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Evaluating several biomarkers as predictors of aortic stiffness in young and older Africans, not consuming alcohol based on self-report

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ABSTRACT

Aims: Black populations from sub-Saharan Africa have a high prevalence of cardiovascular disease, which places significant strain on public health systems. Aortic stiffness is a prominent risk factor for cardiovascular disease development. We reported earlier that excessive alcohol use predicts aortic stiffness. However, we require a better understanding of other biomarkers involved in stiffness development, beyond alcohol use. Therefore, we determined which biomarkers (metabolic, inflammatory, endothelial activation and oxidative stress) relate to aortic stiffness in young and older black South Africans, self-reporting no alcohol-use.

Methods: We included cross-sectional data from young (aged 24.7 ± 3.24 years) black adults participating in the African Prospective study on the Early Detection and Identification of Cardiovascular Disease and Hypertension (African-PREDICT) study (N = 216), and five-year follow-up data from older (aged 61.6 ± 9.77 years) black adults (N = 322) participating in the South African leg of the Prospective Urban and Rural Epidemiology study, conducted in the North West Province (PURE-SA-NWP). We excluded all participants self-reporting alcohol use. We determined biomarkers from blood samples, and measured carotid-femoral pulse wave velocity (PWV).

Results: Of all biomarkers investigated in multivariable-adjusted regression analyses, only plasma glucose ($R^2 = 0.24$, $\beta = 0.21$, $p < 0.001$) and glycated haemoglobin ($R^2 = 0.22$, $\beta = 0.17$, $p = 0.002$) independently predicted PWV five years later in older adults. We found no other associations in young or older black adults.

Conclusion: Dysglycaemia independently predicted aortic stiffness after five years in older black adults. Life-course management of body weight and sugar intake are important in preventing early vascular ageing and subsequent cardiovascular disease development in Africa.

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1. Introduction

Stiffness of the large arteries, which is reflected by carotid-femoral pulse wave velocity (PWV) [1], predicts cardiovascular events and mortality better than blood pressure [2,3]. The high incidence of cardiovascular disease in the black population of sub-Saharan Africa [4] places additional strain on the public health systems that also have to deal with the high prevalence of communicable diseases such as HIV and tuberculosis [5]. Therefore, the identification of early predictive risk factors for arterial stiffness is an important public health target, as it will help to direct the planning and implementation of prevention strategies that specifically address the development of cardiovascular disease in Africa.

Arterial stiffness is influenced by age, blood pressure and the properties of the arterial wall [6]. However, traditional cardiovascular risk factors such as dyslipidaemia, hyperglycaemia [7], inflammation [8], endothelial function and oxidative stress [9] are also known to modulate arterial structure and function by contributing to endothelial dysfunction and vascular remodeling [10], and by influencing the release of vasoactive substances in the large arteries [11].

Previously, we found alcohol use to be the main predictor of aortic stiffness over 10 years in black adults (mean age 65 years) [12] and that the liver enzyme, gamma-glutamyltransferase, independently associated with arterial stiffness in young black adults (mean age 24 years) [13]. However, in a country where excessive alcohol use is common and poses a significant threat to cardiovascular health [12,14], the associations of arterial stiffness with other important vascular biomarkers may be masked by a cardiometabolic profile associated with alcohol use. We therefore excluded alcohol users from the present study and determined whether biomarkers known to modulate arterial structure and function, such as metabolic, inflammatory and endothelial activation markers, as well as oxidative stress, relate to aortic stiffness in young and older black South Africans who self-reported no alcohol use.

2. Methods

To address the aims of this sub-study, we included data from two studies conducted in South Africa, namely the African Prospective study on the Early Detection and Identification of Cardiovascular Disease and Hypertension (African-PREDICT) study, and the South African leg of the international Prospective Urban and Rural Epidemiology study, conducted in the North West Province (PURE-SA-NWP). For this manuscript, cross-sectional African-PREDICT data and cross-sectional and longitudinal PURE-SA data were used for analyses. The detailed methods of the two studies are described elsewhere [12,13], but herewith a succinct description of aspects relevant to this paper.

2.1. *Ethical considerations*

The Health Research Ethics Committee of the North-West University gave approval for the African-PREDICT Study, the PURE-SA baseline (2010) and follow-up (2015) study, as well as this sub-study. All procedures comply with the Declaration of Helsinki. Before measurements commenced, all procedures were explained to the participants, after which written informed consent was given.

