

Development and Validation of a Simple Risk Model for Predicting Metabolic Syndrome (MetS) in Midlife: A Cohort Study

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Purpose: To develop and validate a simple risk model for predicting metabolic syndrome in midlife using a prospective cohort data.

Design: Prospective cohort study.

Participants: A total of 7626 members of the 1958 British birth cohort (individuals born in the first week of March 1958) participated in the biomedical survey at age 45 and have completed information on metabolic syndrome.

Methods: Variables utilised were obtained prospectively at birth, 7, 16, 23 and 45 years. Multivariable logistic regression was used to develop a total of ten (10) MetS risk prediction models taking the life course approach. Measures of discrimination and calibration were used to evaluate the performance of the models. A pragmatic criteria developed was used to select one model with the most potential to be useful. The internal validity (overfitting) of the selected model was assessed using bootstrap technique of Stata.

Main Outcome Measure: Metabolic syndrome was defined based on the NCEP-ATP III clinical criteria.

Results: There is high prevalence of MetS among the cohort members (19.6%), with males having higher risk as compared to females (22.8% vs 16.4%, $P < 0.001$). Individuals with MetS are more likely to have higher levels of HbA1c and low HDL-cholesterol. Similarly, regarding the individual components of MetS, male cohort members are more likely to have higher levels of glycaemia (HbA1c), BP and serum triglycerides. In contrast, female cohort members have lower levels of HDL-cholesterol and higher levels of waist circumference. Furthermore, a total of ten (10) MetS risk prediction models were developed taking the life course approach. Of these, one model with the most potential to be applied in practical setting was selected. The model has good accuracy (AUROC 0.91 (0.90, 0.92)), is well calibrated (Hosmer-Lemeshow 6.47 (0.595)) and has good internal validity.

Conclusion: Early life factors could be included in a risk model to predict MetS in midlife. The developed model has been shown to be accurate and has good internal validity. Therefore, interventions targeting socioeconomic inequality could help in the wider prevention of MetS. However, the validity of the developed model needs to be further established in an external population.

Keywords: metabolic syndrome, prediction model, risk score, development and validation of risk model, 1958 British birth cohort, national child development study

Introduction

Worldwide, the prevalence of Metabolic Syndrome (MetS) - “a clustering of risk factors which includes hypertension, central obesity, impaired glucose metabolism with insulin resistance, and dyslipidemia”¹ is high and rising, with nearly one in four adults affected.² The diagnosis of MetS increases an individual’s risk of developing CVD by two to threefold, T2DM by fivefold and all-cause mortality by twofold.³ Furthermore, MetS is recognised as a useful tool for identifying individuals at increased risk of CVD and T2DM. Hence, the WHO stress that it should be viewed as a premorbid state of CVD and T2DM rather than a distinct clinical disease.⁴

There is increased popularity in the use of risk prediction models in public health/ clinical practice, partly due to availability of large datasets, advanced statistical methods and computational power.⁵ Furthermore, abdominal obesity is generally presumed to be central to the diagnosis of MetS, but, not all individuals with obesity have MetS and vice

versa.⁶ Without a valid test, it may not be possible to detect or suspect MetS in non-obese individuals.⁷ Identifying the subset of individuals (both obese and non-obese) with MetS is necessary and could have implications on subsequent management approach.⁷ Thus, an accurate and reliable MetS prediction model could be used in screening individuals at increased risk of MetS. Focusing on assessing risk of MetS provides a single unifying theme which could enable clinicians to identify an individual's global risk of CVD and T2DM (holistic approach).⁸ Therefore, both from clinical and public health perspective, early identification and control of MetS is of great significance, as it could result in the reduction of T2DM and CVD related morbidity and mortality.

Previous evidence suggests that the risk of MetS starts early on in life^{9,10} and persists into adulthood.¹¹ This makes it appropriate to use life course approach in the studies of MetS.¹² Early life risk factors are as important in the development of MetS as adult risk factors. In order to effectively prevent and manage MetS, an approach which is holistic and equitable should be employed, focusing on risk factors (both biological and psychosocial) acquired at different stages of life.¹³ Therefore, the purpose of this study is to develop and validate a simple prediction model taking a life course approach using a prospective birth cohort data to forecast risk of MetS in midlife.

Subjects and Methods

Participants

The 1958 British birth cohort, also known as the National Child Development Study (NCDS). The full details of the cohort are previously provided.¹⁴ Briefly, the cohort consists of 18,558 individuals born in the first week of March 1958 in Britain. It was originally set-up to investigate the factors (both obstetric and social) responsible for the high perinatal mortality (stillbirth rate). In subsequent years, the NCDS was adjusted and used for monitoring how the members are developing (educationally, physically and socially) as they grow from infancy to adulthood. Since its inception, regular prospective follow-ups have been conducted both in childhood and adulthood.

