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Photoplethysmography-Derived Arterial Stiffness Index Delivered Greater Cardiovascular Prevention Value to Non-Elderly: A Retrospective Cohort Study Based on UK Biobank

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Keywords: arterial stiffness | non-elderly | photoplethysmography | primary prevention | UK biobank

ABSTRACT

Photoplethysmography-derived arterial stiffness index (ASI) has been proven to be associated with various cardiovascular diseases. The present study aims to determine whether the predictive value of ASI varies between elderly and non-elderly and whether ASI improves the discrimination and reclassification ability of the updated Systematic Coronary Risk Evaluation (SCORE2) in different age groups. This retrospective study included UK Biobank participants with ASI recordings. Multivariable Cox proportional hazard models were used to estimate the associations between ASI and major adverse cardiovascular events (MACE) in different age groups. The difference in C-statistic, integrated discrimination improvement (IDI), and continuous net reclassification improvement (NRI) were calculated to test the predictive performance of ASI beyond SCORE2 in the elderly and non-elderly. A total of 127 045 participants were included in the primary analysis. During a median of 11.7 years, 2606 (10.7%) and 4408 (4.3%) MACE were identified in the elderly and non-elderly, respectively. The non-elderly exhibited a greater extent of increased risk for MACE with higher ASI (HR, 1.314 [1.280–1.350] vs. HR, 1.066 [1.026–1.107]). Furthermore, the IDI and continuous NRI of ASI beyond SCORE2 for MACE were more than two times higher for non-elderly individuals than their elderly counterparts (IDI, 0.0481% [0.0182%–0.0953%] vs. IDI, 0.0010% [−0.0052% to 0.0295%]; NRI, 8.76% [6.83% to 10.60%] vs. NRI, 3.27% [−3.92% to 5.97%]). Our findings suggested that ASI should primarily be utilized for primary cardiovascular prevention in individuals below 65.

Hongyu Chen and Fangfang Fan contributed equally to this work.

1 | Introduction

Cardiovascular disease (CVD) is still the leading cause of mortality globally [1]. Despite a remarkable 34.9% decline in the age-standardized mortality rate of CVDs worldwide, dropping from 358.4 per 100 000 in 1990 to 233.2 per 100 000 in 2022, there has been a conspicuous surge in the number of fatalities attributed to CVDs [2]. Notably, the incidence and prevalence are remarkably rising in the younger population, indicating that the CVD burden in young people is also higher and higher globally [3]. Thus, we should place equal emphasis on the elderly and non-elderly populations.

More precise individual prevention necessitates more accurate risk assessment methodologies grounded in potent predictors [4]. Arterial stiffness is a robust predictor of a broad spectrum of cardiovascular pathologies and mortality [5], including coronary heart disease [6], stroke [7], and hypertension [8]. Pulse wave velocity (PWV), quantifying the rate at which the pulse propagates along the arterial wall, is an established and non-invasive indicator of arterial stiffness [5]. In recent decades, various devices based on photoplethysmography (PPG) have emerged to capture pulse waveform signals from more peripheral locations like fingers or toes [9], propelling the arterial stiffness assessment in the general population to a larger extent and progressively contributing to the primary prevention.

Arterial stiffness index (ASI), calculated from the pulse wave of the PPG device, has been observed to be moderately correlated with carotid-femoral PWV (cfPWV) [10] and fairly associated with various CVDs [11], depression [12], and osteoporosis [13]. Vallée found the added value of ASI in atherosclerotic cardiovascular disease (ASCVD) risk determination and the nonlinear relationship between ASI and 10-year ASCVD risk estimating by the pooled cohort equations model [14]. However, existing studies have predominantly focused on population-wide analyses of ASI efficacy, with a limited investigation into age-stratified outcomes that could identify subgroups deriving maximal preventive benefits. As previously stated, the growing cardiovascular burden on the non-elderly has not received proportionate concern [15]. Personalized prevention strategies for this population are strongly advocated to emerge as a key focus. Given the widespread use of PPG-based devices like wristbands, pulse oximeters, smart rings, hearables, smartwatches, webcams, and smartphones among younger non-elderly [16], we should capitalize on this technological momentum and investigate whether ASI demonstrates enhanced preventive efficacy in the younger age group.

