.8

*Correlation (Pearson) males: chronological age to *Z*-adjusted log T/S LTL ratio −0.23 (r^2 = 0.05) and cardiac BioAge to *Z*-adjusted log T/S LTL ratio −0.22 (r^2 = 0.04). Correlation (Pearson) females: chronological age to *Z*-adjusted log T/S LTL ratio −0.19 (r^2 = 0.03) and cardiac BioAge to *Z*-adjusted log T/S LTL ratio −0.18 (r^2 = 0.03). BioAge = biological age; LTL = leukocyte telomere length.

chronological peer group had significantly higher mean systolic blood pressure, HbA_{1c}, and 10-year Pooled Cohort Equation–derived atherosclerotic cardiovascular disease scores compared with those individuals in the bottom quartile. Consistent with other published data, we observed that a worsening biomarker profile and an increased atherosclerotic cardiovascular disease risk were associated with leukocyte telomere length shortening for both males and females.[11,12,14,19,20] The rate of telomere shortening throughout life is determined by both endogenous (genetic) and external (nongenetic) factors.[21,22] Although the exact mechanism behind leukocyte telomere length shortening and cardiovascular disease remains to be elucidated, it has been hypothesized that leukocyte telomere length may reflect both an individual's cumulative inflammatory exposure and oxidative stress and their genetically determined capacity to repair vascular damage.[11] Multiple confounding risk factors and reverse causation mean that any observed associations between leukocyte telomere length and cardiovascular disease should be interpreted with caution; however, studies using Mendelian randomization provide compelling evidence for a relationship between leukocyte telomere length shortening and an increased risk of both atherosclerotic cardiovascular events and an increased risk of hypertension.[12,23,24] Irrespective of the mechanism by which leukocyte telomeres shorten, our findings indicate that, whether assessed by traditional biomarkers or leukocyte telomere length, our novel cardiac BioAge DL model could be used as a novel surrogate biomarker for cardiac health. A critical component to the provision of public health is accurate risk prediction as it enables focused preventive action and tailored disease management strategies. Accurate disease prediction also facilitates "precision medicine," the identification of subgroups within a wider population who have different disease risks, prognosis, and responses to treatment due to differences in their habitat, physiology, and other characteristics.[25] The utilization of novel biomarkers, like leukocyte telomere length testing, in tandem with tradition measures of atherosclerotic cardiovascular disease risk such as the Pooled Cohort Equation, is one approach to the provision of more "precise" interventions to reduce the risk of atherosclerotic cardiovascular disease events. Although such approaches have merit, the cost and practicalities of providing leukocyte telomere length testing remain significant barriers to its widespread adoption. Arguably one of the more important contributions that artificial intelligence will play within the health care ecosystem is to improve the effectiveness and precision of the traditional population-based risk predictions.[26,27] Optometry has a unique and critical role as the community provider of quality public eye health care and through clinical examination and targeted investigation, Optometrists have been providing precision eye health care for decades. Until now, optometry's focus has been on ocular disease, but with the emergence of artificial intelligence algorithms, such as our cardiac BioAge DL model, which have been designed specifically to stratify an individual's risk of systemic disease by examining retinal images, there is now the potential for optometrists to extend the provision of precision medicine beyond their traditional scope of practice. As retinal photographs are routinely captured in optometry practices, these algorithms can be deployed without significant additional investment in primary care, a feature that makes these technologies particularly

TABLE 3. Mean biomarkers for individuals in the top quartile of cardiac BioAge (Q1) compared with the bottom quartile (Q4) across all telomere length deciles

	Males			Females		
	Q1 cardiac BioAge, mean (Sd)	**Q4 cardiac BioAge, mean (Sd)**	**p**	**Q1 cardiac BioAge, mean (Sd)**	**Q4 cardiac BioAge, mean (Sd)**	**p**
Cardiac BioAge	57 (2.0)	54 (8.4)	<0.001	57 (1.4)	52 (1.7)	<0.001
SBP (mm Hg)	140 (0.8)	135 (1.1)	<0.001	136 (1.5)	127 (1.6)	<0.001
HbA_{1c} (mmol/mol)	37 (0.5)	35 (0.6)	<0.001	36 (0.4)	34 (0.4)	<0.001
10-y ASCVD PCE risk score*	8% (1.0)	7% (1.2)	0.04	3% (0.5)	2% (0.4)	<0.001

*Ten-year ASCVD PCE risk score = 10-year risk of an atherosclerotic cardiovascular disease event as calculated by the Pooled Cohort Equation. ASCVD = atherosclerotic cardiovascular disease; BioAge = biological age; HbA_{1c} = hemoglobin A_{1c}; PCE = Pooled Cohort Equation; SBP = systolic blood pressure; Sd = standard deviation.

