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Research article

Population-derived cut-off for HbA1c could enhance the identification of metabolic syndrome among non-diabetic population

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ABSTRACT

Background: Metabolic syndrome (MetS) is a multifactorial disorder and a predisposing factor for diabetes, heart diseases, and stroke. Glycated haemoglobin (HbA1c) has recently received considerable attention as a potential marker to identify subjects at risk of MetS. This study aimed at assessing the performance of fasting plasma glucose (FPG), the American Diabetes Association (ADA) HbA1c cut-off, and a population-derived HbA1c (pHbA1c) cut-off value as the glycaemic criterion for MetS in a non-diabetic population.

Methods: In this cross-sectional study, we recruited 728 non-diabetic Ghanaian adults. Venous blood sample was obtained and fasting plasma insulin and glucose, HbA1c, lipid profile, blood pressure and anthropometric measurements were performed for each respondent.

Results: The prevalence of MetS using the FPG, ADA HbA1c and pHbA1c criteria were 35.2%, 38.5% and 41.8%, respectively. The pHbA1c cut-off identified 6.6% and 3.3% more subjects with MetS when compared with FPG and the ADA HbA1c cut-offs, respectively while the ADA HbA1c cut-off identified 3.3% more subjects with MetS compared with the FPG criterion. The ADA HbA1c criterion showed a substantial agreement ($\kappa = 0.79$) with the FPG criterion while pHbA1c showed an almost perfect concordance ($\kappa = 0.82$) with the FPG criterion and an excellent sensitivity and specificity for identifying subjects with MetS in the study population.

Conclusion: Screening of MetS by introduction of the ADA HbA1c criterion in addition to the traditional FPG criterion enhances the detection of more people with MetS. However, the use of population-derived HbA1c cut-off value could potentially identify even greater number of high risk subjects in that specific population.

1. Introduction

Metabolic syndrome (MetS) is a multifactorial disorder. It is diagnosed based on clustering of closely related cardiovascular risk factors such as hypertension, obesity, hyperglycaemia, and dyslipidaemia. MetS is used as a clinical tool for the identification of patients with metabolic risk of cardiovascular diseases (CVD) [1, 2], and serves as a predictor of cardiovascular events and diabetes [3]. Insulin resistance is the primary pathophysiologic mechanism; however, due to the difficulties and the complex nature of the direct measurement of insulin sensitivity, some anthropometric, hemodynamic, and biochemical parameters have been employed in the diagnosis of MetS [4]. Various organizations have proposed different criteria for the diagnosis of MetS which have led to disparities in the identification of high risk subjects. This consequently resulted in the need for harmonization of the criteria for defining MetS (Joint Interim Statement-JIS) [5].

Despite the coherence in the harmonized definition, there are inter-population variabilities in the cut-off values for fasting plasma glucose (FPG). Moreover, the use of point glucose estimation may not be reliable. This heralded the proposal for the utilization of glycated hemoglobin (HbA1c) as one of the diagnostic criteria for diabetes and the categorization of subjects with increased risk for diabetes. As result, the American Diabetes Association (ADA) proposed that HbA1c value of 5.7–6.4% should be considered a criterion for increased risk for diabetes [6].

HbA1c is a predictor for diabetes [7] and used in the monitoring of long-term glycaemic control as it is the index of mean blood glucose over a period of three months. Advantages of its use over the fasting plasma glucose include the convenience of not requiring a fasting sample,

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requiring less time and the superior technical attributes [6]. Furthermore, HbA1c captures chronic hyperglycaemia, including postprandial glucose spikes in contrast to daily pre-prandial glucose snapshot offered by FPG [8]. Although it is debatable, some cross-sectional [9, 10, 11], case-control [3], follow-up [12], prospective observational [13], and large-scale longitudinal [8] studies have reported HbA1c to be a better predictor of cardiovascular risk compared to FPG even among non-diabetic population. Moreover, we have previously reported the usefulness of the ADA HbA1c cut-off over FPG for MetS diagnosis among non-diabetic population in Ghana [14]. Nonetheless, evidence suggests that the cut-off for HbA1c might differ by ethnicity due to significant discordance in the association between HbA1c and FPG in diverse populations [15, 16].