In the present study, based on the UK biobank, we investigated whether the predictive value of ASI toward CVD varied across different age groups. Furthermore, we evaluated if ASI adds predictive value to SCORE2, a newly developed algorithm for predicting the 10-year risk of first-onset CVD in European populations [17].

2 | Methods

2.1 | Study Participants

UK Biobank is a large-scale biomedical database and research resource encompassing genetic, lifestyle, and health information and biological samples from over half a million individuals across the UK. The detailed design and access have been described elsewhere [18].

The initial assessment visit obtained 169 738 ASI measurements from recruited participants. Firstly, we excluded 871 participants aged less than 40 or more than 69 to match the calculation criteria of SCORE2. Then, 6095 participants having already encountered cardiovascular outcomes at baseline were excluded. Furthermore, 35 638 participants with missing data on essential variables for the following analysis were excluded, including body mass index (BMI), smoking status, blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, glycated hemoglobin (HbA1c), diagnosis of diabetes mellitus and hypertension, insulin and antihypertensive drugs taking. Additionally, 89 participants with ASI values below or above 4 standard deviations of the mean were excluded. Finally, 127 045 participants were included in the analysis (Figure 1). We stratified all participants into elderly (equal to or more than 65 years) and non-elderly (less than 65 years). The following analyses were performed separately in each group.

The North West Multi-Center Ethics Committee granted ethical approval to UK Biobank, and all participants gave written informed consent. This research has utilized the UK Biobank Resource under Application Number 73201.

2.2 | Measurement of ASI

Registered nurses were trained and certified to use the PulseTrace PCA2 (CareFusion, San Diego, USA), an infra-red sensor clipped to the end of the finger and asked the participant to breathe in and out slowly five times in a relaxed fashion to obtain the stable pulse waveform over a 10–15 s time frame. ASI was derived from the ratio of standing height to the transit time between incident and reflected pulse waves. This methodology has been validated by comparing it with carotid-femoral PWV, which remains the clinical gold standard for arterial stiffness assessment [19].

2.3 | Primary and Secondary Outcomes

The primary outcome was 3-point major adverse cardiovascular events (MACE), defined as a composite of cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke [20]. The secondary outcomes included each component of MACE. The incidence of outcomes was defined according to the ICD, Ninth Revision (ICD-9), and ICD-10, and the Office of Population Censuses and Surveys Classification of Interventions and Procedures, version 4.

2.4 | Ascertainment of Other Variables

Current smoking was defined as "No" if participants had never or previously smoked or as "Yes" if they were current smokers. BMI was calculated as weight (in kg) divided by height*height (m^2).

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice while the participant was in a relaxed

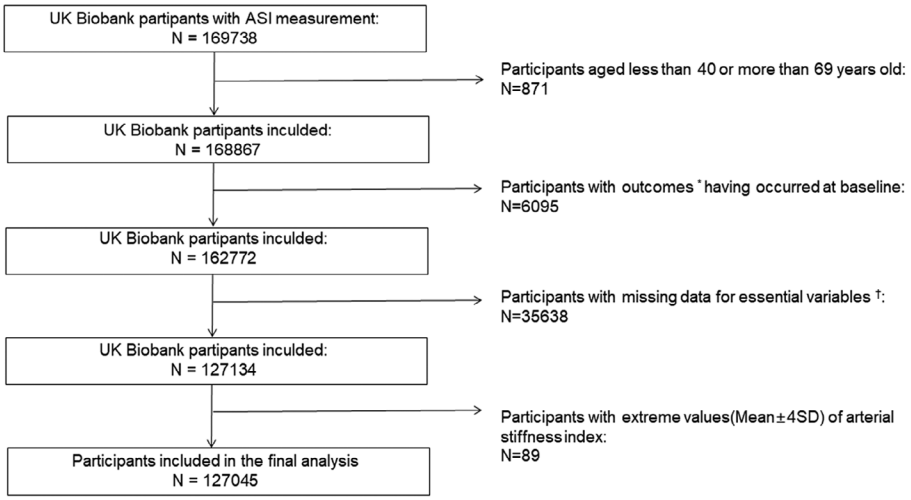

FIGURE 1 | Flow chart of progressively excluding participants unqualified for analysis.

