

# Contents lists available at ScienceDirect International Journal of Cardiology Cardiovascular Risk and Prevention



journal homepage: www.journals.elsevier.com/international-journal-of-cardiologycardiovascular-risk-and-prevention

# Estimated pulse wave velocity added additional prognostic information in general population: Evidence from National Health and Nutrition Examination Survey (NHANES) 1999-2018

Zhe Zhou<sup>a,b,c,1</sup>, Xiaoling Liu<sup>d,e,1</sup>, Wanyong Xian<sup>f</sup>, Yan Wang<sup>g</sup>, Jun Tao<sup>a,b,c,\*\*</sup>, Wenhao Xia<sup>a, b, c, h,</sup>

<sup>a</sup> Department of Hypertension and Vascular Disease, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China

<sup>b</sup> NHC Key Laboratory of Assisted Circulation, Sun Yat-Sen University, Guangzhou, China

National-Guangdong Joint Engineering Laboratory for Diagnosis and Treatment of Vascular Diseases, Guangzhou, China

<sup>d</sup> Department of Cardiology, Shantou Central Hospital, China

<sup>e</sup> Department of Critical Care Medicine, Shantou Central Hospital, China

<sup>f</sup> The Fourth People's Hospital of Nanhai District of Foshan City, Foshan, China

<sup>g</sup> Health Management Center of the First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China

<sup>h</sup> Guangxi Hospital Division of the First Affiliated Hospital, Sun Yat-sen University, China

ARTICLE INFO

Handling Editor: D Levy

#### ABSTRACT

Background: As an indicator of arterial stiffness, there is controversy over whether estimated pulse wave velocity (ePWV) add additional prognostic information other than cardiovascular risk factors or traditional risk estima-Keywords: tion model in general population. Estimated pulse wave velocity Methods: Data from National Health and Nutrition Examination Survey in 1999-2018 was analyzed. Cardio-Cardiovascular risk factor vascular risk factors were collected and Framingham Risk Score (FRS) was calculated. Using all-cause and car-Framingham risk Score diovascular mortality as outcomes, Cox and restricted cubic spline (RCS) analysis was performed. Receiver National Health and Nutrition examination operator characteristic (ROC) curves, Harrell's C-statistic and net reclassification index (NRI) analysis were used Survey to assess whether ePWV adds additional predictive value. Clinical outcome Results: The association between ePWV and outcomes was independent of cardiovascular risk factors (HR = 1.23) [95%CI 1.23–1.50] per m/s for all-cause mortality, and 1.52 [1.30–1.78] for cardiovascular mortality) and FRS (1.22 [1.12-1.32] for all-cause mortality, and 1.32 [1.10-1.59] for cardiovascular mortality). Except for ePWV and all-cause mortality adjusted by FRS, a liner association was found between ePWV and outcomes. For predictive value, the area under ROC and C-index of the model added with ePWV was higher than the one with FRS or risk factors alone (P < 0.01). The elevated ePWV upgraded 1338456 subjects from high-intermediate to high FRS category, and NRI was 3.61 % and 2.62 % for all-cause and cardiovascular deaths, respectively (all P <0.001). Conclusions: In general population, the present study demonstrated the association between ePWV and all-cause,

cardiovascular mortality is independent of cardiovascular risk factors and traditional risk estimated model. ePWV also added additional information to them in predicting clinical outcomes.

## 1. Background

Arterial stiffness characterized by increased pulse wave velocity

(PWV) is a common finding in hypertension, independently related to poor clinical prognosis [1-4]. At present, increasing evidence showed that the risk of adverse clinical events was significantly elevated for

https://doi.org/10.1016/j.ijcrp.2023.200233

Received 6 October 2023; Received in revised form 4 December 2023; Accepted 21 December 2023 Available online 4 January 2024

2772-4875/© 2023 Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

<sup>\*</sup> Corresponding author. Department of Hypertension and Vascular Disease, The First Affiliated Hospital, Sun Yat-Sen University, No. 58 Zhongshan 2nd Rd, Guangzhou 510080, China.

<sup>\*\*</sup> Corresponding author. Department of Hypertension and Vascular Disease, The First Affiliated Hospital, Sun Yat-Sen University, No. 58 Zhongshan 2nd Rd, Guangzhou 510080, China.

E-mail addresses: taojungz123@163.com (J. Tao), xiawhao@mail.sysu.edu.cn (W. Xia).

<sup>&</sup>lt;sup>1</sup> Z. Zhou and Xiaoling Liu contributed equally.

individuals with arterial stiffness regardless of hypertension status [5–7], indicating that PWV is an important marker in diseases and healthy life span management.

Nowadays, carotid femoral PWV (cfPWV) and brachial ankle PWV (baPWV) are the most widely used PWV indexes [8], and are both valuable in clinical risk assessments [9]. However, it requires expensive equipment and experienced personnel to measure these indexes, which limits its popularization. Considering their potential benefit in cardio-vascular diseases (CVDs) management, it is an urgent need to simplify their measurements. As the manifestation of vascular aging, arterial stiffness is a consequence caused by multiple cardiovascular risk factors, attributed mostly to aging and hypertension. Therefore, it is considered that PWV can be calculated by model based on age, blood pressure (BP) and their interactions. According to this, estimated PWV (ePWV) is proposed as a substitute for PWV [10].

Previous research showed that ePWV had a good consistency with both cfPWV and baPWV [11], and further investigation found that ePWV was closely related to the incidence of new-onset hypertension [12], cardiovascular events [13,14], all-cause [13,15] and specific-cause mortality [15]. However, there is still controversy over whether the association between ePWV and adverse clinical outcomes is independent of traditional cardiovascular risk estimation model or risk factors. Previous researches aiming in this issue either excluded the CVDs population [16,17] or conducted in specific population with increased cardiovascular risk [15,18] or established CVDs [19]. Thus, it is not yet known whether their conclusions can be extrapolated to the general population. Considering the widespread application of cardiovascular risk assessment and potential benefit of ePWV appraisement, it is necessary to further evaluate whether ePWV provide additional prognostic information. Moreover, it was now recognized that the relationship between PWV and clinical outcomes was significantly affected by several risk factors including sex [20], ethnicity [21], obesity [22], etc., while relevant evidence in ePWV is still insufficient.

To this end, using a nationally representative sample from National Health and Nutrition Examination Survey (NHANES), we examined whether the association between ePWV with all-cause and cardiovascular mortality was independent of a traditional cardiovascular risk estimation model, Framingham Risk Score (FRS), or risk factors. In addition, we also tested whether ePWV can add additional prognostic information to FRS and cardiovascular risk factors.

### 2. Methods

#### 2.1. Study design and participants

This study analyzed publicly available data from the National Health and Nutrition Examination Survey (NHANES) in 1999–2018 (htt p://wwwn. cdc.gov/nchs/nhanes).

62089 participants were available for demography and basic information. After excluding patients younger than 20 years old (n = 9749), without blood pressure (BP) record (n = 2665), history of malignancy (n = 4631), missing biochemical examination data (n = 25237), missing medical or behavior information, including diabetes mellitus status (n = 585), smoking information (n = 14), body mass index (BMI, n = 222), ineligible for follow-up information (n = 30), 18956 participants were included in the analysis. For FRS analysis, we further excluded 6074 participants as they were unsuitable for FRS model evaluation (Fig. 1).

## 2.2. Assessment of covariates

Age, sex, ethnicity (Mexican American, Non-Hispanic Black, Non-Hispanic White, Other Hispanic and other race), current smoker (yes or no), total cholesterol (TC), Low density lipoprotein cholesterol (LDL-C), triglyceride (TG), High density lipoprotein cholesterol (HDL-C) was recorded. Body mass index (BMI) was calculated as weight (kg)/height squared (m<sup>2</sup>). eGFR was estimated by CKD-EPI formula [23]. Systolic



Fig. 1. Flow chart of study population.

blood pressure (SBP) and diastolic blood pressure (DBP) were measured using mercury sphygmomanometers, and the average value were used for further analysis. Pulse pressure (PP) was calculated as the difference of SBP and DBP. Hypertension was defined as either SBP  $\geq$ 140 mmHg, DBP  $\geq$ 90 mmHg, usage of anti-hypertensive agents or self-reported history. Diabetes mellitus was defined as a self-report history. Dyslipidemia was defined as either TC  $\geq$  240 mg/dl, LDL-C>160 mg/dl, TG > 200 mg/dl, HDL-C <40 mg/dl or usage of lipid-lowering agents with defined history of hyperlipidemia according to guideline [24]. FRS was calculated in the individuals without established CVDs and aged 30 to 75  $^{25}$ .

#### 3. Calculation of ePWV

Using mean blood pressure (MBP) and age, ePWV was calculated by the formula as described in the Reference Values for Arterial Stiffness Collaboration [10]. MBP was calculated as follows:  $MBP = DBP+0.4 \times (SBP-DBP)$ .

For the individuals without major cardiovascular factors, ePWV was calculated as:

ePWV = 4.62–0.13  $\times$  age+0.0018  $\times$  age [2]+0.0006  $\times$  age  $\times$  MBP+0.0284  $\times$  MBP.

And for the individuals with major cardiovascular risk factors, ePWV was calculated as:

$$\label{eq:epwv} \begin{split} ePWV &= 9.58 \text{--}0.40 \times age + 4.56 \times 0.001 \times age \text{ [2]} - 2.62 \times 0.00001 \\ \times age \text{ [2]} \times \text{MBP} + 3.17 \times 0.001 \times age \times \text{MBP- } 1.83 \times 0.01 \times \text{MBP.} \end{split}$$

Based on the report of the Reference Values for Arterial Stiffness Collaboration [10], major cardiovascular factors were defined as hypertension, current smoker, dyslipidemia and diabetes mellitus. Besides, established CVDs, including coronary heart disease, congestive heart failure, heart attack, stroke was also treated as major cardiovascular risk factors simultaneously.

#### 3.1. Endpoints and follow-up

Using ICD-10 code, the primary endpoint was defined as all-cause mortality, and the secondary endpoint was cardiovascular mortality during the follow up until 31 December 2019.

#### 3.2. Statistical analyses

Appropriate weighting was conducted for statistical analysis according to the advice of NHANES website (https://wwwn.cdc.gov/nch s/nhanes/tutorials/Module 3. aspx). For baseline characteristics, Continuous variables were summarized by means (standard error, SE), and categorical variables were summarized by unweighted number (weighted %).

In the primary analysis, using all-cause or cardiovascular death as outcome variable separately, Kaplan-Meier estimates was applied to describe the difference among quartile groups of ePWV, and log-rank test was used to compare the difference. Hazard ratios and 95 % confidence intervals (CIs) for the association between baseline ePWV and outcomes was calculated by Cox regression models, and individual cardiovascular risk factors or FRS was adjusted, respectively. Apart from that, adjusted restricted cubic spline (RCS) analysis was performed to examine whether there was a non-linear relationship between ePWV and outcomes. Secondly, to study whether ePWV could add significant prognostic information to FRS model or cardiovascular risk factors, we constructed receiver operator characteristic (ROC) curves for outcome variables to assess the model with and without ePWV, and the area under ROC curves was calculated by Delong's test. Harrell's C-statistic was used for model discrimination as well.

The magnitude of reclassification was tested using FRS risk categories and net reclassification improvement for upper quartile of ePWV. FRS categories was defined as follows: low (<10 %), low-intermediate (10 %< and <15 %), intermediate-high (15 %< and <20 %), or high

(>20 %) [25]. According to previous report indicated [16], pharmacological primary prevention is not recommended in subjects with low or low to intermediate FRS category, and such intervention may benefit most for individuals in high FRS. Thus, we conducted net reclassification analysis in intermediate to high FRS category, and net reclassification index (NRI) was calculated.

Subgroup analysis was conducted by following demographic covariates and cardiovascular risk factors including age, sex, ethnicity, BMI stratification, current smoker, dyslipidemia, hypertension, diabetes mellitus, eGFR status, as well as established CVDs, defined by a combination of angina, coronary heart disease, congestive heart failure, heart attack and stroke.