It is against this background that we assessed and compared the performance of fasting plasma glucose with the ADA HbA1c, and evaluated the plausibility of a population-derived HbA1c cut-off value as the dysglycaemic criterion for MetS in a non-diabetic population.

2. Materials and methods

2.1. Study design, population and area

This was a cross-sectional study conducted at St Francis Xavier Hospital, Assin Fosu, Central Region, Ghana. A total of 728 apparently healthy Ghanaian adults, living in Assin Foso were recruited for the study. The population of Assin North Municipality according to the 2010 Population and Housing Census is 161,341 representing 7.3% of the region's total population [17]. The protocol for this study was approved by the Committee on Human Research Publication and Ethics (CHRPE) of the School of Medical Sciences, Kwame Nkrumah University of Science and Technology. All participants gave their written informed consent after the aim and potential risks involved in participation had been explained to them.

2.2. Inclusion and exclusion criteria

Apparently healthy Ghanaian adults between the ages of 30 and 70 years old were included in this study. Subjects clinically diagnosed of hypertension, diabetes or family history of diabetes, and subjects suspected of malignancies, inflammatory disease, as well as subjects on lipid or glucose-lowering medication, or antihypertensive agents were excluded from the study. Subjects with anaemia, thalassemia, and sickle cell as well as subjects with FPG $\geq$ 7.0 mmol/L, classified as diabetics according to the American Diabetes Association [18], were also excluded from the study.

2.3. Blood pressure and anthropometric evaluation

Blood pressure (BP) was measured with an automated blood pressure apparatus (Omron MX3-Omron Matsusaka Co., Ltd. Japan). The average of the two readings taken five minutes apart was recorded as the blood pressure measurement. The weight was measured in light clothing without shoes, in an upright position using a calibrated analogue scale (Seca, Hamburg, Deutschland). Height was measured without shoes using a stadiometer (Seca, Hamburg, Deutschland). Body mass index (BMI) was calculated using the equation; [BMI (kg/m^2) = weight/height^2] [19]. Using a measuring tape, waist circumference (WC) was measured at the narrowest part of the waist between lower end of the twelfth rib and iliac crest, and hip circumference (HC) was measured at the widest part of the hips (below the iliac crest at the level of the greater trochanters). The WC, HC, height as well as other parameters were used to calculate waist to height ratio (WHtR) = WC (m)/height (m), waist to hip ratio (WHR) = WC (m)/HC (m), body adiposity index (BAI) = (HC (cm))/(height $(m)^{1.5}$) –18 [20], and visceral adiposity index (VAI) = WC (m)/(39.68 +(1.88 x BMI)) x [triglyceride (TG)/(1.03)] x ((1.31)/high density lipoprotein (HDL)) for males and (WC (m))/(36.58 +(1.89 x BMI)) x (TG/(0.81))x ((1.52)/HDL) for females [21]. Blood pressure and anthropometric measurements were carried out on each participant by same trained personnel.