fashion, using an automated blood pressure device or a sphygmomanometer if the largest cuff size was too small for the participant or if the electronic blood pressure monitor failed to produce a reading. We performed the following algorithm to adjust automatically measured SBP and DBP since automated devices acquire higher blood pressure in comparison with manual sphygmomanometers [21]:

a. Adjusted SBP = 3.3171+0.9201*SBP+6.0246*sex (male = 1; female = 0);
b. Adjusted DBP = 14.5647+0.8092*DBP+2.0108*sex (male = 1; female = 0).

Total cholesterol, HDL, and LDL cholesterol levels were measured using direct enzymatic methods.

Diabetes mellitus was defined as (1) an HbA1c level ≥ 48 mmol/mol, which is measured by high-performance liquid chromatography analysis, or (2) a self-reported physician diagnosis of diabetes which is confirmed by verbal interview, or (3) current insulin taking. Similarly, hypertension was also determined by three aspects:(1) SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg; (2) self-reported diagnosis of hypertension acquired during the interview stage; and (3) use of antihypertensive drugs.

2.5 | SCORE2 Risk Algorithm

We calculated the 10-year fatal and non-fatal CVD risk for participants using the SCORE2 algorithms, including age, smoking status, SBP, diabetes, total cholesterol, HDL cholesterol, and interactions between the five risk factors mentioned above and age. Then, we calibrated the risk estimates according to risk region and sex-specific recalibration scaling factors [17].

2.6 | Statistics

The participants' baseline characteristics are presented as the mean plus or minus standard deviation or median (interquartile range) for continuous variables or frequency (percentage) for categorical variables. The baseline data were compared among the elderly and non-elderly populations using the Student's *t*-test or Mann–Whitney *U*-test for continuous variables and the Pearson Chi-squared test for categorical variables.

To investigate the age-related variation pattern of ASI, we employed restricted cubic spline regression (RCS) modeling with five knots. Additionally, we compared the RCS model and a linear model using a likelihood ratio test and demonstrated the RCS model significantly improved fit over the linear model (χ^2 = 164.228; degrees of freedom = 3; $p < 0.001$).

Multivariable Cox proportional hazard models were built to explore the relationship between ASI and outcomes in two age groups, respectively. We quantified the added value of ASI to SCORE2 predicting new-onset cardiovascular events through the difference in C-Statistic, IDI, and continuous net reclassification improvement (NRI) [22]. To assess the robustness of our core findings, we conducted sensitivity analyses incorporating three methodological adjustments: (1) restricted analysis excluding participants undergoing antihypertensive, hypoglycemic, or lipid-lowering therapies; (2) re-analyses performed separately for male and female cohorts; and (3) reclassification of participants into elderly and non-elderly subgroups using 60 years as cutoff.

Additionally, we conducted subgroup analyses among the total, elderly, and non-elderly population to evaluate the potential impact of baseline characteristics including age (elderly and non-elderly), sex (male and female), current smoking (Yes and No), BMI (normal, overweight, and obesity), SBP (normal and abnormal), DBP (normal and abnormal), total cholesterol level (normal and abnormal), LDL level (normal and abnormal), HbA1c level (normal and abnormal), history of diabetes and hypertension (Yes and No), and antihypertensive treatment (Yes and No) on the association between ASI and MACE, after adjusting for SCORE2.

TABLE 1 | Comparisons of participant characteristics between elderly and non-elderly.