2.2. *The African-PREDICT study*

2.2.1 Research design

Young (20–30 years of age), apparently healthy black and white men and women were included in the study after an initial screening day. Participants whose mean blood pressure out of 4 measurements $\geq$140 mmHg and/or $\geq$90 mmHg, who were HIV infected, previously diagnosed with a chronic disease, pregnant or breastfeeding were excluded. This sub-study includes cross-sectional analysis of the first 591 black participants. Participants with incomplete PWV data (n = 91), incomplete alcohol use data (n = 6) and who reported using alcohol (n = 278), were excluded. The study population is shown in Fig. 1.

2.3. *The PURE-SA-NWP study*

2.3.1 Research design

Baseline data collection took place in the North West Province of South Africa in 2010, with a 5 year follow-up conducted in 2015. Baseline data collection included 1288 black men and women, aged 38–98 years. Pregnant and lactating women were excluded. Longitudinal data were available for 852 participants. Both cross-sectional and longitudinal analyses were performed for the PURE-SA study in this manuscript. Participants with incomplete PWV data (n = 119), those who were HIV-infected (n = 130) and those who self-reported alcohol use (n = 281) were excluded. Included for this study are 322 participants (Fig. 1).

2.4. *Questionnaires*

The African-PREDICT participants completed a demographic and general health questionnaire, and the PURE-SA-NWP participants completed structured socio-demographic and lifestyle questionnaires. In both studies, alcohol and tobacco use were reported as a yes or no answer.

2.5. *Anthropometric measurements*

For African-PREDICT, height (SECA 213 Portable Stadiometer, SECA, Hamburg, Germany), weight (SECA 813 Electronic Scales, SECA, Hamburg, Germany) and waist circumference (Lufkin Steel Anthropometric Tape (W606PM), Lufkin, Apex, USA) were measured. For PURE-SA-NWP, baseline and follow-up height (Invicta Stadiometer IP 1465, Leicester, UK; Leicester height measure, Seca, Birmingham, UK), weight (Precision Health Scale, A & D Company, Japan) and waist circumference (WC) (Holtain unstretchable metal tape for baseline and Steel tape, Lufkin, Cooper Tools, Apex NC, USA for follow-up) were measured. Standardised methods and calibrated instruments were used in both studies [15]. Body mass index (BMI) was calculated.

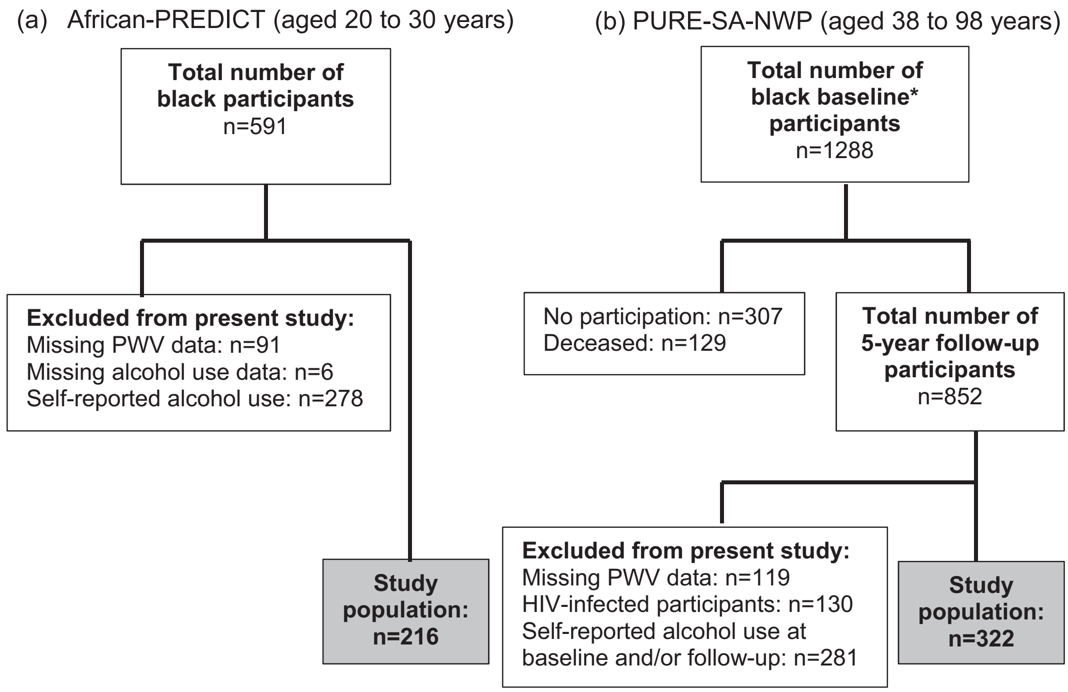

Fig. 1 – Study population: (a) Young black African-PREDICT participants; (b) Older black PURE-SA-NWP participants. *Baseline data collection for this sub-study refers to the 2010 data collection phase of the South African PURE-NWP study.