2.4. Blood sampling, processing and analysis

From each participant, about 5 ml of venous blood was obtained from the antecubital vein after an overnight fast. One milliliter (1 ml) was dispensed into a fluoride oxalate tube, 1ml into EDTA tube, and 3 ml into gel separator tubes. The tubes were placed in a centrifuge and spun at 3000 rpm for 10 min to obtain the plasma and serum. Plasma glucose was measured immediately and the serum for the measurement of other biochemical variables were stored at -20 °C until analysis. Insulin was assayed by sandwich ELISA method (Cat # EIA-2935; DRG International Inc., Springfield Township, USA). Fasting plasma glucose ((FPG): Cat # 20767131-322) and lipid profile (Total Cholesterol (TCHOL): Cat # 03039773-190; Triglycerides (TG): Cat # 20767107-322; High Density Lipoprotein (HDL): Cat # 07528566-190) were estimated enzymatically using Cobas Integra automated Chemistry analyzer (Cobas Integra 400 Plus, Roche Diagnostics, USA). Low density lipoprotein (LDL) concentration was determined using Friedewald's formula: LDL (mmol/L) = TCHOL (mmol/L) – HDL (mmol/L) – [triglyceride (mmol/L)/2.2] [22]. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the HOMA2 calculator. Whole blood was used for HbA1c estimation by turbidimetric inhibition immunoassay (Cat # 04528123-190) using the Cobas Integra automated Chemistry analyzer (Cobas Integra 400 Plus, Roche Diagnostics, USA) as previously described [14]. Briefly, well-mixed EDTA-anticoagulated whole blood was put into sample tubes. The tubes were immediately placed on a rack. Red blood cells were haemolysed by low osmotic pressure and the free haemoglobin subsequently degraded by pepsin to ensure availability of the N-terminal of the beta chain (β-N-terminal) of haemoglobin. Latex particles-bound monoclonal antibodies bind to the β-N-terminal of HbA1c while the remaining free antibodies are agglutinated using synthetic polymers with multiple copies of the β-N-terminal structure of HbA1c. The change in turbidity is measured at 552 nm and the final HbA1c value expressed as a percentage using the formula: HbA1c (%) = (HbA1c/Hb) × 87.6 + 2.27. The test was standardized with an intra-assay %CVs of 0.9%–1.5% and inter-assay %CVs of 1.1%–1.6%. The method for the HbA1c determination is among the 2019 National Glycohemoglobin Standardization Program (NSGP) list of certified methods [23].

Daily calibration and maintenance of the analyzer was performed according to the manufacturer's instructions. Quality control (QC) was assessed using quality control materials provided by the manufacturer [negative and positive controls (high and low HbA1c)] and calibration was performed using manufacturer-supplied calibrator (Cfas HbA1c).

2.5. Definition of metabolic syndrome

The MetS was defined according to the consensus criteria by the Joint Interim Statement (JIS) [5]. Subjects were classified as having MetS by the presence of three or more of the following: elevated WC ($\geq$94 cm and $\geq$80 cm for African male and female, respectively); TG $\geq$ 1.7 mmol/l; HDL <1.0 mmol/l in men and <1.3 mmol/l in women; BP $\geq$ 130/85 mmHg; or FPG $\geq$ 5.6 mmol/l. Dysglycaemia was defined by FPG $\geq$ 5.6 mmol/l or HbA1c $\geq$ 5.7% according to the American Diabetes Association [18].

2.6. HbA1c cut-off value for the prediction MetS

In this study, we employed the receiver operating characteristic (ROC) curve analysis to obtain a study population specific HbA1c cut-off value (represented as pHbA1c) for the prediction of MetS as described by Park et al [9]. The cut-off was based on the HbA1c value which corresponds to the FPG value of 5.6 mmol/L (100 mg/dL) diagnostic of

dysglycaemia as defined by the American Diabetes Association [18]. A pHbA1c value of 5.4% was derived which showed an almost perfect agreement (κ = 0.82) with the FPG-based criterion. Diagnosis of pHbA1c-based MetS was done by replacing FPG in the Joint Interim Statement (JIS) [5] with pHbA1c cutoff of 5.4%.

2.7. Data analysis

All categorical data were presented as frequencies (percentages) and continuous data as mean ± SD. Chi-squared/Fisher exact test used to compare categorical variables and independent t-test was used to compared continuous data. Pearson's correlation was used to evaluate the association between HbA1c and cardiovascular risk factors. The kappa (κ) statistic was used to evaluate the agreement between FPG- and HbA1c-based criteria for MetS. The sensitivity, specificity, positive predictive (PPV) and negative predictive (NPV) values of the HbA1c criteria were evaluated using the FPG-based criterion as the reference. Reliability was expressed as the J index [(TP×TN) - (FP×FN)]/[(TP + FN) (TN + FP)]. A p value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS version 25.0.

3. Results

The mean age of the study population was 50.4 (±10.1) years. A higher proportion of the participants were female (56.0%). Participants with MetS had significantly elevated haemodynamic, and anthropometric indices compared with subjects without MetS. Higher lipid profile parameters, fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR), and HbA1c as well as lower HDL were found among participants with MetS compared with participants without MetS across all three criteria (Table 1).