Characteristic	Total	Age groups, years		
		Elderly (65–69)	Non-elderly (40–64)	*p* value
***N* (%)**	127045 (100.0)	24358 (19.2)	102687 (80.8)	—
Age (years)	58.00 [50.00, 63.00]	67.00 [66.00, 68.00]	55.00 [48.00, 61.00]	<0.001
Male sex (%)	57805 (45.5)	11973 (49.2)	45832 (44.6)	<0.001
White races (%)	116533 (91.7)	23168 (95.1)	93365 (90.9)	<0.001
Current smoking (%)	12671 (10.0)	1661 (6.8)	11010 (10.7)	<0.001
Medical history (%)				
Diabetes mellitus	6897 (5.4)	1978 (8.1)	4919 (4.8)	<0.001
Hypertension	59296 (46.7)	16173 (66.4)	43123 (42.0)	<0.001
Medication history (%)				
Antihypertensive drug	1250 (1.0)	8286 (34.0)	16741 (16.3)	<0.001
Insulin	25027 (19.7)	310 (1.3)	940 (0.9)	<0.001
Cholesterol-lowering drug	20845 (16.4)	7549 (31.0)	13296 (12.9)	<0.001
BMI (kg/m^2)	27.36 (4.76)	27.48 (4.38)	27.34 (4.84)	<0.001
SBP (mm Hg)	132.87 (17.75)	140.74 (17.59)	131.00 (17.27)	<0.001
DBP (mm Hg)	82.02 (8.35)	82.08 (8.13)	82.01 (8.41)	0.195
ASI(m/s)	9.28 (3.03)	9.99 (3.29)	9.11 (2.94)	<0.001
Total cholesterol (mg/dL)	221.82 (43.74)	219.37 (46.54)	222.40 (43.04)	<0.001
HDL-C (mg/dL)	56.89 (14.91)	57.01 (15.09)	56.87 (14.86)	0.19
LDL-C (mg/dL)	138.51 (33.25)	136.19 (34.92)	139.06 (32.82)	<0.001
HbA1c (mmol/mol)	35.30 [32.80, 37.90]	36.40 [34.10, 39.20]	35.00 [32.50, 37.60]	<0.001
SCORE2 risk	0.04 [0.02, 0.06]	0.07 [0.06, 0.09]	0.03 [0.02, 0.05]	<0.001

Note: Values are given as the mean with standard deviation, median with interquartile range, or number (percentage).
Abbreviations: ASI, arterial stiffness index; BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SCORE 2, the updated Systematic Coronary Risk Evaluation.

All analyses were performed using R version 4.4.1. A two-sided p value < 0.05 was considered a statistically significant difference.

3 | Results

3.1 | Study Population

We eventually analyzed 127 045 participants whose baseline information is presented in Table 1. Based on a cutoff age of 65 years, we divided the study population into two groups whose median and interquartile range of age were 67.00 [66.00, 68.00] and 55.00 [48.00, 61.00], respectively. The elderly individuals exhibited poorer overall health compared to their non-elderly counterparts. Significant disparities in cardiovascular risk factors were observed between the two age groups, with the elderly population showing significantly higher levels of ASI, BMI, SBP, the prevalence of diabetes and hypertension, and therefore SCORE2 risk.

Our study revealed a consistently upward but gradually slowing trend in ASI as individuals age, non-elderly individuals demonstrated a more pronounced correlation between age and ASI (Figure 2).

3.2 | Association of ASI With Outcomes in Elderly and Non-Elderly

During the median follow-up period of 11.7 years (IQR: 11.4–12.0 years), a total of 2606 (10.7%) and 4408 (4.3%) MACE were identified in the elderly and non-elderly, of which 1213 (5.0%) and 2413 (2.3%) were myocardial infarction and 1309 (5.4%) and 1830 (1.8%) were stroke and 667 (2.7%) and 820 (0.8%) were CVD mortality. Additionally, we observed significant interacting effects of the above age group on the relationship between ASI and MACE (p for interaction < 0.001), myocardial infarction (p for interaction < 0.001), stroke (p for interaction < 0.001), and CVD mortality (p for interaction < 0.001).