For all analyses, a 2-tailed P < 0.05 was considered statistically significant. Statistical analyses were performed by R software (Version 4.2.1, http://www.R-project.org, The R Foundation).

#### 4. Results

#### 4.1. Baseline characteristics

Totally, 18956 participants with a mean age of 45.95 years old were included, and 12814 participants with a mean age of 48.38 years old were included for FRS related analysis. Baseline characteristics of the study population were presented in Table 1, and the distribution of ePWV was presented in Figure S1.

### 4.2. Association between estimated pulse wave velocity and mortality

During a median follow-up of 9.25 years (interquartile range, 5.17–13.9 years), 2429 (12.8 %) all-cause mortality and 791 (6.2 %)

# Table 1

Baseline charac	cteristic of	study	popul	lation.
-----------------	--------------	-------	-------	---------

Variable	Population used for individual risk factor estimation	Population used for Framingham risk estimation
Age, years	45.95 (0.21)	48.38 (0.17)
Sex (Female, %)	9531 (50.28 %)	6597 (51.48 %)
Race/ethnicity, %		
Mexican	3495 (18.44 %)	2447 (19.1 %)
American		
Non-Hispanic	3913 (20.64 %)	2654 (20.71 %)
Black		
Non-Hispanic	8007 (42.24 %)	5216 (40.71 %)
White		
Other Hispanic	1700 (8.97 %)	1198 (9.35 %)
Other Races	1841 (9.71 %)	1299 (10.14 %)
BMI	28.67 (0.09)	29.03 (0.10)
SBP, mmHg	121.04 (0.21)	121.34 (0.21)
DBP, mmHg	70.74 (0.19)	72.42 (0.16)
MBP, mmHg	90.86 (0.14)	91.99 (0.15)
PP, mmHg	50.29 (0.21)	48.92 (0.21)
ePWV, m/s	7.95 (0.02)	7.98 (0.02)
TC, mg/dl	193.86 (0.45)	199.74 (0.53)
LDL-C, mg/dl	115.98 (0.38)	120.76 (0.44)
HDL-C, mg/dl	53.80 (0.21)	54.30 (0.23)
TG, mg/dl	120.40 (0.83)	123.47 (0.86)
UA, μmol/l	324.26 (0.85)	322.00 (1.04)
eGFR, ml/min/	95.96 (0.30)	94.46 (0.28)
1.73 m [2]		
Current smoker, %	4068 (21.46 %)	2762 (21.55 %)
Hypertension, %	7673 (40.48 %)	5194 (40.53 %)
Diabetes mellitus,	3356 (17.7 %)	2200 (17.17 %)
%		
Dyslipidemia, %	8528 (44.99 %)	5750 (44.87 %)

Aberrations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; ePWV, estimated pulse wave velocity; PP, pulse pressure; TC, total cholesterol; LCL-C, Low density lipoprotein cholesterol; HDL-C, High density lipoprotein cholesterol; TG, triglyceride; High density lipoprotein cholesterol.

cardiovascular mortality events occurred in population for cardiovascular risk factors analysis. And 1084 all-cause mortality, 274 cardiovascular mortality events occurred in the population for FRS analysis. Kaplan–Meier analysis revealed that there were stepwise increases in all-cause and cardiovascular mortality with an increase of ePWV, and the difference across groups was statistically significant (Log-rank P < 0.001, Fig. 2). Cox regression analysis found significant association between ePWV with all-cause and cardiovascular mortality, and these results remained similar after adjusting individual cardiovascular risk factors or FRS (Table 2).

To test if there were non-linear relationship between ePWV and outcomes, RCS model was performed. After adjusting potential risk factors and FRS separately, expect for the association between ePWV and all-cause mortality adjusted by FRS (*P* for non-linear <0.05), other tests showed a liner association between ePWV and outcome variables (*P* for non-linear >0.05, Figure S2).

# 4.3. Subgroup analysis

To test the robustness of association between ePWV and prognosis, subgroup analysis was performed. After adjusting cardiovascular risk factors, except for non-Hispanic black, other Hispanic and current smoker, the association between ePWV and all-cause mortality remained significant. In addition to the above factors, BMI stratification, hypertension as well as eGFR status also influenced the association between ePWV and cardiovascular mortality. To be noticed, FRS adjusting further impaired this association (Fig. 3)

#### 4.4. Prediction and reclassification analysis

The prognostic value of ePWV and FRS was assessed by ROC curve analysis and Harrell's *C*-statistic. Results showed that either for all-cause or cardiovascular mortality, the area under the ROC constructed by models added with ePWV were slightly higher than models with FRS or risk factors alone (Figure S3). The results of Harrell's *C*-statistic showed a better performance for the models added with ePWV as well (Table 3).

Reclassifying individuals with high-intermediate FRS category and ePWV  $\geq$ 8.92 m/s (The upper quartile) to high FRS category, upgraded 1338456 subjects with 205913 all-cause and 46257 cardiovascular deaths, giving NRIs of 3.61 % and 2.62 % (all *P* < 0.001), respectively (Table S1).

#### Table 2

Association between estimated Pulse Wave velocity and outcomes.

Model	All-Cause mortality (HR, 95% CI)	Cardiovascular mortality (HR, 95% CI)
Crude model	1.69 (1.65–1.73)	1.83 (1.77–1.89)
Model 1	1.35 (1.21–1.50)	1.52 (1.30–1.78)
Model 2	1.22 (1.12–1.32)	1.32 (1.10–1.59)

Model 1 was adjusted for age, sex, ethnicity, BMI, MBP, PP, current smoker, dyslipidemia, UA, Diabetes mellitus and eGFR; Model 2 was adjusted was for FRS.

#### 5. Discussion

To the best of our knowledge, this is the first prospective large cohort study investigating the prognostic value of ePWV in general population. The current research found that the association between ePWV and adverse clinical outcomes was independent of traditional cardiovascular risk estimation model (FRS) and risk factors. Linear correlation was observed between ePWV and outcomes after adjusting FRS and cardiovascular risk factors except for all-cause mortality adjusted by FRS. Besides, the model including both ePWV and FRS provides better prediction than FRS alone, indicating that ePWV is a valuable tool for risk estimation. To be noticed, although the association between ePWV and adverse clinical outcomes remains significant in most subgroups after adjusting cardiovascular risk factors, different results occurred after adjusting FRS.

Interests has been drawn in analyzing the association between arterial stiffness and adverse outcomes over the past few decades, and ePWV was proposed as a novel index for its measurement [10]. Compared with measured PWV, ePWV is easier to obtain, and there is no significant difference in predicting clinical outcomes [11]. However, there is lack of evidence whether the association between ePWV and prognosis is independent of traditional cardiovascular risk assessment models and risk factors in general population. Our findings add useful information to this topic.

It should be noted that ePWV was originally derived from a population with majority of Caucasian [10], and our article showed that the association between ePWV and adverse clinical outcomes did not reach statistical significance after adjusting risk factors in non-Hispanic black and other Hispanic. Considering that ethnic factors significantly influence the progression of arterial stiffness and its association with prognosis [21], better estimated models may need to be proposed in different



Fig. 2. Kaplan-Meier analysis of all-cause and cardiovascular mortality in different ePWV stratification.