Systolic blood pressure, BMI, WHtR, BAI, VAI, total cholesterol, triglyceride, LDL, and FPG were found to be positively related with HbA1c, whereas HDL showed a significant negative correlation with HbA1c in both the unadjusted and adjusted models (Table 2).

The prevalence of MetS using the FPG, ADA HbA1c and pHbA1c criteria were 35.2%, 38.5% and 41.8%, respectively. The prevalence of MetS was higher among females compared to males across all criteria. The pHbA1c cut-off identified 6.6% and 3.3% more subjects with MetS when compared with FPG and the ADA HbA1c cut-offs, respectively. Similarly, the ADA HbA1c cut-off identified 3.3% more subjects with MetS compared with the FPG criterion in this study population (Table 3).

Among the subjects with MetS by either FPG or ADA HbA1c (n = 304), an overlap of 232 (31.9%) was observed showing a substantial agreement (κ = 0.79) between the FPG and ADA HbA1c criterion for MetS (Figure 1A). On the other hand, of the 312 subjects diagnosed with MetS by either FPG or the pHbA1c cut-off, an overlap of 248 (34.1%) and an almost perfect concordance (κ = 0.82) was observed (Figure 1B).

Using the FPG-based criterion as the reference, both ADA HbA1c and pHbA1c cut-offs presented with excellent sensitivities and specificities in identifying subjects with MetS among the entire study population. The pHbA1c cut-off, however, had higher sensitivities compared to the ADA HbA1c criterion though the ADA HbA1c criterion presented with marginally higher specificities. Furthermore, the area under the curve (AUC) and reliability of the pHbA1c criterion was consistently higher than the ADA HbA1c criterion (Table 4).

Table 1. Baseline characteristics of the study population.

Criteria	Total (n = 728)	FPG-based criterion		ADA HbA1c-based criterion		pHbA1c-based criterion	
		MetS positive	MetS negative	MetS positive	MetS negative	MetS positive	MetS negative
Age (years)	50.4 ± 10.1	50.13 ± 10.5	50.5 ± 10.0	51.1 ± 10.9	49.8 ± 9.5	51.1 ± 10.9	49.8 ± 9.5
Sex*							
Male	320 (44.0)	88 (27.5)	232 (72.5)‡	88 (27.5)	232 (72.5)‡	88 (27.5)	232 (72.5)‡
Female	408 (56.0)	168 (41.2)	240 (58.8)	168 (41.2)	240 (58.8)	216 (52.9)	192 (47.1)
SBP	117.8 ± 13.8	125.7 ± 11.1	113.5 ± 13.3†	125.7 ± 9.0	112.1 ± 13.9†	125.7 ± 9.0	112.1 ± 13.9†
DBP	75.0 ± 9.4	77.4 ± 8.9	73.7 ± 9.4†	77.3 ± 8.7	73.4 ± 9.5†	77.3 ± 8.7	73.4 ± 9.5†
WC	92.0 ± 11.9	101.7 ± 9.7	86.8 ± 8.4†	99.5 ± 10.5	86.7 ± 8.8†	99.5 ± 10.5	86.7 ± 8.8†
BMI	25.8 ± 5.0	29.2 ± 5.3	23.9 ± 3.7†	28.7 ± 5.0	23.7 ± 3.8†	28.7 ± 5.0	23.7 ± 3.8†
WHR	0.9 ± 0.1	0.9 ± 0.1	0.8 ± 0.1†	0.9 ± 0.1	0.8 ± 0.1†	0.9 ± 0.1	0.8 ± 0.1†
WHtR	0.6 ± 0.1	0.6 ± 0.1	0.5 ± 0.1†	0.6 ± 0.1	0.5 ± 0.1†	0.6 ± 0.1	0.5 ± 0.1†
BAI	31.4 ± 6.6	34.2 ± 7.0	29.8 ± 5.8†	34.4 ± 6.6	29.2 ± 5.6†	34.4 ± 6.6	29.2 ± 5.6†
VAI	2.5 ± 2.1	4.1 ± 2.5	1.6 ± 1.1†	3.8 ± 2.4	1.6 ± 1.1†	3.8 ± 2.4	1.6 ± 1.1†
FPG	4.9 ± 0.7	5.1 ± 0.7	4.7 ± 0.7†	5.1 ± 0.7	4.7 ± 0.7‡	5.1 ± 0.7	4.7 ± 0.7†
TCHOL	4.4 ± 1.1	4.5 ± 1.2	4.2 ± 1.0§	4.6 ± 1.1	4.2 ± 1.0‡	4.6 ± 1.1	4.2 ± 1.0‡
TG	1.4 ± 0.6	1.9 ± 0.6	1.1 ± 0.5†	1.7 ± 0.6	1.1 ± 0.5†	1.7 ± 0.6	1.1 ± 0.5†
HDL	1.2 ± 0.4	1.0 ± 0.4	1.3 ± 0.3†	1.0 ± 0.3	1.3 ± 0.3†	1.0 ± 0.3	1.3 ± 0.3†
LDL	2.9 ± 1.1	3.2 ± 1.1	2.7 ± 1.0‡	3.2 ± 1.1	2.7 ± 1.0†	3.2 ± 1.1	2.7 ± 1.0†
Insulin	15.4 ± 7.7	17.9 ± 8.5	14.1 ± 6.9†	18.0 ± 8.4	13.6 ± 6.6†	18.0 ± 8.4	13.6 ± 6.6†
HOMA-IR	3.4 ± 1.9	4.2 ± 2.0	2.9 ± 1.6†	4.1 ± 2.0	2.8 ± 1.6†	4.1 ± 2.0	2.8 ± 1.6†
HbA1c	5.2 ± 0.8	5.6 ± 0.7	5.0 ± 0.8†	5.7 ± 0.7	4.9 ± 0.7†	5.7 ± 0.7	4.9 ± 0.7†