2.6. *Cardiovascular measurements*

After a 10 min rest period, duplicate office blood pressure measurements (Dinamap® ProCare 100 Vital Signs Monitor, GE Medical Systems, Milwaukee, USA) were made on both arms of African-PREDICT participants with 5 min intervals. The participant was in a seated position. For the PURE-SA-NWP participants, the validated OMRON HEM-757 and OMRON M6 (Omron Healthcare, Kyoto, Japan) devices were used to measure duplicate sitting blood pressure after a 10 min rest at baseline and follow-up, respectively. Mean arterial pressure (MAP) was calculated for both studies.

For both studies, the carotid-femoral PWV was determined in duplicate with the SphygmoCor® XCEL device (AtCor Medical Pty. Ltd., Sydney, Australia) with the participant in supine position. The transit-distance method was used to measure PWV along the descending thoraco-abdominal aorta. The 80% rule was applied for the calculation of the distance used.

2.7. *Biological sampling*

Blood samples were taken from the antebrachial vein of each fasting participant. Using standardised methods to prepare serum and plasma in the laboratory, it was stored at −80 °C until analysis. In the cases of blood collection in a rural area as part of the PURE-SA-NWP study, samples were snap frozen and stored at −20 °C for not more than 5 days. The samples were then transported to the laboratory and stored at −80 °C.

2.8. *Biochemical analysis for African-PREDICT*

An enzymatic colorimetric method (Cobas Integra 400 Roche® Clinical System, Roche Diagnostics, Indianapolis, IN) was used to determine serum total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), triglycerides (TG), gamma-glutamyltransferase (GGT) and creatinine.

Serum high sensitivity C-reactive protein (CRP), fasting glucose in fluoride plasma, as well as glycosylated haemoglobin (HbA1c) from EDTA whole blood, were determined with the Cobas Integra 400 Roche® Clinical System (Roche Diagnostics, Indianapolis, IN). Interleukin-6 (IL-6), intercellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule 1 (VCAM-1) were determined with high sensitivity Quantikine ELISA kits (R&D systems, Minneapolis, MN USA). Serum peroxides, representing reactive oxygen species (ROS), were determined with high-throughput spectrophotometric assay and analysed on a Synergy H4 hybrid microplate reader (BioTek, Winooski, VT, USA).

2.9. *Biochemical analysis for PURE-SA-NWP*

We analysed baseline and follow-up serum TC, HDL-C, LDL-C, TG, creatinine, CRP, glucose, and GGT with the Cobas Integra 400 plus Roche Clinical System, and HbA1c levels with the D-10 Haemoglobin testing system (Bio-Rad #220-0101). Baseline IL-6 was determined with an electrochemiluminescence immunoassay (Elecsys 2010, Roche, Basel, Switzerland). Baseline ICAM-1 and VCAM-1 levels were determined in serum with sandwich ELISAs (Human sICAM-1 and human sVCAM-1 assay, IBL, Hamburg, Germany). Baseline serum peroxides (ROS), were determined with high-throughput spectrophotometric assay [Synergy H4 hybrid microplate reader (BioTek, Winooski, VT, USA)].

Creatinine clearance (CrCl) [16] and the estimated glomerular filtration rate [eGFR CKD-EPI(Cr)] in ml/min/1.73 m^2 were calculated [17] for both studies.

2.10. Statistical analyses

We used Statistica version 13 (StatSoft, Inc., Tulsa, OK, USA) and prepared graphs using GraphPad Prism Version 5.03 (GraphPad Software Inc., California, USA). Descriptive statistics including the mean and standard deviation were performed on data with a normal distribution. Abnormally distributed variables were logarithmically transformed and the central tendency and spread described as the geometric mean and the 5th and 95th percentiles. For the PURE-SA-NWP study, the 5-year changes in continuous variables were determined with dependent (paired) t-tests, and for categorical variables, with the Wilcoxon test. We performed multivariate linear regression analysis with PWV as the dependent variable to test associations with various markers in young and older black adults who self-reported not using alcohol. Each model included one main independent variable (an inflammatory, endothelial activation, oxidative stress or metabolic marker) and a set model of covariates listed in the footnote in Table 2. In addition, we used analysis of covariance (ANCOVA) to determine the differences in PWV between tertiles of glucose, while adjusting for age, sex, BMI and MAP.