# A

# B

Subgroup	Total Number	Events		HR (95% CI)	P for interaction	Subgroup	Total Number	Events		HR (95% CI)	P for interaction
Age					< 0.001	Age					< 0.001
<65	14849	813	-	1.97 (1.74 to 2.22)		<65	14849	212		1.96 (1.61 to 2.40)	)
≥65	4054	1616	-	1.69 (1.59 to 1.78)		≥65	4054	579	—	1.85 (1.67 to 2.04)	)
Sex					0.42	Sex					0.03
Female	9500	1048	-	1.33 (1.13 to 1.57)		Female	9500	336		1.63 (1.26 to 2.11)	)
Male	9403	1381		1.35 (1.17 to 1.56)		Male	9403	455		1.38 (1.10 to 1.74)	
Ethnicity					0.01	Ethnicity					0.23
Non-Hispanic White	7994	1384		1.39 (1.22 to 1.60)		Non-Hispanic White	7994	450		1 49 (1.19 to 1.86)	
Non-Hispanic Black	3894	468	-	1 15 (0 97 to 1 36)		Non-Hispanic Black	3894	161		1 15 (0.81 to 1.64)	
Mexican American	3484	366	<u> </u>	1.31 (0.97 to 1.77)		Mexican American	3484	111		- 1 74 (1 04 to 2 94)	
Other Hispanic	1695	120 -		0.83 (0.40 to 1.71)		Other Hispanic	1695	37 -		0.24 (0.04 to 1.44)	
Other	1926	01		1.74 (1.15 to 2.62)		Other	1926	22		- 1 77 (1 02 to 3 06)	
DMI	1000	91		1.74 (1.15 to 2.05)	0.004	DMI	1030	32		- 1.77 (1.03 to 3.00)	0.14
BMI	5700	700		4 40 /0 00 10 4 440	0.004	BMI	5700	007		4 40 40 07 1- 4 00	0.14
<25	5/62	762		1.19 (0.98 to 1.44)		<25	5/62	207		1.18 (0.87 to 1.60)	)
25-30	6385	859		1.54 (1.32 to 1.80)		25-30	6385	284		- 2.17 (1.61 to 2.92)	
>30	6756	808		1.32 (1.12 to 1.57)		>30	6756	300	-	1.20 (0.88 to 1.65)	)
Current smoker					< 0.001	Current smoker					0.03
No	14851	1869	-	1.36 (1.19 to 1.56)		No	14851	643		1.62 (1.30 to 2.02)	)
Yes	4052	560	+	1.05 (0.86 to 1.28)		Yes	4052	148		1.02 (0.67 to 1.55)	)
Hypertension					0.004	Hypertension					0.36
No	11259	745	-	1.16 (1.00 to 1.35)		No	11259	187		0.91 (0.62 to 1.33)	)
Yes	7644	1684	-	1.08 (1.01 to 1.16)		Yes	7644	604	H	1.14 (1.02 to 1.27)	)
eGFR					< 0.001	eGFR					< 0.001
<60	1344	665		1.42 (1.04 to 1.93)		<60	1344	251		1.54 (0.89 to 2.64)	
≥60	17559	1764		1.37 (1.21 to 1.55)		≥60	17559	540		1.63 (1.33 to 2.01)	
Dyslipidemia					< 0.001	Dyslipidemia					0.15
No	10407	955		1.37 (1.17 to 1.60)		No	10407	288		1.48 (1.14 to 1.02)	
Ves	8496	1474	_	1.40 (1.22 to 1.62)		Vas	8496	503		1.40 (1.14 to 1.02)	
Diabotos mollitus	0400	1474		1.40 (1.22 to 1.02)	< 0.001	Diabatas mallitus	0400	500		1.01 (1.20 to 2.00)	< 0.001
biabetes menitus	45550	1022		1 41 41 24 1- 1 60	< 0.001	biabetes menitus	45550	E 4 4		4 C4 /4 25 to 4 04	< 0.001
No	10009	1033		1.41 (1.24 to 1.60)		NO	10009	014		1.01 (1.35 to 1.91)	
Yes	3344	796		1.44 (1.10 to 1.78)		Yes	3344	211		1.70 (1.12 to 2.56)	
Established CVD					< 0.001	Established CVD					< 0.001
		1709		1.43 (1.26 to 1.61)		No	17041	487		1.70 (1.41 to 2.06)	)
No	17041	1100				140					
No Yes	17041 1862	720		1.27 (1.02 to 1.58)		Yes	1862	304		1.56 (1.13 to 2.17)	)
No Yes Overall	17041 1862 18903	720 791	-	1.27 (1.02 to 1.58) 1.35 (1.21 to 1.50) 3		Yes Overall	1862 18903	304 791	0.5 1 2	1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3	)
No Yes Overall	17041 1862 18903	720 791 0.5	512	1.27 (1.02 to 1.58) 1.35 (1.21 to 1.50) 3	D faz interestia	Yes Overall D	1862 18903	304 791	0.5 1 2	1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3	) ) P for interaction
No Yes Overall C Subgroup	17041 1862 18903 Total Number	720 791 0.5	512	1.27 (1.02 to 1.58) 1.35 (1.21 to 1.50) 3 HR (95% Cl)	P for interactic	Yes Overall D Subgroup	1862 18903 Total Number	304 7910 Events	0.5 1 2	1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% CI)	P for interaction
No Yes Overall C Subgroup Age	17041 1862 18903 Total Number	720 791 0.5 Events	5 1 2	1.27 (1.02 to 1.58) 1.35 (1.21 to 1.50) 3 HR (95% Cl)	P for interactic 0.04	Yes Overall D Subgroup Age	1862 18903 Total Number	304 7910 Events	0.5 1 2	1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl)	P for interaction 0.01
No Yes Overall C Subgroup Age <55	17041 1862 18903 Total Number 10809	720 791 0.5 Events	5 1 2	1.27 (1.02 to 1.58) 1.35 (1.21 to 1.50) 3 HR (95% Cl) 1.02 (0.89 to 1.1	P for interactic 0.04 7)	Yes Overall D Subgroup Age <65	1862 18903 Total Number 10809	304 791 Events	0.5 1 2	1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl) 1.21 (0.84 to 1.72) 0.77 (2.74 t+ 1.67)	P for interaction 0.01
No Yes Overall C Subgroup Age <55 265	17041 1862 18903 Total Number 10809 1969	720 791 0.5 Events 598 496	5 1 2	1.27 (1.02 to 1.58) 1.35 (1.21 to 1.50) 3 HR (95% Cl) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2	P for interactic 0.04 7) 5)	Yes Overall D Subgroup Age <65 ≥65	1862 18903 Total Number 10809 1969	304 791 Events 134 142	0.5 1 2	1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.25)	P for interaction 0.01
No Yes Overall C Subgroup Age <65 265 Sex	17041 1862 18903 Total Number 10809 1969	720 791 Events	5 1 2	1.27 (1.02 to 1.58) 1.35 (1.21 to 1.50) 3 HR (95% Cl) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2	P for interactic 0.04 5) 0.44	Yes Overall D Subgroup Age <65 265 Sex	1862 18903 Total Number 10809 1969	304 7910 Events 134 142	0.5 1 2	1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.26)	P for interaction 0.01 0.51
No Yes Overall C Subgroup Age <65 ≥65 ≥65 Sex Female	17041 1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578	720 791 Events 598 496 474		1.27 (1.02 to 1.58) 1.35 (1.21 to 1.50) 3 HR (95% CI) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3	P for interactic 0.04 7) 5) 0.44 3)	Yes Overall D Subgroup Age ≪65 ≥65 Sex Female	1862 18903 Total Number 10809 1969 6578	304 7910 Events 134 142 118	.5 1 2	1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.26) 1.23 (0.95 to 1.58)	P for interaction 0.01 0.51
No Yes Overall C Subgroup Age <65 ≥65 Sex Female Male	17041 1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200	720 791 0.5 Events 598 496 474 620		1.27 (1.02 to 1.58) 1.35 (1.21 to 1.50) 3 HR (95% Cl) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.32 (1.18 to 1.4	P for interactic 0.04 7) 0.44 3) 7)	Yes Overall D Subgroup ≪65 ≥65 Sex Female Male	1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200	304 <b>791</b> <b>Events</b> 134 142 118 158		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.25) 1.23 (0.95 to 1.58) 1.58 (1.23 to 2.04)	P for interaction 0.01 0.51
No Yes Overall C Subgroup Age <55 ≥65 Sex Female Male Ethnicity	17041 1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200	720 791 0.5 Events 598 496 474 620		1.27 (1.02 to 1.58) 1.35 (1.21 to 1.50) 3 HR (95% Cl) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.32 (1.18 to 1.4	P for interactic 0.04 5) 0.44 3) 7) 0.09	Yes Overall D Subgroup Age <65 265 Sex Female Male Ethnicity	1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200	304 <b>791</b> <b>Events</b> 134 142 118 158		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.26) 1.23 (0.95 to 1.58) 1.58 (1.23 to 2.04)	P for interaction 0.01 0.51
No Yes Overall C Subgroup Age <65 ≥65 Sex Female Male Ethnicity Non-Hispanic White	17041 1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216	720 791 0.5 598 496 474 620 537	5 1 2	1.27 (1.02 to 1.56) 1.35 (1.21 to 1.50) 3 HR (95% Cl) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.32 (1.18 to 1.4 1.19 (1.07 to 1.3	P for interactic 0.04 7) 5) 0.44 3) 7) 0.09 3)	Yes Overall D Subgroup Age <65 265 Sex Female Male Ethnicity Non-Hispanic White	1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216	304 <b>791</b> Events 134 142 118 158 121		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.26) 1.23 (0.95 to 1.58) 1.58 (1.23 to 2.04) 1.06 (0.82 to 1.36)	P for Interaction 0.01 0.51
No Yes Overall C Subgroup Age <85 >85 Sex Female Male Ethnicity Non-Hispanic White Non-Hispanic White	17041 1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654	720 791 0.5 598 496 474 620 537 257		1.27 (1.02 to 1.58) 1.35 (1.21 to 1.50) 3 HR (95% Cl) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.32 (1.18 to 1.4 1.19 (1.07 to 1.3 1.24 (1.12 to 1.3	P for interactic 0.04 7) 5) 0.44 3) 7) 0.09 3) 6)	Yes Overall D Subgroup Age <65 ≥65 Sex Female Male Ethnicity Non-Hispanic White Non-Hispanic Black	1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654	304 <b>791</b> Events 134 142 118 158 121 83		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.26) 1.23 (0.95 to 1.58) 1.58 (1.23 to 2.04) 1.66 (0.82 to 1.36) - 1.77 (1.04 to 3.02)	P for interaction 0.01 0.51
No Yes Overall C Subgroup Age <65 ≥65 Sex Female Male Ethnicity Non-Hispanic White Non-Hispanic White Non-Hispanic Black Mexican American	17041 1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2447	720 791 0.5 598 496 474 620 537 257 209		1.27 (1.02 to 1.56) 1.35 (1.21 to 1.50) 3 HR (95% Cl) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.32 (1.18 to 1.4 1.19 (1.07 to 1.3 1.24 (1.12 to 1.3 1.24 (1.12 to 1.3 1.22 (1.04 to 1.4	P for interactic 0.04 5) 0.44 3) 7) 0.09 3) 6) 2)	Yes Overall D Subgroup Age <85 265 Sex Female Male Ethnicity Non-Hispanic Make Mon-Hispanic White Non-Hispanic White	1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 22654 2447	304 <b>791</b> <b>Events</b> 134 142 118 158 121 83 49		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.25) 1.23 (0.95 to 1.58) 1.58 (1.23 to 2.04) 1.06 (0.82 to 1.36) - 1.77 (1.04 to 3.02) 1.23 (0.95 to 1.58)	P for interaction 0.01 0.51
No Yes Overall C Subgroup Age <85 265 Sex Female Maile Ethnicity Non-Hispanic Black Mexica American Other Hispanic	17041 1862 <b>18903</b> <b>Total Number</b> 10809 1969 6678 6200 5216 2654 2654 2447 1198	720 791 0.5 598 496 474 620 537 257 209 50	512	1.27 (1.02 to 1.56) 1.35 (1.21 to 1.50) 3 HR (95% Cl) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.32 (1.18 to 1.4 1.19 (1.07 to 1.3 1.24 (1.12 to 1.3 1.24 (1.12 to 1.3 1.22 (1.48 to 1.4 1.19 (1.07 to 1.3 1.24 (1.12 to 1.3) 1.24 (1.12 to 1.3	P for interactic 0.04 0.44 0.9 0.09 0.09 0.9 0.09 0.09 0	Yes Overall D Subgroup Age <65 265 Sex Female Male Ethnicity Non-Hispanic White Non-Hispanic White Non-Hispanic White Non-Hispanic Mark	1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2654 2447 1198	304 <b>791</b> <b>Events</b> 134 142 118 158 121 83 49 12		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.26) 1.23 (0.95 to 1.58) 1.58 (1.23 to 2.04) 1.06 (0.82 to 1.36) 1.77 (1.04 to 3.02) 1.23 (0.95 to 1.58) 1.38 (1.09 to 1.75)	P for interaction 0.01 0.51