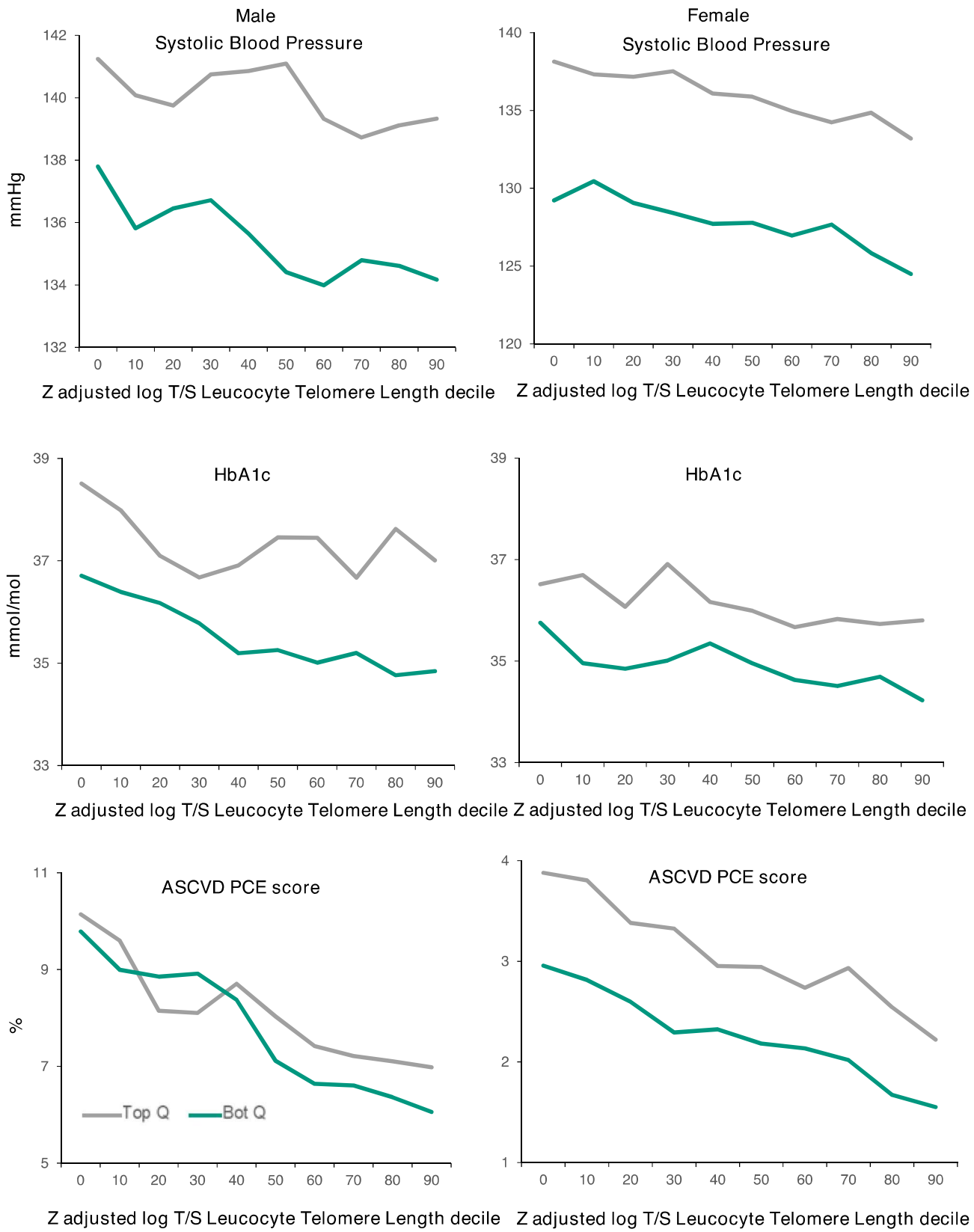

FIGURE 2. Distribution of the mean biomarkers for male and female individuals in the top quartile of cardiac BioAge top quartile (TopQ) compared with the bottom quartile (BotQ), categorized by *Z*-adjusted log T/S leukocyte telomere length decile. BioAge = biological age.

relevant to low-resource settings. As such, these tools not only have the potential to make atherosclerotic cardiovascular disease risk assessment more affordable and accessible but may also improve patient outcomes by both facilitating early intervention and increasing the public awareness of this issue.

The principal limitation of this study is that it is a cross-sectional study of individuals in the UK Biobank whose leukocyte telomere length, retinal images, and traditional biomarkers were measured at one point in time. As such, although our DL model can categorize individuals into low- and high-risk groups for cardiovascular disease based on the traditional biomarkers, and we observed the expected relationship between worsening biomarkers, increasing cardiac BioAge, and leukocyte telomere length shortening, it is not possible to determine whether these associations are causative. Further studies using longitudinal data are therefore required to elucidate the relationship between leukocyte telomere length, aging, and "disease." As is the case in all studies of DL algorithms, further studies of the algorithm in other datasets are required to demonstrate whether the results are generalizable to other datasets and other races and ethnicities beyond those found in the UK Biobank. Finally, although leukocyte telomere length may be inversely associated with cardiovascular disease risk in large population-based studies, the validity of this metric as a clinical tool to predict an individual's cardiovascular disease risk and its magnitude remains to be proven.[28]

CONCLUSIONS

In this cross-sectional cohort study conducted on individuals in the UK Biobank who had relevant biomarker data, retinal images, and leukocyte telomere length data, increasing cardiovascular disease risk, as assessed by both traditional biomarkers, atherosclerotic cardiovascular disease risk scoring, and a DL cardiac BioAge cardiovascular disease risk model, was inversely related to leukocyte telomere length. At a population level, our data support the growing body of evidence that suggests leukocyte telomere length shortening is a surrogate marker for increasing cardiovascular disease risk and that this risk can be captured by suitably trained DL models. If these results can be replicated in other large population-based datasets, DL models like ours may offer the potential to significantly improve access to atherosclerotic cardiovascular disease risk detection strategies as the risk predictions these models produce do not require multiple clinical and laboratory assessments to generate an individual's atherosclerotic cardiovascular disease risk score.

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