Between the years 2002 and 2003 (cohort members aged 44/45 years), follow up was conducted in a form of a biomedical survey. The main purpose of the survey was to objectively collect measures of disease and biomedical risk factors to address a wide range of specific hypotheses relating to anthropometry, cardiovascular system, respiratory system and allergic diseases, visual and hearing impairment, and mental health. This survey was carried out by registered research nurses who visited cohort members at their homes or specified research clinics within that period. A total of 9377 cohort members participated in the survey. However, only 8585 participants consented for all the four parts of the investigation.

In terms of demography, the 1958 British birth cohort is predominantly white (typical representation of Great Britain at the beginning of the cohort). Nevertheless, the sample has been shown to represent the national population concerning many socioeconomic characteristics during follow-ups at 33 years as well as the 45 year survey.¹⁵

The 1958 British birth cohort data is managed by the United Kingdom Data Service, based at the University of Essex, UK. We accessed the anonymized data after obtaining a formal permission from them. In the same vein, the ethical approval for this study was granted by Institute for Health Research Ethics Committee, University of Bedfordshire.

Variables

Predictors

This study utilised predictors that are well established in the literature and clinically relevant.

Sociodemographic Characteristics

The main demographic variables considered are gender and socioeconomic status.

Socioeconomic conditions/Social class: participants' childhood social class is defined according to registrar general's classification of the father's occupation in 1958 (OPCS, 1987). Where this information is not available, the father's occupation at age 7 is used. Furthermore, cohort members' socioeconomic conditions at age 21/23 years and 33/ 45 years were used.¹² Categorisation is same as the social categories at birth (I–V). Based on the above, a binary variable of social class was generated as (Non-manual vs manual).¹²

Early Life Predictors

Early-life factors were all recorded prospectively at birth (birth weight, gestational age and childhood social class) or at age 7 (BMI at 7 years, household crowding and family history of T2DM).

Birth weight: The study participants' birth weight was recorded in pounds and ounces. Before analysis, this was converted to kilograms (kg) and categorised into quartiles.

Gestational age: participants' gestational age as reported by mothers was recorded in days. This was converted to weeks and gestational age less than 38 weeks is defined as "Preterm".¹⁶

Family history of T2DM: this was elicited during the survey conducted at age 7 with response Yes or No. In this analysis, family history of T2DM is treated as a binary variable.

BMI at 7 years: Participants' weight (kg) and height (cm) measured during the follow-up at age 7 were used to compute BMI (kg/m²) at 7.

Household overcrowding: was assessed by determining the ratio of the number of individuals by the total number of rooms in a given house. Household having ≥ 1.5 persons per room is considered overcrowded.¹²

Adolescence/Early Adulthood Factors (16 and 23 Years)

BMI at 16 and 23 years: Participants' weight (kg) and height (cm) measured during the follow-up at ages 16 and 23 years were used to compute BMI (kg/m²) for the respective ages. BMI was classified based on standard adult categories as; underweight <18.5 kg/m², normal 18.5–24.9, overweight 25–29.9 and obese ≥ 30 kg/m².

Socioeconomic status at 16 and 23 years: Same as above.

Adulthood Predictors (45 Years)

Blood pressure, HDL-cholesterol, triglycerides, waist circumference and high HbA1c, are the adult predictors considered in this study.^{2,17–20} See below for description.

Outcome Variables

In this study, the primary outcome of interest is MetS defined based on the NCEP-ATP III clinical criteria. Information regarding the individual components of MetS was collected during the NCDS biomedical survey (when cohort members were 43–45 years) by a trained registered research nurse, using standard protocols. However, because fasting plasma glucose (FPG) was not recorded in the biomedical survey, glycosylated haemoglobin (HbA1c) was used as a proxy variable.^{12,21,22} MetS is identified at the age of 43–45 years old if three or more of the following occurred:

Blood Pressure

Blood pressure was measured in a quiet room using an Omron 705CP automated sphygmomanometer (Omron, Tokyo, Japan). A hypertension variable was generated as systolic blood pressure of 130 mmHg or higher, or diastolic blood pressure of 85 mmHg or higher. Hypertension was assessed as a binary outcome, using the above definition.