No Yes Overall C Subgroup Age <85 >85 Sex Female Male Ethnicty Non-Hispanic Black Mexican American Other Hispanic	17041 1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2447 1198 1299	720 791 0.5 Events 598 496 474 620 537 257 209 50 41		1.27 (1.02 to 1.58) 1.35 (1.21 to 1.50) 3 HR (95% Cl) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.32 (1.18 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.12 (1.28 to 2.3 1.07 (0.68 to 1.6	P for interactic 0.04 7) 0.44 3) 0.09 3) 0.09 2) 2) 2) 8)	Yes Overall D Subgroup Age <65 ≥65 Sex Female Male Ethnicity Non-Hispanic White Non-Hispanic Black Mexican American Other Hispanic Other	1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2447 1198 1299	304 <b>791</b> <b>Events</b> 134 142 118 158 121 83 49 12 12		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.25) 1.23 (0.95 to 1.58) 1.58 (1.23 to 2.04) 1.06 (0.82 to 1.36) - 1.77 (1.04 to 3.02) 1.23 (0.95 to 1.58) 1.38 (1.09 to 1.75) 3.38 (1.90 to 1.75) 3.38 (1.90 to 1.50) 3.38 (1.90 t	P for interaction 0.01 0.51 0.5
No Yes Overall C Subgroup Age ⊲85 ≥65 Sex Female Male Ethnicity Non-Hispanic White Non-Hispanic White Non-Hispanic Black Mexican American Other Hispanic	17041 1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2447 1198 1299	720 791 0.5 598 496 474 620 537 209 50 41		1.27 (1.02 to 1.56) 1.35 (1.21 to 1.50) 3 HR (95% Cl) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.32 (1.18 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.17 (1.28 to 2.3 1.07 (0.68 to 1.6	P for interactic 0.04 0.4 0.4 0.44 0.09 0.09 0.14 0.09 0.14	Yes Overall D Subgroup Age <65 266 Sex Female Male Ethnicity Non-Hispanic Black Mexican American Other Hispanic Other BMI	1862 <b>18903</b> <b>Total Number</b> 1969 6578 6200 5216 2654 2447 1198 1299	304 <b>791</b> <b>Events</b> 134 142 118 158 121 83 49 12 12 12		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.25) 1.23 (0.95 to 1.58) 1.58 (1.23 to 2.04) - 1.77 (1.04 to 3.02) 1.23 (0.95 to 1.58) 1.38 (1.09 to 1.78) 2.48 (1.23 to 5.02)	<ul> <li>P for interaction</li> <li>0.01</li> <li>0.51</li> <li>0.5</li> <li>0.65</li> </ul>
No Yes Overall C Subgroup Age <65 >65 Sex Female Maile Ethnicity Non-Hispanic White Non-Hispanic Black Mexican American Other Hispanic Other BMI	17041 1862 <b>18903</b> <b>Total Number</b> 10809 1969 6678 6200 5216 2654 2447 1198 1299 3506	720 791 0.5 598 496 496 474 620 537 257 209 50 41 324		1.27 (1.02 to 1.56) 1.35 (1.21 to 1.50) 3 HR (95% Cl) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.32 (1.18 to 1.4 1.19 (1.07 to 1.3 1.24 (1.12 to 1.3 1.24 (1.12 to 1.3 1.24 (1.12 to 1.3 1.24 (1.12 to 1.3 1.27 (1.46 to 1.4 1.73 (1.28 to 2.3 1.07 (0.68 to 1.6 1.19 (1.01 to 1.4	P for interactic 0.04 0.44 0.9 0.44 0.09 0.09 0.19 0.14 1	Yes Overall D Subgroup Age <65 265 Sex Female Maie Ethnicity Non-Hispanic White Non-Hispanic White Non-Hispanic White Non-Hispanic White Non-Hispanic White Non-Hispanic Other BMI <25	1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2854 2447 1198 1299 3506	304 <b>791</b> <b>C</b> <b>Events</b> 134 142 118 158 121 83 121 83 121 57		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.26) 1.23 (0.95 to 1.50) 1.58 (1.23 to 2.04) 1.06 (0.82 to 1.36) 1.23 (0.95 to 1.50) 1.23 (1.09 to 1.75) 2.48 (1.23 to 5.02) 1.30 (0.91 to 1.86)	P for Interaction 0.01 0.51 0.5
No Yes Overall C Subgroup Age <85 >85 Sex Female Male Ethnicty Non-Hispanic Black Mexican American Other Hispanic Other Hispanic Other BBII <25 30	17041 1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2447 1198 1299 3506 4481	720 791 0.5 Events 598 496 474 620 537 257 209 50 41 324 368		1.27 (1.02 to 1.58) 1.35 (1.21 to 1.50) 3 HR (95% Cl) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.32 (1.18 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.73 (1.28 to 2.3 1.07 (0.68 to 1.5 1.19 (1.01 to 1.4 1.19 (1.01 to 1.4 1.19 (0.91 to 1.4 1.15 (0.98 to 1.3)	P for interactic 0.04 7) 0.44 3) 7) 0.09 3) 6) 2) 2) 2) 8) 0.14 1) 6)	Yes Overall D Subgroup Age <65 ≥65 Sex Female Male Ethnicity Non-Hispanic White Non-Hispanic Black Mexican American Other Hispanic Other BMI <25 25-30	1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2447 1198 1299 3506 4481	304 <b>791</b> <b>Events</b> 134 142 118 158 121 83 49 12 12 12 57 96		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.26) 1.23 (0.95 to 1.58) 1.58 (1.23 to 2.04) 1.06 (0.82 to 1.36) - 1.77 (1.04 to 3.02) 1.38 (1.95 to 1.58) 1.38 (1.90 to 1.75) 3.38 (1.90 to 1.75) 1.38 (1.90 to 1.75) 1.38 (1.90 to 1.75) 1.38 (1.90 to 1.75) 1.30 (0.91 to 1.86) 1.67 (1.17 to 2.40)	P for interaction 0.01 0.51 0.5
No Yes Overall C Subgroup Age ⊲85 ≥65 Sex Female Male Ethnicity Non-Hispanic White Non-Hispanic White Non-Hispanic Whate Mexican American Other BMI <25 25-30 ≥30	17041 1862 18903 Total Number 10809 1969 6578 6200 5216 2654 2447 1198 1299 3506 4481 4481	720 791 0.5 598 496 474 620 537 209 50 41 324 368 402		1.27 (1.02 to 1.56) 1.35 (1.21 to 1.50) 3 HR (95% Cl) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.32 (1.18 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.19 (1.01 to 1.4 1.19 (1.01 to 1.4 1.19 (1.01 to 1.4 1.15 (0.98 to 1.5 1.19 (1.01 to 1.4 1.15 (0.98 to 1.3 1.19 (1.04 to 1.3 1.19 (1.04 to 1.3 1.19 (1.01 to 1.4) 1.19 (1.04 to 1.3 1.19 (1.04 to 1.3)	P for interactic 0.04 0.4 0.4 0.44 0.09 0.09 0.09 0.14 0.14 1) 6) 7,	Yes Overall D Subgroup Age <65 266 Sex Female Male Ethnicity Non-Hispanic Black Mexican American Other Hispanic Other Hispanic Black Other BMI <25 25-30 2-30	1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2447 1198 1299 3506 4481 4791	304 <b>791</b> <b>Events</b> 134 142 118 158 121 83 49 12 12 57 96 123		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.25) 1.23 (0.95 to 1.58) 1.58 (1.23 to 2.04) 1.06 (0.82 to 1.36) 1.23 (0.95 to 1.58) 1.38 (1.09 to 1.75) 2.48 (1.23 to 5.02) 1.30 (0.91 to 1.86) 1.30 (0.91 to 1.86) 1.31 (1.92 to 1.61) 1.32 (0.92 to 1.61) 1.32 (0.92 to 1.61) 1.32 (0.92 to 1.61) 1.30 (0.91 to 1.86) 1.37 (1.04 to 3.02) 1.30 (0.91 to 1.86) 1.37 (1.92 to 1.61) 1.30 (0.91 to 1.86) 1.37 (1.92 to 1.61) 1.31 (0.92 to 1.61) 1.31 (0.92 to 1.61) 1.32 (0.92 to 1.61)	P for interaction 0.01 0.51 0.5 0.65
No Yes Overall C Subgroup Age <65 ≥65 Sex Female Male Ethnicity Non-Hispanic White Non-Hispanic White Non-Hispanic White Non-Hispanic White Non-Hispanic White Non-Hispanic White Non-Hispanic Biat Other Hispanic Other BMI <25 25-30 ≥30 Current smoker	17041 1862 18903 Total Number 10809 1969 6678 6200 5216 2654 2447 1198 1299 3506 4481 4791	Top           720           791           0.5           598           496           474           620           537           257           209           50           41           324           368           402		1.27 (1.02 to 1.56) 1.35 (1.21 to 1.50) 3 HR (95% Cl) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.32 (1.18 to 1.4 1.19 (1.07 to 1.3 1.24 (1.12 to 1.3 1.22 (1.04 to 1.4 1.73 (1.28 to 2.3 1.07 (0.68 to 1.6 1.19 (1.01 to 1.4 1.15 (0.98 to 1.3 1.19 (1.04 to 1.3)	P for interactic 0.04 0.4 0.4 0.4 0.09 0.09 0.14 0.09 0.14 0.14 0.14 0.14 0.14 0.14 0.14	Yes Overall D Subgroup Age <65 ≥65 Sex Female Male Ethnicity Non-Hispanic White Non-Hispanic White Non-Hispanic White Non-Hispanic White Non-Hispanic White Non-Hispanic White Non-Hispanic White Non-Hispanic White Non-Hispanic Other BMI <25 25-30 25-30 230 Current smoker	1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 22447 1198 1299 3506 4481 4791	304 <b>791</b> <b>Events</b> 134 142 118 158 121 83 121 83 121 57 96 123		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.26) 1.23 (0.95 to 1.58) 1.58 (1.23 to 2.04) 1.06 (0.82 to 1.36) 1.77 (1.04 to 3.02) 1.23 (0.95 to 1.58) 1.38 (1.09 to 1.75) 2.48 (1.23 to 5.02) 1.30 (0.91 to 1.86) 1.67 (1.17 to 2.40) 1.21 (0.92 to 1.61)	P for interaction 0.01 0.51 0.5 0.65 0.24
No Yes Overall C Subgroup Age <85 >867 Female Male Ethnicty Non-Hispanic White Non-Hispanic White Non-Hispanic Black Mexican American Other Hispanic Other BMI <25-30 ≥3.0 23.0 Current smoker No	17041 1862 18903 Total Number 10809 1969 6578 6200 5216 2654 2447 1198 1299 3506 4481 4791 10028	720 791 0.5 598 496 474 620 537 257 209 50 41 324 368 402 736		1.27 (1.02 to 1.56) 1.35 (1.21 to 1.50) 3 HR (95% Cl) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.32 (1.18 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.73 (1.28 to 2.3 1.07 (0.68 to 1.5 1.19 (1.01 to 1.4 1.15 (0.98 to 1.3 1.19 (1.04 to 1.3 1.19 (1.04 to 1.3 1.19 (1.04 to 1.3 1.19 (1.04 to 1.3) 1.19 (1.04 to 1.3) 1.11 (1.28 to 1.5)	P for interactic 0.04 7) 0.44 3) 0.09 3) 6 5 2) 2) 2) 8 0.14 1) 6 0.14 1) 5 0.01 5 5	Yes Overall D Subgroup Age <65 ≥65 Sex Female Male Ethnleity Non-Hispanic White Non-Hispanic Black Mexican American Other Hispanic Other Hispanic Other Blant extra American Other Hispanic Other State Sate Sate Sate Sate Sate Sate Sate	1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2447 1198 1299 3506 4481 4791 10028	304 <b>791</b> <b>Events</b> 134 142 118 158 121 83 49 12 12 12 57 96 123 195		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% CI) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.26) 1.23 (0.95 to 1.58) 1.58 (1.23 to 2.04) 1.06 (0.82 to 1.36) - 1.77 (1.04 to 3.02) 1.38 (1.23 to 5.02) 1.38 (1.23 to 5.02) 1.30 (0.91 to 1.86) 1.67 (1.17 to 2.40) 1.21 (0.92 to 1.61) 1.55 (1.26 to 1.90)	P for interaction 0.01 0.51 0.5 0.65