Unless otherwise indicated, data are presented as Mean ± SD. Categorical data were compared between MetS and non-MetS groups using Chi-squared/Fisher exact tests. Continuous data were compared using independent t-test was used to compared continuous data. SBP; Systolic blood pressure, DBP; Diastolic blood pressure, WC; Waist Circumference, BMI; Body Mass Index, WHR; Waist-to-Hip ratio, WHtR; Waist-to Height ratio, BAI; Body Adiposity Index. VAI; Visceral Adiposity Index. FPG; Fasting Plasma Glucose, TCHOL; Total Cholesterol, TG; Triglycerides, HDL; High Density Lipoprotein, LDL; Low Density Lipoprotein, HOMA-IR, Homeostatic Model Assessment for Insulin Resistance, HbA1c; Glycated haemoglobin, ADA; American Diabetes Association, pHbA1c; Population-specific HbA1c; SD; Standard deviation.
†; Significant at $p < 0.0001$.
‡; Significant at $p < 0.01$.
§; Significant at $p < 0.05$.
* data is presented as n (%).

Table 2. Association between HbA1c and cardiovascular risk factors among the entire study population.

Variables	Unadjusted model		Adjusted model	
Haemodynamic	r	p-value	r	p-value
SBP	0.15	0.004	0.15	0.005
DBP	0.06	0.268	0.06	0.269
Anthropometric				
BMI	0.33	<0.0001	0.31	<0.0001
WHR	0.10	0.058	0.09	0.097
WHtR	0.32	<0.0001	0.29	<0.0001
BAI	0.34	<0.0001	0.33	<0.0001
VAI	0.30	<0.0001	0.29	<0.0001
Biochemical				
TCHOL	0.13	0.016	0.12	0.028
TG	0.24	<0.0001	0.24	<0.0001
HDL	-0.27	<0.0001	-0.31	<0.0001
LDL	0.17	0.001	0.17	0.001
FPG	0.37	<0.0001	0.35	<0.0001

Pearson's correlation was used to evaluate the association between HbA1c and cardiovascular risk factors. The adjusted model was evaluated using partial correlation after controlling for age and sex. r; correlation coefficient, SBP; Systolic blood pressure, DBP; Diastolic blood pressure, BMI; Body Mass Index, WHR; Waist-to-Hip ratio, WHtR; Waist-to Height ratio, BAI; Body Adiposity Index. VAI; Visceral Adiposity Index. FPG; Fasting Plasma Glucose, TCHOL; Total Cholesterol, TG; Triglycerides, HDL; High Density Lipoprotein, LDL; Low Density Lipoprotein.