Blood Glucose (Glycated Haemoglobin (HbA1c))

In the biomedical survey, HbA1c was investigated using ion-exchange high-performance liquid chromatography (HLC-723GHbA1c 2.2; Tosoh Corp, Tokyo Japan). This technique has been adjudged to be standard and reproducible.^{23,24} In this analysis, high blood glucose variable was derived based on the data of glycated hemoglobin at age 45 years. Noteworthy, HbA1c $\geq 6.5\%$ has been shown to be a good predictor of diabetes in previous modelling studies.^{25,26} But for the purpose of identifying MetS, a lower cut-off point of HbA1c $\geq 6.0\%$ (which corresponds to pre-diabetes)^{21,22} is usually considered. Therefore, the cut-off point of HbA1c $\geq 6.0\%$ is used in this study. High blood glucose was treated as a binary variable during further analysis.

HDL-Cholesterol

Enzymatic methods with an autoanalyser (Olympus AU640, Japan) were used to measure High-density lipoprotein cholesterol (HDL-C). Based on the data available for HDL-cholesterol, a low HDL cholesterol variable was generated.

Low HDL-cholesterol was defined as <0.40 g/L for men and <0.50 g/L for women (NCEP, 2001) and was treated as a binary outcome variable during further statistical analysis.

Triglycerides

Triglycerides were also measured using enzymatic methods with an autoanalyser (Olympus AU640, Japan). Triglycerides level of ≥ 150 mg/dL was used as the cut-off level in this study and was treated as a binary outcome variable during further statistical analysis.

Abdominal Obesity

During the survey, waist circumference (WC) was measured using a tension tape at an imaginary meeting point between the lower rib and upper part of pelvis, in the mid-axillary line.²⁷ During the procedure, participants were requested to be in a loose dress with the belt removed and relax their muscles of abdomen by breathing in and out. WC was measured and recorded to the nearest 1 centimeter (cm). In this study, abdominal obesity variable was generated as WC ≥ 102 cm for men or ≥ 88 cm for women.¹

Covariates

The potential confounders included in this study were selected a priori based on the literature.

Early Life

Early life potential socioeconomic/ psychosocial stress: Proxy variables on birth and perinatal conditions were chosen to capture the heading and subsequent MetS. These include:

Maternal smoking during pregnancy: (no smoking, variable smoker, moderate smoker, heavy smoker),

Type of delivery: (vaginal, emergency caesarean, elective caesarean),

Mother's parity: number of children previously borne by a mother in 1958,

Mother's age at birth (23 years or less, 24 to 27 years, 28 to 31 years, and 32 years or more)

Foetal distress: No distress, Yes distress

Breastfed: collected at 7 years (no, yes for less than 1 month, yes more than 1 month).¹²

Adult Health Behaviours/Lifestyle

During the biomedical survey, information concerning the above mentioned was collected from the cohort members through the means of the computer-assisted self-administered interview (CASI).

Smoking status: is categorised as non-smoker (individuals who have never smoked), ex-smoker (smoked one or more cigarette per day in the past, but have currently stopped smoking) or current smoker (smoke one or more cigarettes per day).

Drinking status: is coded as non-drinker, 1–2 drinks per day, 3–4 drinks per day, 5–6 drinks per day, and ≥ 7 drinks per day.

Physical activity: level of physical activity is defined as

highly active (vigorous exercise at least once per week), moderately active (moderate exercise at least once per week) and not active (hardly ever/never moderate-vigorous exercise).¹²

BMI at 45 years: classified as; underweight <18.5 kg/m², normal 18.5–24.9, overweight 25–29.9 and obese ≥ 30 kg/m².

Statistical Methods

Descriptive Statistics

The study uses the information of 7626 members of the 1958 British birth cohort who have complete data regarding all components of MetS at 45 years. Chi-square test of association was initially conducted in order to test the association between MetS, its individual components, the selected predictors and confounders. The level of significance was set at $P = 0.05$.

Model Development

Variables Selection

Variables included in the logistic regression models were selected a priori based on the literature and clinical/public health relevance. Further, their significance to the understanding of the life course origin of MetS was also considered.

Model Specification

Using the stepwise logistic regression technique, various combination of the predictors was used to build models starting with gender and father's social class at birth. Variables were included sequentially taking a life course approach. No pre-specified inclusion criteria were set. The only parameters of interest assessed are the stability and fit of the produced models. A total of 10 models with good fit and stability were initially selected for further assessment of performance. The analysis was performed both on complete cases and multiply imputed data.

Predictive Performance of the Developed Models

For the purpose of this study, the performance of the prediction models was assessed using the measures of discrimination and calibration.

Discrimination

This refers to the ability of a predictive risk model to distinguish participants that will develop the disease in context from those that will not.²⁸ This is often assessed using sensitivity, specificity, and the Receiver Operator Characteristic (ROC) curve.²⁸

In this study discrimination is assessed using measures of sensitivity, specificity and AUROC.