No Yes Overall C Subgroup Age «65 ≥65 Sex Female Male Ethnicity Non-Hispanic Mhite Non-Hispanic Black Mexica American Other Hispanic Other Hispanic Other BMI <25 25-30 ≥30 Current smoker No Yes	17041 1862 18903 Total Number 10809 1969 6578 6200 5216 2654 2447 1198 1299 3506 4481 4791 10028 2750	720 791 0.5 598 496 474 620 537 209 50 41 324 368 402 736 358		1.27 (1.02 to 1.56) 1.35 (1.21 to 1.50) 3 HR (95% Cl) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.32 (1.18 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.19 (1.01 to 1.4 1.17 (1.68 to 1.5 1.19 (1.01 to 1.4 1.15 (0.98 to 1.3 1.19 (1.01 to 1.4 1.15 (0.98 to 1.3 1.19 (1.04 to 1.3 1.19 (1.01 to 1.4 1.15 (0.98 to 1.3 1.19 (1.04 to 1.3 1.19 (1.01 to 1.4 1.15 (0.98 to 1.3 1.19 (1.04 to 1.3 1.11 (0.96 to 1.2 1.11 (0.96 to 1.5 1.11 (0.96 to 1.5 1.11 (0.96 to 1.5)	P for interactic 0.04 0.4 0.4 0.4 0.4 0.09 0.09 0.09 0.09 0.14 1 0 0.14 1 0 0.14 1 0 0.14 1 0 0.1 0 0 0 0 0 0 0 0 0 0 0 0 0	Yes Overall D Subgroup Age <65 266 Sex Female Male Ethnicity Non-Hispanic Black Mexican American Other Hispanic White Non-Hispanic White Non-Hispanic White Non-Hispanic White Non-Hispanic Other BMI <25 25-30 230 Current smoker No Yes	1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2447 1198 1299 3506 4481 4791 10028 2750	304           791		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.25) 1.23 (0.95 to 1.58) 1.58 (1.23 to 2.04) 1.06 (0.82 to 1.36) 1.23 (0.95 to 1.58) 1.38 (1.09 to 1.75) 2.48 (1.23 to 5.02) 1.30 (0.91 to 1.86) 1.67 (1.17 to 2.40) 1.21 (0.92 to 1.61) 1.55 (1.26 to 1.90) 1.55 (1.26 to 1.90) 1.56 (0.74 to 1.48)	P for interaction 0.01 0.51 0.5 0.65 0.24
No Yes Overall C Subgroup Age <55 ≥65 Sex Female Male Ethnicity Non-Hispanic Vhilte Non-Hispanic Vhite Non-Hispanic Vhite Current smoker No Yes	17041 1862 18903 10809 1969 6678 6200 5216 2654 2447 1198 1299 3506 4481 4791 10028 2750	Toto           720           791           0.5           598           496           474           620           537           257           209           50           41           324           368           402           736           358		1.27 (1.02 to 1.58) 1.35 (1.21 to 1.50) 3 HR (95% Cl) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.32 (1.18 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.12 (1.28 to 1.3 1.07 (0.68 to 1.6 1.19 (1.01 to 1.4 1.15 (0.98 to 1.3 1.19 (1.04 to 1.3 1.19 (1.04 to 1.3 1.19 (1.04 to 1.3 1.19 (1.04 to 1.3 1.11 (0.96 to 1.2 1.11 (0.96 to 1.2	P for interactic 0.04 0.04 0.09 0.09 0.09 0.09 0.09 0.14 0.14 0.14 0.01 0.01 0.01 0.01 0.01	Yes Overall D Subgroup Age <65 ≥65 Sex Female Male Ethnicity Non-Hispanic White Non-Hispanic Black Mexican American Other Hispanic Other BMI <25 25-30 230 Current smoker No Yes Hypertension	1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2654 2447 1198 1299 3506 4481 4791 10028 2750	304           791		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.26) 1.23 (0.95 to 1.58) 1.58 (1.23 to 2.04) 1.06 (0.82 to 1.36) 1.77 (1.04 to 3.02) 1.23 (0.95 to 1.58) 1.38 (1.09 to 1.76) 2.48 (1.23 to 5.02) 1.30 (0.91 to 1.86) 1.67 (1.17 to 2.40) 1.21 (0.92 to 1.61) 1.55 (1.26 to 1.90) 1.05 (0.74 to 1.48)	P for Interaction 0.01 0.51 0.5 0.65 0.65
No Yes Overall C Subgroup Age <85 >867 Female Male Ethnicty Non-Hispanic White Non-Hispanic White Non-Hispanic Black Mexican American Other Hispanic Other BMI <25-30 25-30 25-30 25-30 25-30 No Yes Hypertension No	17041 1862 18903 Total Number 10809 1969 6578 6200 5216 22654 2447 1198 1299 3506 4481 4791 10028 2750 7604	720 791 0.5 598 496 474 620 537 257 209 50 41 324 368 402 736 358 419		1.27 (1.02 to 1.56) 1.35 (1.21 to 1.50) 3 HR (95% Cl) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.22 (1.18 to 1.4 1.19 (1.07 to 1.3 1.22 (1.18 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.73 (1.28 to 2.3 1.07 (0.68 to 1.6 1.19 (1.01 to 1.4 1.5 (0.98 to 1.3 1.19 (1.04 to 1.3 1.11 (0.96 to 1.2 1.26 (1.08 to 1.4	P for interactic 0.04 0.4 0.03 0.09 0.001 0.001 0.001	Yes Overail D Subgroup Age ≪65 ≥65 Sex Female Maie Ethnicity Non-Hispanic White Non-Hispanic Black Mexican American Other Hispanic Black Mexican American Other Hispanic Other BMI <25 25-30 ≥30 Current smoker No Yes Hypertension No	1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2447 1198 1299 3506 4481 4791 10028 2750 7604	304 <b>791</b> <b>Events</b> 134 142 118 158 121 83 49 12 12 12 57 96 123 195 81 82		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% C)) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.26) 1.23 (0.95 to 1.58) 1.58 (1.23 to 2.04) 1.06 (0.82 to 1.36) - 1.77 (1.04 to 3.02) 1.38 (1.23 to 5.02) 1.38 (1.23 to 5.02) 1.30 (0.91 to 1.86) 1.67 (1.17 to 2.40) 1.21 (0.92 to 1.61) 1.55 (1.26 to 1.90) 1.05 (0.74 to 1.48) 1.18 (0.75 to 1.85)	P for interaction 0.01 0.51 0.5 0.65 0.24 0.1
No Yes Overail C Subgroup Age <85 265 Sex Female Male Ethnicity Non-Hispanic White Non-Hispanic Black Mexican American Other Hispanic Black State Mexican Mexican American No No Yes	17041 1862 18903 Total Number 10809 1969 6578 6200 5216 2654 2447 1198 1299 3506 4481 4791 10028 2750 7604	Total         Total           720         791         0.5           791         0.5         0.5           598         496         0.5           474         620         5           537         209         50           411         368         402           736         368         402           736         358         419		1.27 (1.02 to 1.56) 1.35 (1.21 to 1.50) 3 HR (95% CI) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.22 (1.18 to 1.4 1.19 (1.07 to 1.3 1.22 (1.18 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.19 (1.01 to 1.4 1.19 (1.01 to 1.4 1.15 (0.98 to 1.6 1.19 (1.04 to 1.3 1.41 (1.28 to 1.5 1.11 (0.96 to 1.2 1.11 (0.96 to 1.2 1.26 (1.08 to 1.4 1.26 (1.28 to 1.5 1.11 (0.96 to 1.2 1.26 (1.08 to 1.4 1.26 (1.28 to 1.4) 1.26 (1.28 to 1.4 1.26 (1.28 to 1.4) 1.26 (1.28 to 1.4)	P for interactic 0.04 0.4 0.4 0.4 0.4 0.09 0.09 0.09 0.09 0.14 0.01 0.02	Yes Overall D Subgroup Age <65 266 Sex Female Male Ethnicity Non-Hispanic Black Mexican American Other Hispanic Black Mexican American Other Hispanic Mukk Mexican American Other Hispanic Other BMI <25 25-30 230 Current smoker No Yes Hypertension No Yes	1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2447 1198 1299 3506 4481 4791 10028 2750 7604 5174	304 <b>791</b> <b>Events</b> 134 142 118 158 121 158 121 123 122 12 12 12 12 12 12 12 12 1		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.26) 1.23 (0.95 to 1.58) 1.58 (1.23 to 2.04) 1.06 (0.82 to 1.36) 1.23 (0.95 to 1.58) 1.38 (1.09 to 1.75) 2.48 (1.23 to 5.02) 1.30 (0.91 to 1.86) 1.57 (1.17 to 2.40) 1.21 (0.92 to 1.61) 1.55 (1.26 to 1.90) 1.05 (0.74 to 1.48) 1.18 (0.75 to 1.85) 1.38 (1.07 to 1.85) 1.38 (1.17 to 16.3)	P for interaction 0.01 0.51 0.5 0.65 0.24 0.1
No Yes Overall C Subgroup Age <55 >65 Sex Female Male Ethnicity Non-Hispanic White Non-Hispanic White Non-Hispanic Uther Non-Hispanic Ball Other Hispanic Other BMI <25 25-30	17041 1862 18903 10809 1969 6678 6200 5216 2654 2447 1198 1299 3506 4481 4791 10028 2750 7604 5174	T20           720           781           0.5           598           496           474           620           537           257           209           50           41           324           368           402           736           358           419           675		1.27 (1.02 to 1.58) 1.35 (1.21 to 1.50) 3 HR (95% Cl) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.32 (1.18 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.73 (1.28 to 2.3 1.07 (0.68 to 1.6 1.19 (1.01 to 1.4 1.15 (0.98 to 1.3 1.19 (1.04 to 1.3 1.19 (1.04 to 1.3 1.19 (1.04 to 1.3 1.11 (0.96 to 1.2 1.12 (0.16 to 1.4 1.12 (0.16 to 1.4 1.24 (1.12 to 1.3)	P for interactic 0.04 7) 0.44 3) 0.09 3) 0.09 3) 0.09 3) 0.14 1) 0.15 1) 0.14 1) 0.01 1) 0.2 1) 0.2 1) 0.2 1) 0.2 1) 0.2 1) 0.2 1) 0.14 1) 0.2 1) 0.14 1) 0.14 1) 0.14 1) 0.14 1) 0.14 1) 0.14 1) 0.14 1) 0.14 1) 0.14 1) 0.14 1) 0.14 1) 0.14 1) 0.14 1) 0.14 1) 0.14 1) 0.14 1) 0.14 1) 0.14 1) 10 10 10 10 10 10 10 10 10 10 10 10 10	Yes Overall D Subgroup Age <65 ≥65 Sex Female Male Ethnicity Non-Hispanic White Non-Hispanic White Non-Hispanic Black Mexican American Other Hispanic Other BMI <25 25-30 250 25-30 250 Current smoker No Yes Hypertension No Yes	1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2447 1198 1299 3506 4481 4791 10028 2750 7604 5174	304           791		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.26) 1.23 (0.95 to 1.58) 1.58 (1.23 to 2.04) 1.06 (0.82 to 1.36) 1.77 (1.04 to 3.02) 1.23 (0.95 to 1.58) 1.38 (1.23 to 5.02) 1.30 (0.91 to 1.86) 1.67 (1.17 to 2.40) 1.21 (0.92 to 1.61) 1.55 (1.26 to 1.90) 1.56 (1.26 to 1.90) 1.56 (1.26 to 1.90) 1.56 (1.26 to 1.85) 1.38 (1.17 to 1.63) 1.38 (1.17 to 1.63)	P for interaction 0.01 0.51 0.5 0.65 0.24 0.1
No Yes Overall C Subgroup Age <65 >65 Sex Female Male Ethnicity Non-Hispanic White Non-Hispanic White Non-Hispanic Black Mexican American Other Hispanic Black Mexican American Other Hispanic Other Ball <25-30 2	17041 1862 18903 Total Number 10809 1969 6578 6200 5216 22654 2447 1198 1299 3506 4481 4791 10028 2750 7604 5174 428	720 791 0.5 598 496 474 620 537 257 209 50 41 324 368 402 736 358 419 675 111		1.27 (1.02 to 1.56) 1.35 (1.21 to 1.50) 3 HR (95% CI) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.32 (1.18 to 1.4 1.19 (1.07 to 1.3 1.24 (1.12 to 1.3 1.22 (1.04 to 1.4 1.73 (1.28 to 2.3 1.07 (0.68 to 1.6 1.19 (1.01 to 1.4 1.5 (0.98 to 1.3 1.19 (1.04 to 1.3 1.11 (0.96 to 1.2 1.26 (1.08 to 1.4 1.24 (1.12 to 1.3 1.11 (0.86 to 1.4 1.24 (1.12 to 1.3)	P for interactic 0.04 0.44 0.09 0.09 0.09 0.09 0.09 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.01 0.03 0.001 0.03 0.001 0.03 0.03 0.03 0.03 0.04 0.09 0.04 0.09	Yes Overail D Subgroup Age <65 ≥65 Sex Female Maie Ethnleity Non-Hispanic White Non-Hispanic Black Mexican American Other Hispanic Black Mexican American Other Hispanic Other BMI <25 25-30 ≥30 Current smoker No Yes Hypertension No Yes eGFR <60	1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2447 1198 1299 3506 4481 4791 10028 2750 7604 5174 428	304 <b>791 C Events</b> 134 142 118 158 121 83 49 12 12 12 57 96 123 195 81 82 194 33		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% CI) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.25) 1.23 (0.95 to 1.58) 1.58 (1.23 to 2.04) 1.06 (0.82 to 1.36) - 1.77 (1.04 to 3.02) 1.23 (0.95 to 1.58) 1.38 (1.23 to 5.02) 1.30 (0.91 to 1.86) 1.67 (1.17 to 2.40) 1.21 (0.92 to 1.61) 1.55 (1.26 to 1.90) 1.05 (0.74 to 1.48) 1.18 (0.75 to 1.85) 1.38 (1.17 to 1.63) 0.77 (0.46 to 1.29)	P for interaction 0.01 0.51 0.5 0.65 0.24 0.1