The non-elderly population exhibited a greater extent of increased risk for cardiovascular events with higher ASI levels, as compared to the elderly population (Table 2): MACE (HR: 1.314; 95% CI: 1.280–1.350 vs. HR: 1.066; 95% CI: 1.026–1.107), myocardial infarction (HR: 1.347; 95% CI: 1.300–1.396 vs. HR: 1.095; 95% CI:

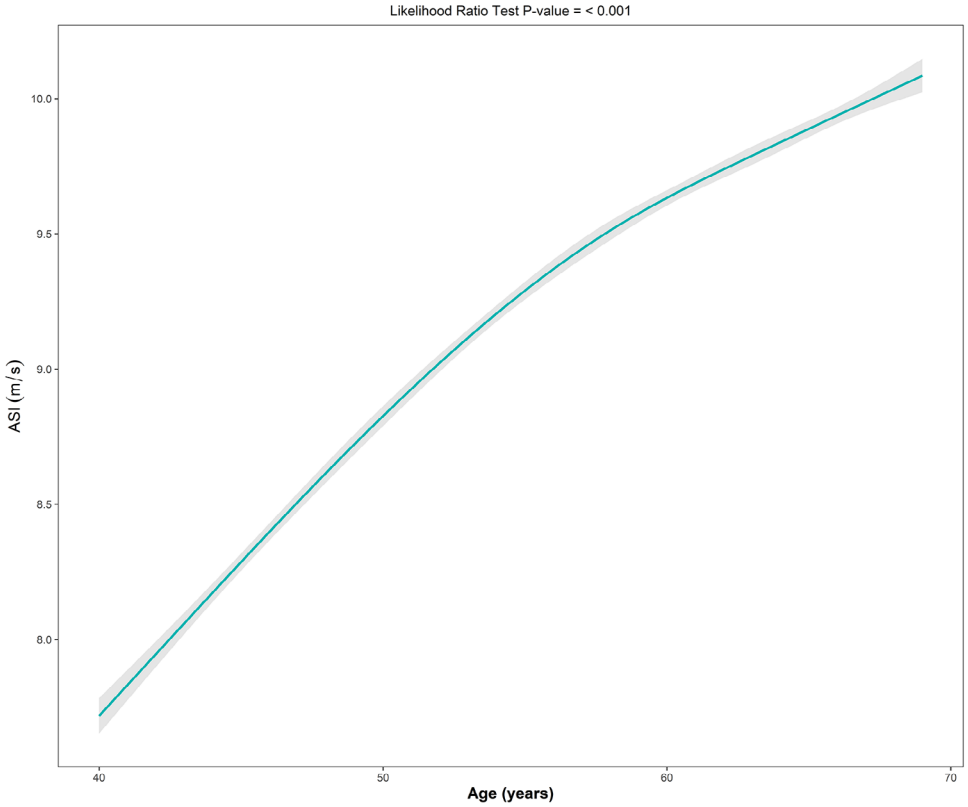

FIGURE 2 | Restricted cubic spline plot of the association between arterial stiffness index and advancing age.

TABLE 2 | Association of arterial stiffness index with major adverse cardiovascular events in elderly and non-elderly.

Outcomes	Age group	HR [95% CI][a]			
		Model 1[b]	Model 2[b]	Model 3[b]	Model 4[b]
MACE	Elderly	1.066 [1.026–1.107]	1.019 [0.979–1.060]	0.994 [0.956–1.035]	1.001 [0.963–1.041]
	Non-elderly	1.314 [1.280–1.350]	1.125 [1.093–1.158]	1.062 [1.031–1.093]	1.076 [1.045–1.107]
MI	Elderly	1.095 [1.036–1.157]	1.031 [0.972–1.092]	1.006 [0.949–1.067]	1.010[0.953–1.069]
	Non-elderly	1.347 [1.300–1.396]	1.148 [1.104–1.194]	1.079 [1.037–1.123]	1.091 [1.049–1.135]
Stroke	Elderly	1.021 [0.967–1.078]	1.000[0.946–1.056]	0.977 [0.924–1.032]	0.985 [0.932–1.040]
	Non-elderly	1.251 [1.199–1.305]	1.088 [1.041–1.138]	1.033 [0.988–1.081]	1.049 [1.003–1.097]
CVD mortality	Elderly	1.140 [1.059–1.227]	1.079 [0.999–1.165]	1.044 [0.966–1.129]	1.052 [0.975–1.135]
	Non-elderly	1.362 [1.281–1.447]	1.127 [1.055–1.205]	1.059 [0.989–1.133]	1.069 [1.001–1.142]

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction.
[a]Hazard ratio with 95% CI estimated using arterial stiffness index per SD change in m/s is shown per Cox proportional hazards model for MACE, myocardial infarction, stroke, and CVD mortality in the elderly and non-elderly (using 65 years old as cutoff).
[b]Model 1 was crude. Model 2 was adjusted for age and sex. Model 3 was adjusted age, sex, mean arterial pressure, diabetes mellitus, smoking, and body mass index. Model 4 was adjusted age, sex, and SCORE2 risk.