3. Results

The characteristics of the young African-PREDICT and older PURE-SA-NWP populations (both for baseline and 5-year follow up) are shown in Table 1. The young adults (35.2% men) had a mean age of approximately 25 years. Hypertension prevalence based on clinic blood pressure on the day of data collection was 10.2%. When comparing the older PURE-SA-NWP participants at baseline and five years later, they had an increased waist circumference ($p < 0.001$) and a higher heart rate ($p < 0.001$). Diastolic blood pressure and mean arterial pressure were lower at follow-up ($p < 0.001$). All lipids, except for triglycerides, decreased significantly over 5 years, but the TG/HDL-C ratio showed an increasing trend ($p = 0.058$). Serum glucose increased significantly with 0.21 mmol/l ($p = 0.008$), but HbA1c decreased by 0.27% (<0.001). Levels of GGT also decreased over 5 years ($p = 0.005$). Fewer participants smoked at follow-up (39.9% vs. 20.8%, $p < 0.001$) , while more participants used anti-hypertensive medication (30.5% vs. 39.1%, $p = 0.011$) and statins ($p = 0.002$).

In Fig. 2. we plotted PWV against age for the young and older black populations, while adjusting for MAP. In the African-PREDICT participants, all within a narrow age bracket of 20–30 years, no trend for PWV with age was found. For the PURE-SA-NWP participants, a significant trend for increased PWV was evident from age 40 to ≥85 years (p for trend <0.001).

To identify associations with PWV for the young and older participants, as well as predictors of PWV after 5 years in the older group, we performed multivariate-adjusted regression analyses with PWV as the dependent variable, and each possible predictor as the main independent variable in the young and older group (Table 2). For the young group, apart from significant independent associations with MAP (all $p < 0.001$), sex ($p < 0.002$) and BMI (negatively) ($p \leq 0.042$) (shown in Supplementary Table S1), we found no significant associations with metabolic, inflammatory, endothelial activation or oxidative stress markers. In the older group, apart from significant associations with age, BMI (negatively), MAP and heart rate (all $p \leq 0.028$), PWV associated significantly with baseline glucose ($R^2 = 0.24$, $\beta = 0.21$, $p < 0.001$) and HbA1c ($R^2 = 0.22$, $\beta = 0.17$, $p = 0.002$). The full models with glucose and HbA1c, as main independent variable, are shown in Supplementary Table S1.

In Fig. 3. we plotted PWV against tertiles of glucose in the younger and older groups after adjusting for MAP and other covariates. Baseline and follow-up tertiles of glucose were calculated for the older group. Only in the older group, PWV increased with the tertiles of baseline (p for trend = 0.013) and follow-up glucose levels (p for trend = 0.007).

3.1. Sensitivity analyses

For the older group, we repeated the multiple regression analyses while excluding participants who were using diabetes medication and whose fasting glucose and HbA1c values were above the cut-off points (≥7.0 mmol/l for glucose and ≥6.5% for HbA1c) [18]. Upon exclusion of participants with glucose (n = 30) and HbA1c (n = 74) above the cut-off points [first separately, and secondly as a combined variable with either glucose or HbA1c above cut-off, or diabetes medication use (n = 77)] both glucose and HbA1c became non-significant in their separate models.

We calculated the 5-year percentage change for glucose, HbA1c, BMI, MAP and HR and included these variables in a multivariate regression model along with age, sex, locality, follow-up tobacco and anti-hypertension medication use. However, no significant result was found for 5-year percentage change in glucose ($p = 0.55$) or HbA1c ($p = 0.46$). We also performed cross-sectional multivariate-adjusted regression analyses with PWV as the dependent variable and 5-year follow-up covariates in the older group (Supplementary Table S2). PWV associated significantly with follow-up glucose ($R^2 = 0.22$, $\beta = 0.15$, $p = 0.005$), HbA1c ($R^2 = 0.22$, $\beta = 0.13$, $p = 0.017$) and TG/HDL-C ($R^2 = 0.21$, $\beta = 0.11$, $p = 0.048$).