No Yes Overall C Subgroup Age <65 265 Sex Female Male Ethnicity Non-Hispanic White Non-Hispanic Black Mexica A merican Other Hispanic Black No Secondor Black No No No No No No No No No No No No No	17041 1862 18903 Total Number 10809 1969 6578 6200 5216 2654 2447 1198 1299 3506 4481 4791 10028 2750 7604 5174 428 12350	Toto         Toto           791         0.5           791         0.5           598         496           474         620           537         209           50         41           324         368           402         736           358         419           675         111           983         111		1.27 (1.02 to 1.56) 1.35 (1.21 to 1.50) 3 HR (95% CI) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.22 (1.18 to 1.4 1.19 (1.07 to 1.3 1.22 (1.18 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.19 (1.01 to 1.4 1.17 (0.68 to 1.6 1.19 (1.01 to 1.4 1.15 (0.98 to 1.3 1.11 (0.46 to 1.3 1.21 (1.28 to 1.5 1.11 (0.96 to 1.2 1.26 (1.08 to 1.4 1.24 (1.12 to 1.3 1.11 (0.86 to 1.4 1.24 (1.12 to 1.3) 1.11 (0.86 to 1.4 1.24 (1.12 to 1.3)	P for interactic 0.04 0.4 0.4 0.4 0.09 0.01 0.01 0.09 0.01 0.09 0.01 0.09 0.01 0.09 0.01 0.09 0.01 0.09 0.01 0.02 0.02 0.01 0.02 0.02 0.01 0.02 0.02 0.02 0.02 0.01 0.02 0.03 0.02 0.03 0.02 0.03 0.02 0.03 0.05 0.02 0.05 0.0	Yes Overall D Subgroup Age <65 265 Sex Female Male Ethnicity Non-Hispanic Molte Male Ethnicity Non-Hispanic White Non-Hispanic White Non-Hispanic White Non-Hispanic White Non-Hispanic White Non-Hispanic Molte Cher Hispanic Other Hispanic Other Hispanic Other BMI <25 25-30 230 Current smoker No Yes Hypertension No Yes eGFR <60 260	1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2447 1198 1299 3506 4481 4791 10028 2750 7604 5174 428 12350	304 <b>791</b> <b>Events</b> 134 142 118 158 121 83 121 83 121 123 123 123 123 123 123 12		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.26) 1.23 (0.95 to 1.58) 1.58 (1.23 to 2.04) 1.06 (0.82 to 1.36) 1.77 (1.04 to 3.02) 1.23 (0.95 to 1.58) 1.38 (1.09 to 1.75) 2.48 (1.23 to 5.02) 1.30 (0.91 to 1.86) 1.67 (1.17 to 2.40) 1.21 (0.92 to 1.61) 1.55 (1.26 to 1.90) 1.05 (0.74 to 1.48) 1.38 (1.17 to 1.63) 0.77 (0.46 to 1.29) 1.39 (0.11 ta 10.75)	P for interaction 0.01 0.51 0.5 0.65 0.24 0.1 0.02
No Yes Overall C Subgroup Age <55 >65 Sex Female Male Ethnicity Non-Hispanic White Non-Hispanic Back Mexican America Other Hispanic Other Hispanic Other Hispanic Other Sach Cutrent Smoker No Yes Hypertension No Yes EGFR <50 250 250 250 250 250 250 250 250 250 2	17041 1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2447 1198 1299 3506 4481 4791 10028 2750 7604 5174 428 12350	T20           720           781           0.5           598           496           474           620           537           257           209           50           41           324           368           402           736           358           419           675           111           983		1.27 (1.02 to 1.58) 1.35 (1.21 to 1.50) 3 HR (95% Cl) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.32 (1.18 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.73 (1.28 to 2.3 1.07 (0.68 to 1.6 1.19 (1.01 to 1.4 1.15 (0.98 to 1.3 1.19 (1.04 to 1.3 1.11 (0.66 to 1.2 1.26 (1.08 to 1.4 1.24 (1.12 to 1.3 1.11 (0.66 to 1.4 1.21 (1.11 to 1.3	P for interactic 0.04 7) 0.44 3) 0.09 3) 0.09 3) 0.14 1 3 0.14 1 5 9 <0.01 5 9 <0.001 7 0.2 3 3 <0.01 5 5 <0.14 1 5 5 5 5 5 5 5 5 5 5 5 5 5	Yes Overall D Subgroup Age <65 ≥65 Sex Female Male Ethnicity Non-Hispanic White Non-Hispanic Black Mexican American Other Hispanic Other BMI <25 25-30 250 Current smoker No Yes Hypertension No Yes eGFR <60 260 Dosilioidemia	1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2447 1198 1299 3506 4481 4791 10028 2750 7604 5174 428 12350	304           791		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.26) 1.23 (0.95 to 1.58) 1.58 (1.23 to 2.04) 1.06 (0.82 to 1.36) 1.77 (1.04 to 3.02) 1.23 (0.95 to 1.58) 1.38 (1.23 to 5.02) 1.30 (0.91 to 1.86) 1.67 (1.17 to 2.40) 1.21 (0.92 to 1.61) 1.55 (1.26 to 1.90) 1.56 (1.26 to 1.90) 1.56 (1.26 to 1.90) 1.57 (1.74 to 1.48) 1.18 (0.75 to 1.85) 1.38 (1.17 to 1.63) 0.77 (0.46 to 1.29) 1.39 (1.13 to 1.71)	P for interaction 0.01 0.51 0.5 0.65 0.24 0.1 0.02 0.79
No Yes Overall C Subgroup Age <85 ≥85 Sex Female Male Ethnicity Non-Hispanic White Non-Hispanic White Non-Hispanic White Non-Hispanic Black Mexican American Other Hispanic Other Hispanic Other Santon Other Santon Sa	17041 1862 18903 Total Number 10809 1969 6578 6200 5216 22654 2447 1198 1299 3506 4481 4791 10028 2750 7604 5174 428 12350 7049	Top           720           791           0.5           598           496           474           620           537           209           50           411           324           368           402           736           358           419           675           111           983           491		1.27 (1.02 to 1.56) 1.35 (1.21 to 1.50) 3 HR (95% CI) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.32 (1.18 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.73 (1.28 to 2.3 1.07 (0.68 to 1.6 1.19 (1.01 to 1.4 1.5 (0.98 to 1.3 1.19 (1.04 to 1.3 1.11 (0.96 to 1.2 1.26 (1.08 to 1.4 1.24 (1.12 to 1.3 1.11 (0.86 to 1.4 1.21 (1.11 to 1.3 1.11 (0.86 to 1.4 1.21 (1.11 to 1.3)	P for interactic           0.04           0.14           0.1           0.09           0.09           0.09           0.09           0.09           0.09           0.09           0.09           0.01           0.01           0.001           70           0.001           0.2           30           20	Yes Overail D Subgroup Age ≪65 ≥65 Sex Female Maie Ethnicity Non-Hispanic White Non-Hispanic Black Mexican American Other Hispanic Other BMI ≪25 25-30 ≥30 Current smoker No Yes Hypertension No Yes eGFR ≪60 ≥60 ≥60 Dyslipidemia No	1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2447 1198 1299 3506 4481 4791 10028 2750 7604 5174 428 12350 7049	304 <b>791 C Events</b> 134 142 118 158 121 83 49 12 12 12 57 96 123 195 81 82 194 33 243 120		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% CI) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.25) 1.23 (0.95 to 1.58) 1.58 (1.23 to 2.04) 1.06 (0.82 to 1.36) - 1.77 (1.04 to 3.02) 1.38 (1.23 to 5.02) 1.30 (0.91 to 1.86) 1.67 (1.17 to 2.40) 1.21 (0.92 to 1.61) 1.55 (1.26 to 1.90) 1.05 (0.74 to 1.48) 1.38 (1.17 to 1.63) 0.77 (0.46 to 1.29) 1.39 (1.13 to 1.71) 1.29 (0.93 to 1.70)	P for interaction 0.01 0.51 0.5 0.65 0.24 0.1 0.02 0.79
No Yes Overall C Subgroup Age <65 265 5 5 8 5 8 7 Female Male Ethnicity Non-Hispanic Vhite Non-Hispanic Black Mexica A merican Other Hispanic A merican No No No	17041 1862 18903 Total Number 10809 1969 6578 6200 5216 2654 2654 2447 1198 1299 3506 4481 4791 10028 2750 7604 5174 428 12350 7049 5329	Toto         Toto           791         0.5           598         0.5           598         496           474         620           537         209           50         41           324         368           402         736           358         419           675         111           983         491		1.27 (1.02 to 1.56) 1.35 (1.21 to 1.50) 3 HR (95% CI) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.22 (1.18 to 1.4 1.19 (1.07 to 1.3 1.22 (1.18 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.17 (1.68 to 1.6 1.19 (1.01 to 1.4 1.15 (0.98 to 1.6 1.19 (1.01 to 1.4 1.15 (0.98 to 1.3 1.11 (0.68 to 1.4 1.26 (1.08 to 1.4 1.26 (1.08 to 1.4 1.24 (1.12 to 1.3 1.11 (0.66 to 1.4 1.24 (1.12 to 1.3 1.11 (0.66 to 1.4 1.21 (1.11 to 1.3 1.12 (1.11 to 1.3 1.42 (1.22 to 1.6 1.09 (0.65 to 1.6 1.21 (1.11 to 1.3) 1.42 (1.22 to 1.6 1.42 (1.22 to 1.6 1.42 (1.22 to 1.6) 1.42 (1.22 to 1.	P for interactic           0.04           0.14           0.09           0.09           0.09           0.09           0.09           0.09           0.09           0.09           0.09           0.01           0.01           0.2           0.001           0.2           0.2           0.001	Yes Overail D Subgroup Age <65 265 Sex Female Maie Ethnicity Non-Hispanic Mhite Non-Hispanic White Non-Hispanic White Non-Hispanic White Non-Hispanic White Non-Hispanic White Non-Hispanic White Non-Hispanic Mach Other Hispanic Mach Other Hispanic Mach Other Hispanic Other BMI <25 25-30 230 Current smoker No Yes Hypertension No Yes eGFR <60 260 Dyslipidemia No Yes	1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2654 2654 2654 2654 2654 2654 2750 3506 4481 4791 10028 2750 7604 5174 428 12350 7049 5729	304           791		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.26) 1.23 (0.95 to 1.58) 1.23 (0.95 to 1.58) 1.23 (0.95 to 1.58) 1.23 (1.95 to 1.58) 1.38 (1.97 to 1.85) 1.38 (1.17 to 1.63) 0.77 (0.46 to 1.29) 1.39 (1.13 to 1.79) 1.29 (0.93 to 1.78) 1.39 (0.91 to 1.88) 1.38 (1.17 to 1.63) 0.77 (0.46 to 1.29) 1.39 (1.13 to 1.79) 1.29 (0.93 to 1.78) 1.29 (0.93 to 1.78)	P for interaction 0.01 0.51 0.5 0.65 0.24 0.1 0.02 0.79