1.036–1.157), stroke (HR: 1.251; 95% CI: 1.199–1.305 vs. HR: 1.021; 95% CI: 0.967–1.078), and CVD mortality (HR: 1.362; 95% CI: 1.281–1.447 vs. HR: 1.140; 95% CI: 1.059–1.227). Adjusting for age and sex did not change the tendency, further for mean arterial pressure, diabetes mellitus, smoking, and BMI also produced similar results. However, it is worth noting that the association between ASI and cardiovascular outcomes remained significant only in the non-elderly population, so did adjusting for SCORE2. Additionally, both groups showed a weaker relationship between ASI and stroke after adjusting for potential confounders.

3.3 | Incremental Predictive Value of ASI Beyond SCORE2

The discriminatory power and risk reclassification were substantially better with the addition of ASI to SCORE2 for all outcomes in non-elderly individuals (Table 3), whose IDI values for most outcomes are more than twice as much as elderly individuals': MACE (0.0481%; 95%CI: 0.0182% to 0.0953% vs. 0.0010%; 95%CI: -0.0052% to 0.0295%), myocardial infarction (0.0348%; 95% CI: -0.0033% to 0.0776% vs. 0.0070%; 95% CI: -0.0035% to 0.0434%),

TABLE 3 | Reclassification and discrimination statistics for cardiovascular outcomes by arterial stiffness index in elderly and non-elderly.

Outcomes	Age group	ΔC-statistics [95% CI][a]	*p* value	IDI [95% CI][a,b], %	*p* value	Continuous NRI [95% CI] [a,b], %	*p* value
MACE	Elderly	0.00002 [−0.00039 to 0.00061]	0.939	0.0010 [−0.0052 to 0.0295]	0.527	3.27 [−3.92 to 5.97]	0.736
	Non-elderly	0.00067 [−0.00008 to 0.00148]	0.091	0.0481 [0.0182 to 0.0953]	<0.001	8.76 [6.83 to 10.60]	<0.001
MI	Elderly	−0.00010 [−0.00087 to 0.00097]	0.827	0.007 [−0.0035 to 0.0434]	0.338	4.80[−4.55 to 8.01]	0.488
	Non-elderly	0.00056 [−0.00060 to 0.00188]	0.380	0.0348 [−0.0033 to 0.0776]	0.090	11.15 [8.37 to 13.20]	<0.001
Stroke	Elderly	−0.00077 [−0.00311 to 0.00180]	0.539	−0.0017 [−0.0051 to 0.0228]	1.065	−1.05 [−4.08 to 3.41]	0.896
	Non-elderly	0.00071 [−0.00018 to 0.00167]	0.135	0.0083 [0.0003 to 0.0340]	0.020	5.24 [2.15 to 8.31]	<0.001
CVD mortality	Elderly	0.00005 [−0.00151 to 0.00216]	0.959	0.0105 [−0.0028 to 0.0470]	0.139	3.87 [−0.95 to 7.68]	0.070
	Non-elderly	0.00064 [−0.00096 to 0.00244]	0.459	−0.0088 [−0.0445 to 0.0280]	0.776	10.25 [4.81 to 13.97]	<0.001

Abbreviations: CVD, cardiovascular disease; IDI, integrated discrimination improvement; MACE, major adverse cardiovascular events; MI, Myocardial infarction; NRI, net reclassification improvement.

[a]ΔC-statistics, IDI, and continuous NRI were calculated between Cox proportional hazard models incorporating SCORE2 alone and that including SCORE2 plus arterial stiffness index. ΔC-statistics indicates the difference in C-statistics.