4. Discussion

In the present study we aimed to identify possible predictors of aortic stiffness in the cardiovascular disease-prone black population of South Africa. From an array of well-known biomarkers, only dysglycaemia independently predicted aortic stiffness after five years in older black adults who do not consume alcohol. In young, healthy black adults who reported no alcohol consumption, aortic stiffness was within normal ranges (mean 6.26 ± 0.82 m/s) and did not associate with any biomarkers. The lack of any association in the younger black adults may be explained by the health status of this group, as individuals who participated in the African-PREDICT study were free of chronic diseases or hypertension.

Table 1 – Profile of young (African-PREDICT) and older (PURE-SA-NWP) black South Africans who self-reported no alcohol use.

	Young black adults (n = 216)	Older black adults (n = 322)		
	African-PREDICT	PURE-SA-NWP Baseline	PURE-SA-NWP 5-year Follow up	Difference (p)
Age, years	24.7 ± 3.24	56.7 ± 9.77	61.6 ± 9.77	<0.001
Gender, men (%)	76/216 (35.2)	56/322 (17.4)	56/322 (17.4)	–
Locality, urban (%)	216/216 (1 0 0)	125/322 (38.8)	125/322 (38.8)	–
Hypertension, n(%)[a]	22/216 (10.2)	202/322 (62.7)	217/320 (67.8)	0.13
Diabetes, n(%)[b]	0/63 (0.00)	71/315 (22.5)	55/293 (18.7)	0.048
Anthropometric measures				
Body mass index, kg/m^2	25.0 ± 5.74	28.1 ± 6.87	28.2 ± 6.85	0.17
Waist circumference, cm	77.9 ± 11.4	84.2 ± 13.22	91.9 ± 14.69	<0.001
Weight, kg	66.6 ± 15.0	70.3 ± 17.2	70.4 ± 17.1	0.76
Height, m	1.63 ± 0.09	1.59 ± 0.07	1.58 ± 0.08	<0.001
Cardiovascular measures				
SBP, mmHg	116 ± 10.6	136 ± 23.5	134 ± 24.0	0.15
DBP, mmHg	78.0 ± 8.28	87.8 ± 12.8	84.9 ± 13.7	<0.001
Pulse pressure, mmHg	37.1 ± 7.77	48.3 ± 16.3	49.4 ± 15.4	0.19
Heart rate, bpm	65.2 ± 10.6	62.1 ± 15.0	70.3 ± 12.6	<0.001
MAP, mmHg	93.3 ± 7.78	103 ± 15.4	101 ± 16.2	0.002
PWV, m/s	6.26 ± 0.82	–	8.58 ± 1.87	–
Biochemical measures				
Total cholesterol, mmol/l	3.67 (2.65; 4.90)	5.03 (3.44; 6.98)	4.56 (3.01; 6.63)	<0.001
LDL-cholesterol, mmol/l	2.42 (1.42; 3.84)	3.28 (1.82; 5.16)	2.87 (1.51; 4.80)	<0.001
HDL-cholesterol, mmol/l	1.17 (0.81; 1.72)	1.27 (0.76; 2.04)	1.18 (0.74; 1.96)	<0.001
Triglycerides, mmol/l	0.65 (0.35; 1.21)	1.17 (0.59; 2.33)	1.16 (0.61; 2.66)	0.65
TG/HDL-C ratio	0.55 (0.28; 1.22)	0.92 (0.34; 2.66)	0.99 (0.35; 3.34)	0.058
Glucose, mmol/l	4.53 (3.31; 5.56)	5.23 (4.14; 8.11)	5.44 (4.17; 8.61)	0.008
HbA1c, %[c]	5.59 [38] (5.10; 6.09)	6.25 [45] (5.30; 9.60)	5.98 [42] (5.00; 8.80)	<0.001
Inflammatory markers				
C-reactive protein, mg/l	1.32 (0.14; 11.9)	3.57 (0.36; 28.4)	3.42 (0.51; 18.1)	0.31
Interleukin-6, pg/ml	1.32 (0.51; 5.25)	2.97 (0.75; 9.57)	–	–
Oxidative stress				
ROS, U[d]	198 (124; 337)	250 ± 74.4	–	–
GGT, U/l	21.5 (10.1; 54.8)	28.5 (11.7; 84.5)	25.9 (11.1; 80.8)	0.005
Endothelial function				
ICAM-1, ng/ml	125 (25.4; 316.4)	273 (148; 422)	–	–
VCAM-1, ng/ml	656 (401; 1002)	740 (440; 1547)	–	–
Renal function				
CrCl, ml/min	124 (86.7; 193)	94.8 (54.5; 180)	94.5 (48.9; 180)	0.60
eGFR, ml/min/1.73 m^2	134 (104; 155)	106 ± 18.6	106 ± 20.1	0.33
Health behaviour				
Tobacco use, n (%)	20/216 (9.26)	126/316 (39.9)	67/322 (20.8)	<0.001
Medication use				
Anti-hypertensive, n (%)	0/216 (0.00)	98/321 (30.5)	125/320 (39.1)	0.011
Anti-diabetes, n (%)	0/216 (0.00)	16/321 (4.98)	23/320 (7.19)	0.14
Anti-inflammatory, n (%)	1/216 (0.46)	24/321 (7.48)	18/320 (5.63)	0.35
Statins, n (%)	0/216 (0.00)	2/321 (0.62)	18/320 (5.63)	0.002