No Yes Overall C Subgroup Age <65 ≥65 Sex Female Male Ethnicity Non-Hispanic White Non-Hispanic Bak Make Non-Hispanic Bak Mexican American Other Hispanic Other BMI <25 25-30 25-30 Cutrent smoker No Yes Hypertension No Yes eGFR <60 ≥80 Dyslipidemia No Yes	17041 1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2447 1198 1299 3506 4481 4791 10028 2750 7604 5174 428 12350 7049 5729	T20           720           781           0.5           598           496           474           620           537           257           209           50           41           368           402           736           358           419           675           111           983           491           603		1.27 (1.02 to 1.58) 1.35 (1.21 to 1.50) 3 HR (95% Cl) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.32 (1.18 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.32 (1.18 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.73 (1.28 to 2.3 1.07 (0.68 to 1.5 1.19 (1.01 to 1.4 1.15 (0.98 to 1.3 1.19 (1.04 to 1.3 1.11 (0.96 to 1.2 1.26 (1.08 to 1.4 1.22 (1.11 to 1.3 1.11 (0.86 to 1.4 1.21 (1.11 to 1.3 1.42 (1.25 to 1.6 1.09 (0.96 to 1.2	P for interactic 0.04 7 0.44 3 0.09 3 0.09 3 0.09 3 0.14 1 1 0.14 1 1 0 0.14 1 0 0 0 1 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	Yes Overail D Subgroup Age <65 ≥65 Sex Female Male Ethnicity Non-Hispanic Vhite Non-Hispanic Black Mexican American Other Hispanic Other BMI <25 25-30 ≥30 Current smoker No Yes Hypertension No Yes eGFR <60 ≥60 Dyslipidemia No Yes Diabates molifium	1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2447 1198 1299 3506 4481 4791 10028 2750 7604 5174 428 12350 7604 5174 428 12350	304           791		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.26) 1.23 (0.95 to 1.58) 1.58 (1.23 to 2.04) 1.06 (0.82 to 1.36) 1.77 (1.04 to 3.02) 1.23 (0.95 to 1.58) 1.38 (1.23 to 5.02) 1.30 (0.91 to 1.86) 1.67 (1.17 to 2.40) 1.21 (0.92 to 1.61) 1.55 (1.26 to 1.90) 1.56 (1.26 to 1.29) 1.38 (1.17 to 1.63) 0.77 (0.46 to 1.29) 1.39 (1.13 to 1.71) 1.29 (0.93 to 1.79) 1.30 (1.02 to 1.65)	P for interaction 0.01 0.51 0.5 0.65 0.24 0.1 0.02 0.79
No Yes Overall C Subgroup Age <65 ≥65 Sex Female Male Ethnicty Non-Hispanic White Non-Hispanic White Non-Hispanic Black Mexican American Other Hispanic Black Mexican American Other Hispanic Black Mexican American Other Hispanic Black Mexican American Other Spanic Black Mexican American Other Spanic Black Mexican American Other Spanic Black Mexican American Other Spanic Black Mexican American No Yes Current smoker No Yes Co So Dyslipidemia No Yes Diabetes meilitus	17041 1862 18903 Total Number 10809 1969 6578 6200 5216 6200 5216 22654 2447 1198 1299 3506 4481 4791 10028 2750 7604 5174 428 12350 7049 5729	720 791 6.5 598 496 474 620 537 257 209 50 41 324 368 402 736 358 419 675 111 983 491 603 276		1.27 (1.02 to 1.56) 1.35 (1.21 to 1.50) 3 HR (95% CI) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.32 (1.18 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.73 (1.28 to 2.3 1.07 (0.68 to 1.6 1.19 (1.01 to 1.4 1.5 (0.98 to 1.3 1.19 (1.04 to 1.3 1.11 (0.96 to 1.2 1.26 (1.08 to 1.4 1.21 (1.11 to 1.3 1.42 (1.25 to 1.6 1.09 (0.96 to 1.2 1.24 (2.05 to 1.6 1.24 (2.05 to 1.2) 1.24 (2.05 to	P for interactic           0.04           0.14           0	Yes Overail D Subgroup Age ≪65 ≥65 Sex Female Maie Ethnicity Non-Hispanic White Non-Hispanic White Non-Hispanic Black Mexican American Other Hispanic Other BMI ≪25 25-30 ≥30 Current smoker No Yes Hypertension No Yes GGFR ≪60 ≥60 Dyslipidemia No Yes BDiabetes mellitus	1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2447 1198 1299 3506 4481 4791 10028 2750 7604 5174 428 12350 7049 5729 10586	304 <b>791 C Events</b> 134 142 118 158 121 83 121 12 12 57 96 123 195 81 82 194 33 243 120 156 178		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% CI) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.25) 1.23 (0.95 to 1.58) 1.58 (1.23 to 2.04) 1.06 (0.82 to 1.36) - 1.77 (1.04 to 3.02) 1.38 (1.23 to 5.02) 1.30 (0.91 to 1.86) 1.67 (1.17 to 2.40) 1.21 (0.92 to 1.61) 1.55 (1.26 to 1.90) 1.05 (0.74 to 1.48) 1.18 (0.75 to 1.85) 1.38 (1.17 to 1.63) 0.77 (0.46 to 1.29) 1.39 (1.13 to 1.71) 1.29 (0.93 to 1.79) 1.30 (1.02 to 1.66)	P for interaction 0.01 0.51 0.5 0.65 0.24 0.1 0.02 0.79 0.02
No Yes Overall C Subgroup Age ⊲55 ≥65 Sex Female Male Ethnicity Non-Hispanic Vhite Non-Hispanic Vhite Non-Hispanic Black Mexica American Other Hispanic Black Mexica American Description Second Second S	17041 1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2447 1198 1299 3506 4481 4791 10028 2750 7604 5174 428 12350 7049 5729 10586	Toto           720           720           791           0.2           598           496           620           537           209           50           411           324           368           402           736           358           419           675           111           983           491           603           776           319		1.27 (1.02 to 1.56) 1.35 (1.21 to 1.50) 3 HR (95% CI) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.22 (1.18 to 1.4 1.19 (1.07 to 1.3 1.24 (1.12 to 1.3 1.22 (1.04 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.13 (1.28 to 2.3 1.07 (0.68 to 1.6 1.19 (1.01 to 1.4 1.15 (0.98 to 1.3 1.141 (1.28 to 1.5 1.111 (0.86 to 1.4 1.24 (1.12 to 1.3 1.11 (0.86 to 1.4 1.24 (1.12 to 1.3 1.11 (0.86 to 1.4 1.24 (1.12 to 1.3 1.11 (0.86 to 1.4 1.24 (1.12 to 1.3 1.141 (1.25 to 1.6 1.09 (0.96 to 1.2 1.34 (1.20 to 1.4 1.09 (0.96 to 1.2) 1.34 (1.20 to 1.4) 1.34 (1.20 to 1.4) 1.	P for interactic         0.04         0.14         0.09         0.09         0.14         0.01         0.14         0.01         0.01         0.01         0.01         0.2         0.001         0.2         0.001         0.2         0.001         0.2         0.001         0.2         0.001         0.2         0.001         0.2         0.001         0.001         0.001         0.2         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001	Yes Overail D Subgroup Age <65 265 Sex Female Maie Ethnicity Non-Hispanic Black Mexican American Other Hispanic Black Mexican American Other Hispanic Other BMI <25 25-30 230 Current smoker No Yes Hypertension No Yes eGFR <60 260 Dyslipidemia No Yes Diabetes mellitus No Yes	1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2654 2654 2654 2654 2654 2654 2654 2654 2750 7604 5174 428 12350 7604 5174 2750 7604 5174 2750 7604 5174 2750 7049 5729 10586 7192 219	304 <b>791</b> <b>Events</b> 134 142 118 158 121 83 121 83 122 123 123 195 81 123 195 81 194 33 243 120 156 178 98		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.26) 1.23 (0.95 to 1.58) 1.23 (0.95 to 1.58) 1.23 (1.23 to 2.04) 1.06 (0.82 to 1.36) 1.23 (1.09 to 1.76) 1.23 (1.09 to 1.75) 2.48 (1.23 to 5.02) 1.30 (0.91 to 1.86) 1.67 (1.17 to 2.40) 1.21 (0.92 to 1.61) 1.55 (1.26 to 1.90) 1.05 (0.74 to 1.48) 1.38 (1.17 to 1.63) 0.77 (0.46 to 1.29) 1.39 (1.13 to 1.71) 1.29 (0.93 to 1.76) 1.56 (1.20 to 2.03) 1.56 (1.20 to 2.03) 1.56 (1.20 to 2.03) 1.56 (1.20 to 2.03) 1.56 (1.20 to 2.03)	P for interaction 0.01 0.51 0.5 0.65 0.24 0.1 0.02 0.79 0.02
No Yes Overall C Subgroup Age ⊲65 ≥65 Female Male Ethnicity Non-Hispanic White Non-Hispanic White Non-Hispanic Bak Mexican American Other Hispanic Other Hispanic Other BMI <25 25-30 ≥30 Other BMI <25 25-30 ≥30 Cther BMI <25 25-30 ≥80 Current smoker No Yes Hypertension No Yes EGFR <60 ≥80 Dyslipidemia No Yes BNI	17041 1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2447 1198 1299 3506 4481 4791 10028 2750 7604 5174 428 12350 7049 5729 10586 2192 4927 10586	T20           720           781           0.5           598           496           474           620           537           257           209           50           41           368           402           736           358           419           675           111           983           491           603           776           318           700		1.27 (1.02 to 1.56) 1.35 (1.21 to 1.50) 3 HR (95% Cl) 1.02 (0.89 to 1.1 1.08 (0.93 to 1.2 1.17 (1.04 to 1.3 1.32 (1.18 to 1.4 1.19 (1.07 to 1.3 1.22 (1.04 to 1.4 1.13 (1.28 to 1.3 1.07 (0.68 to 1.6 1.19 (1.01 to 1.4 1.13 (1.28 to 1.3 1.19 (1.01 to 1.4 1.15 (0.98 to 1.3 1.19 (1.04 to 1.3 1.11 (0.96 to 1.2 1.26 (1.08 to 1.4 1.22 (1.11 to 1.3 1.11 (0.86 to 1.4 1.21 (1.11 to 1.3 1.42 (1.25 to 1.6 1.09 (0.96 to 1.2 1.34 (1.20 to 1.4 1.08 (0.91 to 1.3 1.34 (1.20 to 1.4 1.34 (1.20 to 1.4) (1.34 to 1.3) (1.34 to 1.34 to 1.	P for interactic           0.04           0.14           0.40           0.14           0.15           0.20           0.21           0.22           0.23           0.24           0.24           0.25	Yes Overail D Subgroup Age <65 ≥65 Sex Female Male Ethnicity Non-Hispanic Vhite Non-Hispanic Black Mexican American Other Hispanic Other BMI <25 25-30 ≥30 Current smoker No Yes Hypertension No Yes EGFR <60 ≥60 Dyslipidemia No Yes Diabetes mellitus No Yes	1862 <b>18903</b> <b>Total Number</b> 10809 1969 6578 6200 5216 2654 2447 1198 1299 3506 4481 4791 10028 2750 7604 5174 428 12350 7604 5174 428 12350 7049 5729 10586 2192 29778	304           791		1.56 (1.13 to 2.17) 1.52 (1.30 to 1.78) 3 HR (95% Cl) 1.21 (0.84 to 1.72) 0.97 (0.75 to 1.26) 1.23 (0.95 to 1.58) 1.58 (1.23 to 2.04) 1.06 (0.82 to 1.36) - 1.77 (1.04 to 3.02) 1.23 (0.95 to 1.58) 1.38 (1.23 to 5.02) 1.30 (0.91 to 1.86) 1.67 (1.17 to 2.40) 1.21 (0.92 to 1.61) 1.56 (1.26 to 1.90) 1.56 (1.26 to 1.90) 1.56 (1.26 to 1.85) 1.38 (1.17 to 1.63) 0.77 (0.46 to 1.29) 1.39 (1.13 to 1.71) 1.29 (0.93 to 1.79) 1.30 (1.92 to 1.65) 1.56 (1.20 to 2.03) 1.56 (1.20 to 2.03) 1.57 (1.56 to 1.56) 1.56 (1.20 to 2.03) 1.57 (1.56 to 1.56) 1.56 (1.20 to 2.03) 1.56 (1.20 to 2.03) 1.57 (1.56 to 1.56) 1.56 (1.20 to 2.03) 1.57 (1.56 to 1.56) 1.56 (1.50 to 2.05) 1.56 (1.50 to 2.05) 1.56 (1.50 to 2.05) 1.56 (1.50 t	P for interaction 0.01 0.51 0.5 0.65 0.24 0.1 0.02 0.79 0.02