Table 3. Prevalence of MetS among the study population.

Number of components	FPG-based criterion			ADA HbA1c-based criterion			pHbA1c-based criterion		
	Total	Male	Female	Total	Male	Female	Total	Male	Female
0	72 (9.9)	56 (7.7)	16 (2.2)	72 (9.9)	56 (7.7)	16 (2.2)	72 (9.9)	56 (7.7)	16 (2.2)
1	192 (26.4)	120 (16.5)	72 (9.9)	176 (24.2)	120 (16.5)	56 (7.7)	168 (23.1)	120 (16.5)	48 (6.6)
2	208 (28.6)	56 (7.7)	152 (20.9)	200 (27.5)	56 (7.7)	144 (19.8)	184 (25.3)	56 (7.7)	128 (17.6)
3	136 (18.7)	48 (6.6)	88 (12.1)	144 (19.8)	40 (5.5)	104 (14.3)	144 (19.8)	32 (4.4)	112 (15.4)
4	96 (13.2)	40 (5.5)	56 (7.7)	104 (14.3)	40 (5.5)	64 (8.8)	104 (14.3)	48 (6.6)	56 (7.7)
5	24 (3.3)	0 (0.0)	24 (3.3)	32 (4.4)	8 (1.1)	24 (3.3)	56 (7.7)	8 (1.1)	48 (6.6)
≥3	256 (35.2)	88 (12.1)	168 (23.1)	280 (38.5)	88 (12.1)	192 (26.4)	304 (41.8)	88 (12.1)	216 (29.7)

FPG; Fasting plasma glucose, HbA1c; Glycated haemoglobin, ADA; American Diabetes Association, pHbA1c; Population-specific HbA1c.

4. Discussion

In this study, the prevalence of MetS using the fasting hyperglycaemia and HbA1c based on the ADA criterion was 35.2% and 38.5%, respectively. Hence, the ADA HbA1c cut-off identified 3.3% more subjects with MetS compared with the FPG criterion as consistent with a follow-up population-based cohort study by de Vegt et al. [24] among older non-diabetics. de Vegt et al. reported that elevated HbA1c was associated with a higher age- and sex-adjusted risk of cardiovascular mortality and suggested that HbA1c is a better predictor of CVD mortality than fasting hyperglycaemia among non-diabetic subjects. This finding is also in harmony with a cross-sectional study by Annani-Akollor et al. [14] among non-diabetic population in Ghana who reported that the use of the ADA HbA1c criterion improves MetS diagnosis compared to FPG.

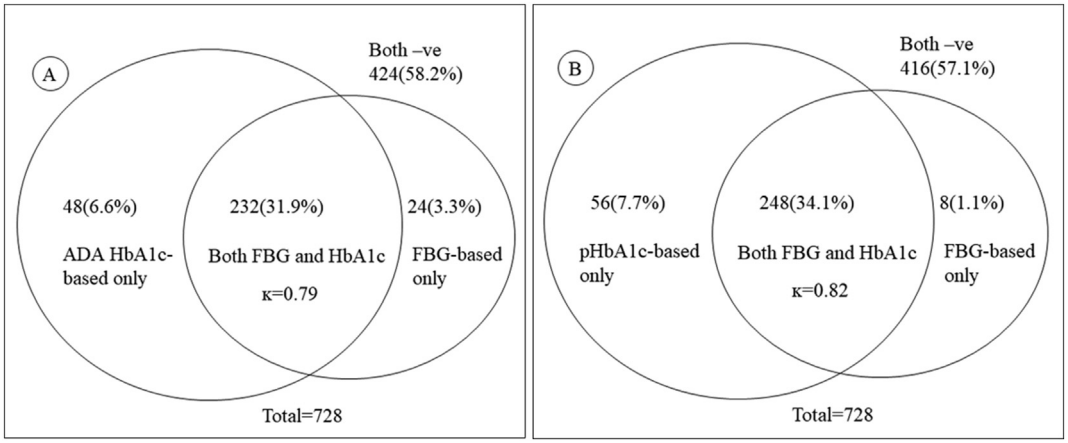

Figure 1. Validation and concordance evaluation between FPG- and HbA1c-based criteria.