Data are arithmetic mean ± standard deviation, geometric mean (5th; 95th percentiles), or % of n.
SBP, systolic blood pressure; DBP, diastolic BP; MAP, mean arterial pressure; PWV, pulse wave velocity; LDL, low density lipoprotein; HDL, high density lipoprotein; TG: HDL-C, triglyceride: high density lipoprotein-cholesterol ratio; HbA1c, glycated haemoglobin; ROS, reactive oxygen species; GGT, gamma-glutamyltransferase; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular adhesion molecule-1; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; tobacco use is self-reported.
ROS for African-PREDICT: n = 61, Glucose for African-PREDICT: n = 161.

[a] Hypertension prevalence: all baseline or follow-up anti-hypertension medication users and/or participants with a clinic blood pressure measurement of SBP ≥ 140 mmHg and/or DBP ≥ 90 m Hg.

[b] Diabetes prevalence: all baseline or follow-up anti-diabetes medication users and/or participants with glucose ≥ 7.0 mmol/l and/or HbA1c ≥ 6.5%.

[c] HbA1c given as mmol/mol in square brackets (IFCC)

[d] ROS units: 1.0 mg H_2O_2/l.

Table 2 – Independent associations of PWV with vascular biomarkers in young (African-PREDICT) and older (PURE-SA) black South Africans who self-reported no alcohol use.

Dependent variable: Carotid-femoral pulse wave velocity, m/s

Main independent variable	*African-PREDICT*				*PURE-SA (baseline covariates)*			
Inflammatory markers	*n*	R^2	*β (95% CI)*	*p*	*n*	R^2	*β (95% CI)*	*p*
CRP, mg/l	182	0.34	−0.06 (−0.21; 0.10)	0.47	310	0.20	−0.05 (−0.16; 0.07)	0.43
IL-6, pg/ml	192	0.34	−0.07 (−0.20; 0.07)	0.34	310	0.20	−0.07 (−0.18; 0.04)	0.19
Endothelial activation markers								
ICAM-1, ng/ml	202	0.34	−0.03 (−0.15; 0.09)	0.62	311	0.20	−0.03 (−0.13; 0.08)	0.61
VCAM-1, ng/ml	202	0.35	0.09 (−0.03; 0.20)	0.14	310	0.20	0.02 (−0.09; 0.12)	0.77
Oxidative stress markers								
ROS, U[a]	61	0.29	−0.16 (−0.44; 0.12)	0.28	315	0.21	0.07 (−0.04; 0.18)	0.21
GGT, U/l	184	0.35	0.10 (−0.02; 0.22)	0.11	307	0.20	0.02 (−0.08; 0.13)	0.67
Metabolic markers								
Glucose, mmol/l	168	0.34	0.04 (−0.09; 0.17)	0.52	314	0.24	0.21 (0.10; 0.31)	<0.001
HbA1c, %	63	0.29	0.14 (−0.09; 0.37)	0.23	315	0.22	0.17 (0.06; 0.27)	0.003
TC, mmol/l	183	0.34	−0.06 (−0.18; 0.06)	0.34	311	0.20	−0.06 (−0.17; 0.04)	0.22
TG, mmol/l	184	0.34	−0.04 (−0.17; 0.09)	0.57	312	0.21	0.10 (−0.004; 0.20)	0.061
LDL-C, mmol/l	167	0.34	−0.06 (−0.18; 0.07)	0.40	311	0.21	−0.10 (−0.20; 0.004)	0.062
HDL-C, mmol/l	184	0.34	−0.03 (−0.16; 0.10)	0.67	311	0.20	−0.06 (−0.17; 0.05)	0.28
TG/HDL-C ratio	184	0.34	−0.02 (−0.15; 0.12)	0.81	311	0.21	0.10 (−0.01; 0.20)	0.072