[b]Timepoint to define event = TRUE/FALSE was 10 years.

stroke (0.0083%; 95% CI: 0.0003% to 0.0340% vs. -0.0017%; 95% CI: -0.0051% to 0.0228%), and CVD mortality (-0.0088%; 95% CI: -0.0445% to 0.0280% vs. 0.0105%; 95% CI: -0.0028% to 0.0470%), so does NRI values: MACE (8.76%; 95% CI: 6.83% to 10.60% vs. 3.27%; 95% CI: -3.92% to 5.97%), myocardial infarction (11.15%; 95% CI: 8.37% to 13.20% vs. 4.80%; 95% CI: -4.55% to -8.01%), stroke (5.24%; 95% CI: 2.15% to 8.31% vs. -1.05%; 95% CI: -4.08% to 3.41%), and CVD mortality (10.25%; 95% CI: 4.81% to 13.97% vs. 3.87%; 95% CI: -0.95% to 7.68%). It is worth noting that statistical significance was observed only in the younger group.

3.4 | Sensitivity Testing and Additional Analysis

Sensitivity analyses revealed that antihypertensive, lipid-lowering, or glucose-lowering medications and sex did not materially affect the core conclusions of the study, demonstrating that ASI confers greater cardiovascular preventive value in non-elderly populations irrespective of pharmacotherapy status and across both genders (Tables S2-S7).

In the overall population, most risk factors moderated the effects of ASI on MACE: age (p for interaction < 0.001), sex (p for interaction = 0.010), SBP (p for interaction < 0.001), DBP (p for interaction = 0.024), HbA1c (p for interaction = 0.001), diabetes (p for interaction < 0.001), hypertension (p for interaction < 0.001), and antihypertensive treatment (p for interaction < 0.001). However, subgroup analyses conducted within each age group suggested that interactions of BMI (p for interaction = 0.008), SBP (p for interaction = 0.002), DBP (p for interaction = 0.005), HbA1c (p for interaction < 0.001), history of diabetes (p for interaction < 0.001) and hypertension (p for interaction < 0.001), and antihypertensive treatment (p for interaction = 0.002) are statistically significant only among the non-elderly participants. For the elderly, none of the above had a notable impact on the association that we have been focusing on (Figs. S1–S3).

4 | Discussion

Through a population-based cohort study encompassing 127 045 participants, we conducted age-stratified analyses to evaluate the association between ASI and incident cardiovascular events. Notably, the results in non-elderly adults (<65 years) demonstrated a significantly higher hazard ratio for most cardiovascular endpoints in multivariable Cox proportional hazards models, even after adjusting for established risk factors. Additionally, the integration of ASI measurements with the SCORE2 algorithm enhanced predictive accuracy and clinical risk reclassification specifically in this population.

Arterial stiffness, characterized by the stiffening of the arterial wall and the loss of Windkessel properties [23], has been established as a valid predictor of cardiovascular events by numerous studies [24, 25]; however, most of which focused on the whole population of all ages. Recent epidemiological data revealed an alarming rise in CVD prevalence among non-elderly adults, paralleling a progressive accumulation of modifiable risk factors and a concomitant surge in premature myocardial infarction cases within this demographic [15, 26]. Therefore, it is imperative to take preventative actions early in adulthood, necessitating innovative and effective risk stratification tools for young adults [15]. From a public health implementation perspective,

arteriosclerosis quantification modalities within population-level primary prevention strategies must be effortless to operate and generalize. ASI, derived through PPG, precisely addresses these critical needs. Accumulating research indicates ASI potentially estimates cardiovascular risk quickly [11, 27–29].

ASI, exhibiting strong correlations with both cfPWV and baPWV, demonstrates significant associations with elevated risks of CVDs, coronary heart disease, heart failure, and metabolic syndrome in the UK Biobank cohort [10–13, 30]. A previous study revealed that elevated ASI levels may enhance the predictive capacity for 10-year ASCVD risk, a composite clinical endpoint encompassing fatal coronary heart disease, nonfatal myocardial infarction, and fatal or nonfatal stroke [14]. Nevertheless, ASI is not the gold standard for quantifying arteriosclerosis. We found it no longer rose parallelly with aging as PWV [5, 31]. Said and colleagues demonstrated that ASI functioned as a predictive indicator for CVD but was surpassed by pulse pressure in terms of predictive effectiveness [11]. Another study indicated that the ASI should not be employed to assess cerebrovascular integrity in older adults [29].