Table 4. Diagnostic performance of the ADA HbA1c and pHbA1c cut-off for diagnosing MetS.

Parameter	ADA HbA1c criterion			pHbA1c criterion		
	Total	Males	Females	Total	Males	Females
Sensitivity (95% CI)	90.6 (84.1–94.7)	100.0 (90.2–100.0)	85.7 (76.5–91.7)	96.9 (91.9–99.0)	100.0 (90.2–100.0)	95.2 (87.9–98.5)
Specificity (95% CI)	89.8 (85.0–93.1)	100.0 (96.0–100.0)	80.0 (71.9–86.2)	88.1 (83.3–91.7)	100.0 (96.0–100.0)	76.7 (68.3–83.3)
PPV (95% CI)	82.9 (76.6–89.1)	100.0 (100.0–100.0)	75.0 (66.3–83.7)	81.6 (75.4–87.7)	100.0 (100.0–100.0)	74.1 (65.8–82.3)
NPV (95% CI)	94.6 (91.7–97.6)	100.0 (100.0–100.0)	88.9 (82.9–94.8)	98.1 (96.3–99.9)	100.0 (100.0–100.0)	95.8 (91.8–99.8)
TP	232	88	144	248	88	160
TN	424	232	192	416	232	184
FP	48	0	48	56	0	56
FN	24	0	24	8	0	8
LR+ (95% CI)	8.9 (6.1–13.1)	-	4.3 (3.0–6.2)	8.1 (5.8–11.6)	-	4.1 (2.9–5.7)
LR- (95% CI)	0.1 (0.1–0.2)	-	0.2 (0.1–0.3)	0.04 (0.01–0.09)	-	0.06 (0.02–0.16)
Accuracy (%)	90.1	100.0	82.4	91.2	100.0	84.3
AUC (%)	90.2	100.0	82.9	92.5	100.0	86.0
Reliability (J index)	80.5	100.0	65.7	85.0	100.0	71.9

The receiver operator curve (ROC) analysis was used to evaluate the diagnostic performance of the ADA HbA1c and pHbA1c using the FPG-based criterion as the reference. Reliability was expressed as the J index [(TP×TN) - (FP×FN)]/[(TP + FN) (TN + FP)]. HbA1c; Glycated haemoglobin, ADA; American Diabetes Association, pHbA1c; Population-specific HbA1c, PPV; Positive predictive value, NPV; Negative predictive value, LR+; Positive likelihood ratio, LR-; Negative likelihood ratio, CI; Confidence interval.

Additionally, Osei et al. [11], in a study to evaluate the significance of HbA1c in MetS among African-American patients with type 2 diabetes, reported that when HbA1c was divided into tertiles: 4.7% (3.3%–4.8%), 5.4% (4.9%–5.6%), and 5.8% (5.7%–6.4%), subjects having HbA1c value within 5.7%–6.4% were more predisposed to the metabolic abnormalities, buttressing the significance of HbA1c as a marker for MetS diagnosis.

Furthermore, HbA1c is associated with increasing prevalence of cardiovascular disease and metabolic syndrome [3, 8, 12, 13]. Eeg-Olofsson et al. [25] found that higher HbA1c levels is linked to increased risks of coronary heart disease, CVD and total mortality; however, low HbA1c levels is associated with no increase in risk. We also found that HbA1c was significantly associated with several CVD risk factors including haemodynamic (systolic blood pressure), anthropometric (BMI, WHtR, BAI, and VAI), and biochemical indices (total cholesterol, triglyceride, LDL, HDL and FPG), reinforcing our previous deposition that HbA1c could serve as a potential marker for CVD [14]. Nonetheless, racial discrepancies necessitate the development of population-specific HbA1c cut-offs.