Data expressed as beta-values and 95% confidence intervals, p-values obtained with multiple regression analyses. Included in each model for African-PREDICT participants is one main independent variable as listed in the table, plus the following covariates: Age, sex, socioeconomic status, body mass index, mean arterial pressure, heart rate, tobacco use. Included in each model for PURE-SA participants is one main independent variable as listed in the table, plus the following covariates: Age, sex, locality, body mass index, follow-up mean arterial pressure, follow-up heart rate, tobacco use, follow-up anti-hypertension medication use. CRP, C-reactive protein; IL-6, interleukin-6; ICAM-1, intercellular adhesion molecule-1, VCAM-1, vascular adhesion molecule-1; ROS, reactive oxygen species; GGT, gamma-glutamyltransferase; HbA1c, glycated haemoglobin; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG/HDL-C, triglyceride/high-density lipoprotein cholesterol ratio.

[a] ROS unit: 1.0 mg H_2O_2/l.

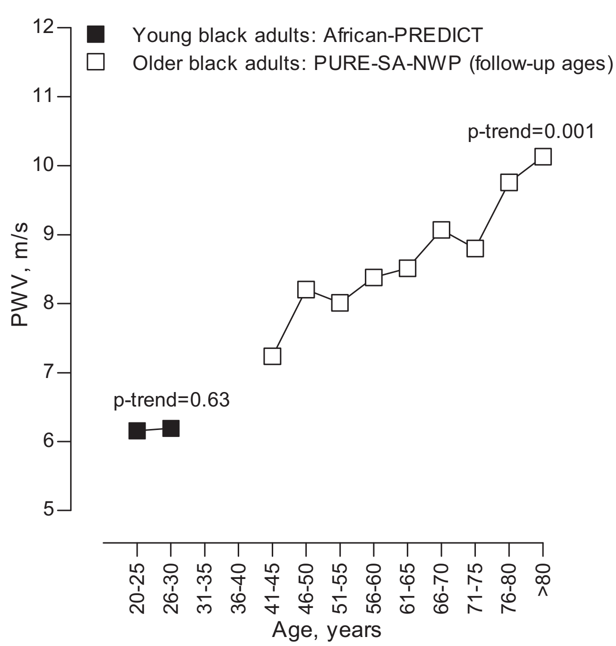

Fig. 2 – Pulse wave velocity plotted against age, adjusted for mean arterial pressure for African-PREDICT and PURE-SA-NWP participants who reported no alcohol use (cross-sectional). PWV, pulse wave velocity.

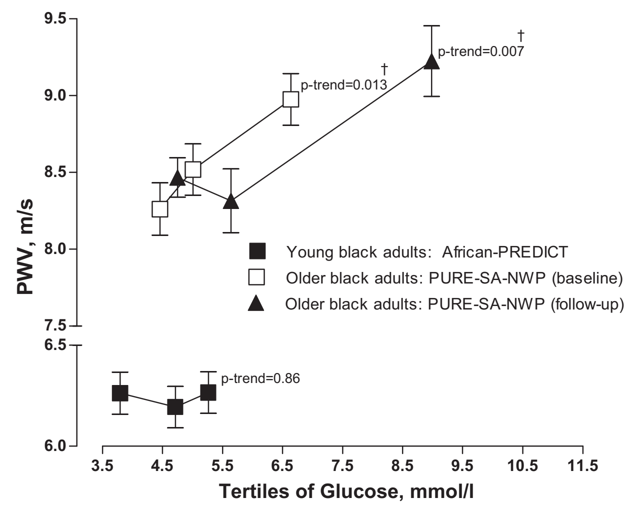

Fig. 3 – Pulse wave velocity plotted against tertiles of glucose, adjusted for age, sex, body mass index and mean arterial pressure for young (African-PREDICT) and older (PURE-SA-NWP) black non-alcohol users (cross-sectionally and longitudinal). PWV, pulse wave velocity. † indicates p-value (<0.05) between tertile 1 and tertile 3. *PWV for PURE-SA study obtained only at follow-up.