In the present study, we found ASI is a reliable predictor for CV events in non-elderly individuals. Furthermore, another age-stratified research revealed that the stronger relationship between ASI and estimated RISK (a score calculated using the Heart Risk Calculator algorithm developed by the ACC/AHA [32]) was presented for the age group 40–54 compared with older groups aging more than 54 [33]. Therefore, we posit that large-scale implementation of ASI monitoring for primary prevention in non-elderly populations may yield substantial public health benefits that offset potential inaccuracies inherent in ASI measurements.

Similar to the analysis conducted in the overall population [11], the association between ASI and stroke did not reach statistical significance in both age groups. A population-based cohort analysis demonstrated that cfPWV lost predictive significance for stroke after multivariable adjustment, with investigators attributing this null association to limited statistical power from a few endpoint events [34]. Similarly, a baPWV study revealed progressive attenuation of effect estimates for stroke following comprehensive covariate adjustment [35]. Accordingly, it is reasonable to hypothesize that arterial stiffness, regardless of the measuring method, may not be able to predict stroke independently of various traditional cardiovascular risk factors including mean pulse pressure, BMI, smoking status, diabetes, and blood lipids, which may play a genuine role in predicting stroke risk. However, further investigation is warranted to confirm it.

Subgroup analyses reaffirmed that aging is a pivotal factor in determining the predictive value of ASI. Among the overall and non-elderly population, healthier individuals, namely, those with normal levels of HbA1c and blood pressure and without a diagnosis of diabetes and hypertension and antihypertensive treatment, showed a significantly higher likelihood of experiencing MACE. However, the "healthy individual effect" disappeared among the elderly. As for the reasons behind the diminishing predictive value of ASI with age, we propose the age-dependent attenuation of the ASI-age correlation is a principal contributing factor. Tanaka and colleagues found both cfPWV and baPWV were significantly and positively associated with age ($r = 0.56$ and 0.64) [31]. It is plausible that ASI has an inherent flaw embedded within its measuring veracity as the peripheral artery stiffens faster than the central one with aging in theory, due to the intrinsic difference between elastic and muscle arteries [36]. However, as we said earlier, it is unwise to ignore such accessible arterial stiffness measurement for primary prevention, particularly among non-elderly adults.

We unveiled the practical prevention value of ASI in the non-elderly for the first time. Additionally, we performed sensitivity and subgroup analyses to ensure the robustness and generalizability of our findings. However, some limitations of this study merit careful consideration when interpreting the results. First, we have excluded participants younger than 40 years old due to the SCORE2 calculation criteria; nonetheless, the risk of new-onset CVD is relatively low before age 40 and then steadily increases thereafter [37]. Second, our findings are primarily derived from European populations and therefore require further validation; however, the unprecedented scale of UK biobank reminds us of the critical importance of harnessing wearable technologies for large-scale disease prevention, particularly in non-elderly populations. Third, ASI is not the gold standard measurement of arterial stiffness; nonetheless, it has been proven that ASI exhibits strong correlations with both cfPWV and baPWV. In conclusion, ASI is a remarkably potential surrogate of PWV when conducting large-scale primary prevention in people younger than 65 years old.

Author Contributions

H.C. and F.F. contributed to the study design, data analysis, and manuscript writing. Z.Y. participated in statistical analysis. Z.Y., Z.L., X.Q., and Y.Z. provided critical intellectual input during manuscript development. X.Q. and Y.Z. oversaw all aspects of the research and analysis. H.C. prepared the manuscript for submission. All authors critically reviewed the manuscript, provided intellectual input, approved the final version, and agreed to submission.

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Ethics Statement

The North West Multi-Center Ethics Committee granted ethical approval to UK Biobank, and all participants gave written informed consent. This research has utilized the UK Biobank Resource under Application Number 73201.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The UK Biobank is an open-access resource, available at the UK Biobank Consortium website upon a data request proposal.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.