Using the ROC curve, a population-specific HbA1c (pHbA1c) cut-off of 5.4%, corresponding to the FPG value of 5.6 mmol/L (100 mg/dL) for dysglycaemia as defined by the American Diabetes Association [18], was developed. The prevalence of MetS using pHbA1c as the diagnostic criterion for dysglycaemia was 41.8%, showing that the pHbA1c cut-off identified 6.6% and 3.3% more subjects with MetS when compared with FPG and the ADA HbA1c cut-offs, respectively. Thus, although diagnosis of MetS based exclusively on fasting hyperglycaemia may involve some risk of overlooking subjects at high risk for CVD which may be remedied by the ADA-HbA1c criterion, the development of population-specific cut-offs for HbA1c could identify a greater number of such high risk subjects in that specific population. It is worth noting however that with less than three components of MetS, pHbA1c presents with different efficiency. As expected, when the presence of MetS components is lower than three, pHbA1c identifies less number of participants compared to FPG-based and ADA-based HbA1c criteria. This implies that caution should be taken when using pHbA1c in assessing CVD, especially in population where <3 MetS components is prevalent. Importantly, the prevalence of MetS was consistently higher among females compared to males across all criteria. This finding is in keeping with previous studies in Ghana [2, 14, 26] and elsewhere [27, 28, 29], and suggests a trend where females are more prone to CVD than males [30]. Therefore, identification of sociodemographic and environmental correlates of MetS, particularly those that affect females, will be critical to the preventive efforts against the increasing prevalence of MetS.

Furthermore, validation and concordance evaluation showed an almost perfect agreement ($\kappa = 0.82$) between pHbA1c and FPG criterion compared with the ADA HbA1c and FPG criterion which presented with a substantial agreement ($\kappa = 0.79$). This implies that, despite the identification of higher number of subjects with MetS by the pHbA1c compared to the ADA HbA1c criterion, there is a lower risk of misdiagnosis when pHbA1c used in this study population.

In assessing and comparing the diagnostic performance of the ADA HbA1c and pHbA1c, we used the FPG-based criterion as the reference. We found that both ADA HbA1c and pHbA1c cut-offs had an excellent sensitivity and specificity for identifying subjects with MetS in the entire study population. The pHbA1c cut-off however presented with higher sensitivities compared to the ADA HbA1c criterion, although the ADA HbA1c criterion presented with marginally higher specificities. Furthermore, the AUCs and reliabilities of the pHbA1c criterion were consistently higher than the ADA HbA1c criterion.

Taken together, it is evident that the use of HbA1c as the criterion for dysglycaemia in defining MetS allows for detection of high risk subjects who may be missed by the traditional FPG-based criterion. Nonetheless, a population specific cut-offs for HbA1c will detect a greater number of high risk subjects in that population with substantial accuracy and reliability compared to the general HbA1c cut-off.

Notwithstanding, this study is limited by its cross-sectional nature as the cause-effect relationship between HbA1c and MetS could not be established. Furthermore, the estimation of blood pressure was based on the average of two measurements at a single visit and biochemical profiling was single point measurement which might have overestimated the prevalence rates, as in many epidemiological studies. Additionally, though subjects with diabetes as well as those with newly diagnosed diabetes were excluded by applying the criteria of fasting hyperglycaemia and HbA1c at baseline, there is a possibility that a number of subjects with postprandial hyperglycaemia were included. However,

HbA1c represents chronic exposure to basal and postprandial hyperglycaemia; thus, minimizes the effect of this limitation on the study findings. Although representative sample size was used in this study, the number of participants recruited for the study remain limited. We recommend a larger scale study to extensively explore the usefulness of the population-specific HbA1c cut-off in MetS diagnosis. Also, future studies should consider establishing a population specific cut-off for WC.

5. Conclusion

Screening for MetS by introduction of the ADA HbA1c criterion in addition to the traditional FPG criterion enhances the detection of more people with MetS. However, the use of population-specific cut-off for HbA1c could identify a greater number of high risk subjects in that specific population.

Declaration

Author contribution statement

M. Annani-Akollor and E. Laing: Conceived and designed the experiments.

O. Addai-Mensah, L. Fondjo and E. Adu: Performed the experiments; Analyzed and interpreted the data.

E. Owiredu: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

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