Fig. 3. Subgroup analysis.

# Table 3

Area Under the Receiver Operator Characteristic Curve in Models With and Without ePWV for all-caused or cardiovascular mortality.

ALL-cause mortality         Cardiovascular mortality           ePWV added         No         Yes         No         Yes           Model 1         0.8564 (0.8448–0.8680)         0.8581 (0.8467–0.8694) <sup>#</sup> 0.8989 (0.8839–0.9139)         0.9004 (0.8855–0.9155)           Model 2         0.7432 (0.7207–0.7657)         0.7453 (0.7222–0.7683) <sup>#</sup> 0.7987 (0.7623–0.8351)         0.8032 (0.7656–0.8407)	Cox regression Models Adjustment	C-index*					
ePWV added         No         Yes         No         Yes           Model 1         0.8564 (0.8448-0.8680)         0.8581 (0.8467-0.8694) <sup>#</sup> 0.8989 (0.8839-0.9139)         0.9004 (0.8855-0.9153)           Model 2         0.7432 (0.7207-0.7657)         0.7453 (0.7222-0.7683) <sup>#</sup> 0.7987 (0.7623-0.8351)         0.8032 (0.7656-0.8407)		ALL-cause mortality		ALL-cause mortality		Cardiovascular mortality	
	ePWV added Model 1 Model 2	No 0.8564 (0.8448–0.8680) 0.7432 (0.7207–0.7657)	Yes 0.8581 (0.8467–0.8694) <sup>#</sup> 0.7453 (0.7222–0.7683) <sup>#</sup>	No 0.8989 (0.8839–0.9139) 0.7987 (0.7623–0.8351)	Yes 0.9004 (0.8855–0.9153) <sup>#</sup> 0.8032 (0.7656–0.8407)		

Model 1 is adjusted for age, sex, ethnicity, BMI, MBP, PP, current smoker, dyslipidemia, UA, Diabetes mellitus and eGFR, Model 2 is adjusted for FRS. #P < 0.01.

ethnicity. Moreover, our results showed that BMI stratification, smoking, eGFR as well as hypertension status impaired the association between ePWV and adverse clinical outcomes after adjusting risk factors. This may be related to the fact that these factors were not specifically considered during ePWV derivation. In addition, patients who undertook antihypertensive agents were not included in the ePWV derivation process [10]. Although a study reported that hypertensives with improved ePWV after anti-hypertensive treatment benefited more [26], further research is needed to explore the value and influencing factors of ePWV in the hypertension treatment. Interestingly, after adjusting FRS model, we observed a quite different result, which may be related to the impact of FRS on different ethnic groups. Apart from that, our results showed that many other stratum indexes like age, sex, BMI etc. also influenced the association between ePWV and adverse clinical outcomes after adjusting FRS, since the FRS model has already taken into account the contribution of these variables, such result may be associated with the repeated adjustments for risk factor.

Our study was the first to investigate the additional risk predictive value of ePWV in general population. In our study, for both the model including FRS or risk factors alone, the predictive ability was significantly increased after added ePWV to the model, which partly consists with the previously reported results [16]. Although the improvement in prediction may not be as large as it would be when adding a novel biomarker, given the easy implementation of ePWV derivation without any additional cost, even a small improvement in risk estimation would be helpful.

However, we acknowledged some limitations in our study. First, office BP was used to calculate ePWV in current research. Considering that out-of-office BP was superior to office BP in the association with end-organ damage [27], research on the difference among ePWV calculated by BP derived from different methods is necessary in the future. Secondly, we could not investigate whether ePWV could increase the predictive power of other cardiovascular risk models in the present study as geographic factors were considered in these models (for example, SCORE [28] and China-PAR [29]). Thus, a comprehensive analysis including other cardiovascular risk models is needed to study whether the results could be extrapolating to populations outside United States. Finally, like other cohort studies, there are still some residual confounding factors that we did not measure in this study.

# 6. Conclusion

In summary, our study demonstrated that the association between ePWV and all-cause, cardiovascular mortality is independent of traditional cardiovascular risk model and risk factors. The models added with ePWV are better than models with traditional cardiovascular risk model or risk factors alone with regard to predicting the risk of all-cause and cardiovascular mortality.

#### Funding

This work was supported by the National Key Research and Development Program (2020YFC2008000) of China, National Natural Science Foundation of China (82270460, 82270458, 92249304), and the Science and Technology Planning Project (202206080004) of Guangzhou.

#### Availability of data and materials

The authors have no conflict of interest to disclose.

# CRediT authorship contribution statement

**Zhe Zhou:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft. **Xiaoling Liu:** Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Wanyong Xian:** Validation, Visualization, Writing – original draft. **Yan Wang:** Conceptualization, Supervision, Validation. **Jun Tao:** Funding acquisition, Project administration, Supervision, Writing – review & editing. **Wenhao Xia:** Funding acquisition, Project administration, Supervision, Writing – review & editing.

#### Declaration of competing interest

None declared.

#### Acknowledgements

The authors thank the National Center for Health Statistics of the Centers for Disease Control and Prevention for sharing the data. Thanks to Zhang Jing (Second Department of Infectious Disease, Shanghai Fifth People's Hospital, Fudan University) for his work on the NHANES database.

#### Abbreviations

NHANES	National Health and Nutrition Examination Survey
BMI	body mass index
SBP	systolic blood pressure
DBP	diastolic blood pressure; MBP: mean blood pressure
PP	pulse pressure
ePWV	estimated pulse wave velocity
eGFR	estimated glomerular filtration rate
TC	total cholesterol
LCL-C	Low density lipoprotein cholesterol
HDL-C	High density lipoprotein cholesterol
TG	triglyceride; High density lipoprotein cholesterol
FRS	Framingham risk score

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2023.200233.

#### References

- A. Tuttolomondo, A. Casuccio, V Della Corte, et al., Endothelial function and arterial stiffness indexes in subjects with acute ischemic stroke: relationship with TOAST subtype, Atherosclerosis 256 (2017) 94–99.
- [2] V. Vaccarino, T.R. Holford, H.M. Krumholz, Pulse pressure and risk for myocardial infarction and heart failure in the elderly, J. Am. Coll. Cardiol. 36 (1) (2000) 130–138.
- [3] S. Laurent, P. Boutouyrie, R. Asmar, et al., Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients, Hypertension 37 (5) (2001) 1236–1241.
- [4] C. Vlachopoulos, K. Aznaouridis, C. Stefanadis, Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and metaanalysis, J. Am. Coll. Cardiol. 55 (13) (2010) 1318–1327.
- [5] Z. Zhou, A.J. Xing, J.N. Zhang, et al., Hypertension, arterial stiffness, and clinical outcomes: a cohort study of Chinese community-based population, Hypertension 78 (2) (2021) 333–341.
- [6] T.J. Niiranen, B. Kalesan, N.M. Hamburg, E.J. Benjamin, G.F. Mitchell, R.S. Vasan, Relative contributions of arterial stiffness and hypertension to cardiovascular disease: the Framingham heart study, J. Am. Heart Assoc. 5 (11) (2016).
- [7] Y. Song, B. Xu, R. Xu, et al., Independent and Joint effect of brachial-ankle pulse wave velocity and blood pressure Control on incident stroke in hypertensive adults, Hypertension 68 (1) (2016) 46–53.
- [8] R.R. Townsend, I.B. Wilkinson, El Schiffrin, et al., Recommendations for improving and standardizing vascular research on arterial stiffness: a scientific statement from the American heart association, Hypertension 66 (3) (2015) 698–722.
- [9] H. Tanaka, M. Munakata, Y. Kawano, et al., Comparison between carotid-femoral and brachial-ankle pulse wave velocity as measures of arterial stiffness, J. Hypertens. 27 (10) (2009) 2022–2027.
- [10] C. Reference Values for Arterial Stiffness, Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values', Eur. Heart J. 31 (19) (2010) 2338–2350.
- [11] S.V. Greve, M.K. Blicher, R. Kruger, et al., Estimated carotid-femoral pulse wave velocity has similar predictive value as measured carotid-femoral pulse wave velocity, J. Hypertens. 34 (7) (2016) 1279–1289.
- [12] H. Chen, W. Wu, W. Fang, et al., Does an increase in estimated pulse wave velocity increase the incidence of hypertension? J. Hypertens. 39 (12) (2021) 2388–2394.

#### Z. Zhou et al.

#### International Journal of Cardiology Cardiovascular Risk and Prevention 20 (2024) 200233

- [13] E. Laugesen, K.K.W. Olesen, C.D. Peters, et al., Estimated pulse wave velocity is associated with all-cause mortality during 8.5 Years follow-up in patients undergoing elective coronary angiography, J. Am. Heart Assoc. 11 (10) (2022) e025173.
- [14] S.Y. Jae, K.S. Heffernan, S. Kurl, S.K. Kunutsor, J.A. Laukkanen, Association between estimated pulse wave velocity and the risk of stroke in middle-aged men, Int. J. Stroke 16 (5) (2021) 551–555.
- [15] C. Liu, H. Pan, F. Kong, et al., Association of arterial stiffness with all-cause and cause-specific mortality in the diabetic population: a national cohort study, Front. Endocrinol. 14 (2023) 1145914.
- [16] J.K.K. Vishram-Nielsen, S. Laurent, P.M. Nilsson, et al., Does estimated pulse wave velocity add prognostic information?: MORGAM prospective cohort Project, Hypertension 75 (6) (2020) 1420–1428.
- [17] K.S. Heffernan, S.Y. Jae, P.D. Loprinzi, Association between estimated pulse wave velocity and mortality in U.S. Adults, J. Am. Coll. Cardiol. 75 (15) (2020) 1862–1864.
- [18] K.S. Heffernan, J.M. Wilmoth, A.S. London, Estimated pulse wave velocity and allcause mortality: findings from the Health and retirement study, Innov Aging 6 (7) (2022) igac056.
- [19] P.C. Hsu, W.H. Lee, W.C. Tsai, et al., Comparison between estimated and brachialankle pulse wave velocity for cardiovascular and overall mortality prediction, J. Clin. Hypertens. 23 (1) (2021) 106–113.
- [20] Y. Lu, R. Pechlaner, J. Cai, et al., Trajectories of age-related arterial stiffness in Chinese men and women, J. Am. Coll. Cardiol. 75 (8) (2020) 870–880.

- [21] A.E. Schutte, R. Kruger, L.F. Gafane-Matemane, Y. Breet, M. Strauss-Kruger, J. K. Cruickshank, Ethnicity and arterial stiffness, Arterioscler. Thromb. Vasc. Biol. 40 (5) (2020) 1044–1054.
- [22] M.E. Safar, S. Czernichow, J. Blacher, Obesity, arterial stiffness, and cardiovascular risk, J. Am. Soc. Nephrol. 17 (4 Suppl 2) (2006) S109–S111.
- [23] A.S. Levey, L.A. Stevens, C.H. Schmid, et al., A new equation to estimate glomerular filtration rate, Ann. Intern. Med. 150 (9) (2009) 604–612.
- [24] S.M. Grundy, N.J. Stone, A.L. Bailey, et al., AHA/ACC/AACVPR/AAPA/ABC/ ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American college of Cardiology/American heart association task force on clinical practice guidelines, Circulation 139 (25) (2018) e1082–e1143, 2019 Jun 18.
- [25] Sr. D'Agostino Rb, R.S. Vasan, M.J. Pencina, et al., General cardiovascular risk profile for use in primary care: the Framingham Heart Study, Circulation 117 (6) (2008) 743–753.
- [26] C. Vlachopoulos, D. Terentes-Printzios, S. Laurent, et al., Association of estimated pulse wave velocity with survival: a secondary analysis of SPRINT, JAMA Netw. Open 2 (10) (2019) e1912831.
- [27] J.E. Schwartz, P. Muntner, I.M. Kronish, et al., Reliability of office, home, and ambulatory blood pressure measurements and correlation with left ventricular mass, J. Am. Coll. Cardiol. 76 (25) (2020) 2911–2922.
- [28] A.L. Catapano, I. Graham, G. De Backer, et al., ESC/EAS guidelines for the management of dyslipidaemias, Eur. Heart J. 37 (39) (2016) 2999–3058, 2016.
- [29] X. Yang, J. Li, D. Hu, et al., Predicting the 10-year risks of atherosclerotic cardiovascular disease in Chinese population: the China-PAR Project (prediction for ASCVD risk in China), Circulation 134 (19) (2016) 1430–1440.