To the best of our knowledge, this is the first evidence indicating the possible predictive value of dysglycaemia for aortic stiffness in black adults who do not consume alcohol. Our result is supported by similar findings in Dutch, Italian and South Korean populations [19–21], however, alcohol users were not excluded in these studies. Diabetes was uncommon in sub-Saharan Africa prior to the 1990s, but its prevalence is on the rise due to factors such as changing cultural practices and dietary habits, urbanisation, and an aging population [22]. In addition, societal obstacles such as poor education, illiteracy, low socio-economic status and weak health systems hinder successful prevention and treatment strategies [23]. In South Africa, alcohol abuse is common and may be a coping-mechanism for the societal obstacles just mentioned [24,25]. Self-reported alcohol use, which is thought to be a reliable indicator of alcohol intake in the PURE-SA-NWP population [26], was a significant independent predictor of arterial stiffness over 10 years in the PURE-SA-NWP population [12]. Building upon this knowledge, the results of the present study indicate that for non-alcohol users, plasma glucose poses the next biggest threat to cardiovascular health. In this population, a change from traditional lifestyles and the increased consumption of unhealthy foods may contribute to dysglycaemia. Indeed, the added sugar and sucrose-sweetened beverage intake of the PURE-SA participants doubled over 5 years, confirming that a nutritional transition has reached rural South Africa [27]. Furthermore, increased sugar intake also associated with increased risk factors for non-communicable diseases [27].

Cardiovascular disease is a common cause of mortality in patients with diabetes [28]. The association of deteriorating glucose tolerance with generalised increases in aortic stiffness may explain the link between impaired glucose tolerance or diabetes, and the increased risk for adverse cardiovascular events such as stroke, heart failure and myocardial infarction [21]. However, even before the clinical diagnosis of diabetes, increased fasting plasma glucose within the normal range associates with increased stiffness [7].

Elevated plasma glucose may affect arterial stiffness via several mechanisms. Chronically increased plasma glucose and hyperinsulinemia increase the activity of the renin-angiotensin-aldosterone system, and the expression of angiotensin type I receptor in vascular tissue, which play a role in the increased production of reactive oxygen species, endothelial dysfunction, cardiovascular tissue fibrosis and vascular remodeling [29]. Furthermore, the nonenzymatic glycation of plasma proteins leads to the production of advanced glycation end products, which may accumulate in cells and disrupt their intra- and extracellular structure and function by cross-linking collagen fibers, proteins and possibly lipids and nucleic acids [30,31].

Results from the Framingham Heart study indicated that diabetes is one of the biggest threats to healthy vascular ageing [32]. Type 2 diabetes prevalence among older people in Africa is estimated to be 13.7% [33]. Recent estimates on the prevalence of diabetes in black South Africans is sparse, but, half a decade ago, a diabetes prevalence of 13.1% was found among black South Africans residing in the Western Cape Province [34]. We found a baseline diabetes prevalence of 22% in the older black adults. These statistics and our results support indicate that diabetes is becoming increasingly prevalent in the black population of sub-Saharan Africa [22], which in turn may lead to increased cardiovascular morbidity and mortality in an already at-risk population. Legislation and taxation on sugar-sweetened beverages in South Africa is likely to be implemented soon [35]. Whether this will curb the growing prevalence of obesity and diabetes remains to be seen.

Our results indicated a negative association between BMI and PWV in both the young and older group. This result is similar to what we found previously in the PURE-SA-NWP population [12]. In a study conducted in the United Kingdom, body fat percentage associated negatively with PWV until the age of 50, whereafter it began to show an increasingly positive association with PWV [36]. Seeing as the PURE-SA-NWP participants are older than 50 years, a different mechanism may be involved, such as differences in socio-economic status, age [37], gender [38]. The exact reason for this association remains largely unknown at this stage, and requires further investigation as it was observed in young and older black adults.

4.1. *Strengths and limitations*

Our study population included specific urban and rural areas in the North West Province of South Africa and may not be applicable to the whole South African population. Insulin data were not available for this study, but it does provide novel longitudinal data on arterial stiffness and biomarkers of vascular function in the understudied black population. Data collection took place under controlled conditions in well-equipped research facilities. In the older group, PWV was measured at follow-up only, which prevents firm conclusions regarding change in arterial stiffness over time. Although the results were consistent after several adjustments, we cannot exclude residual confounding.

5. Conclusion

When comparing the predictive value of an array of cardiovascular biomarkers for aortic stiffness, only dysglycaemia independently predicted aortic stiffness 5 years later in black South Africans who do not consume alcohol. This prioritises the life-course management of a healthy body weight and dietary intake of refined carbohydrates and sugars for the prevention of early vascular ageing and cardiovascular disease in Africans.

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Conflict of interest

All authors declare no conflict of interest.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.diabres.2018.05.048.

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