Calibration

Calibration is a statistical measure that evaluates whether what is being predicted by a risk model appears to be close to what is observed in reality over time.²⁸ It is a further test of a model's predictive power and is usually assessed along with discrimination.

In this study calibration is assessed using Hosmer–Lemeshow goodness-of-fit - estimates using deciles as well as calibration plots.

Missing Values

Missing values were imputed by multiple imputations by chain equations (MICE) method using the imputation by chained equation (ICE) programme of Stata²⁹ in order to account for missing data. The final imputed datasets were based on $m=10$ imputations.

Selecting the Model with the Most Potential to Be Useful

Given the large number of models generated following the stepwise logistic regression, it is necessary to select one (with the most potentials to be used in a real-life setting). Central to this decision is the simplicity and accuracy of the model. To develop risk models which are clinically useful, the models' simplicity and reliability of measurements are vital criteria.^{30,31} Complex models generated through extensive variable selection often lead to over-optimistic predictions.³² Thus, for any prediction model or risk score to be considered useful, it should be *accurate* (statistically significant calibration, and discrimination above 0.70), *generalisable* (externally validated by a separate research team on a different population) and *usable* (has few components that are commonly used in practical setting).³³

Therefore, to prioritize risk models or scores at this stage of the analysis, pragmatic criteria were developed by the research team by modifying the criteria set by Wyatt and Altman³⁰ and Altman et al.³³ MetS risk prediction model is favored if it is *accurate* (has discrimination above 0.70 and statistically significant calibration), *simple to use* (contains few predictors that may not be difficult to obtain in a routine clinical setting). In addition to the above, the model should contain no more than two adult predictors. Finally, the model should contain predictors that can improve equity in the prevention of MetS.³⁴

Adjusting for Potential Confounders

Potential confounders were added to the selected model in sequence; starting with those collected around birth (early life).

Internal Validity of the Selected Model

A random sample was drawn with replacement using the bootstrap command of Stata (Stata, 2015) with 1000 reps in order to test the internal validity of the selected model.

The summary of the stages involved in developing and internally validating the MetS risk prediction model is provided below:

1. Variables selected a priori based on the literature, clinical/ public health relevance and their significance to the understanding of the life course origin of MetS.
2. Multiple logistic regression models created using various combinations of early life predictors and adulthood predictors (life course approach).
3. Ten (10) stable models with good fit were selected for further assessment of performance.
4. Models' performance was assessed using discrimination and calibration.
5. Model with the most potentials to be useful was selected after applying the model selection criteria.
6. Potential confounders were adjusted for sequentially.
7. Internal validity of the selected model was assessed using the bootstrapping technique of Stata.

Results

Sample Characteristics

Table 1 above shows the summary characteristic of the studied sample in respect to MetS.

Of the initial 18,558 cohort members at birth, 9377 participated in the biomedical survey at age 45. Out of these, complete information regarding MetS was obtained from 7626 individuals (81.33%). Therefore, this analysis is based on these 7626 individuals. The sample is almost equally split with males accounting for 3827 (50.2%) and females 3799 (49.8%). Overall, 19.6% of the sample has MetS based on modified NCEP-ATP III criteria. Male cohort members are more likely to develop MetS as compared to females (22.8% vs 16.4%, $P < 0.001$).

Table 2 shows the gender differences in the prevalence of individual components of MetS. Male cohort members are more likely to have higher levels of glycaemia (HbA1c) (61.56% vs 38.44%, $P < 0.001$), hypertension (67.40% vs 32.60%, $P < 0.001$) and serum triglycerides (63.20% vs 36.80%, $P < 0.001$).

On the contrary, female cohort members have lower levels of HDL-cholesterol (67.73% vs 32.27%, $P < 0.001$) and higher levels of waist circumference (53.24% vs 46.76%, $P < 0.001$).

Developing MetS Risk Prediction Models

After performing the stepwise multivariate logistic regression, a total of ten (10) stable prediction models with good fit were generated. The models consists of candidate variables (predictors) ranging from three (3) to seven (7), with the average being approximately five (5).

The logistic regression models developed are displayed in **Tables 3–12**

Performance of the Developed Models

Models Discrimination

Sensitivity analyses as well as ROC analyses were conducted in order to assess the discrimination of the models produced in this study. The ROC curves for all the ten (10) models were produced (see **Figures 1–10**).

The summary of the sensitivity/specificity, discrimination as well as the calibration (performance parameters) of the models is provided in **Table 13.0**. From the table, it is clear that all the models are well discriminated. The values for AUROC ranges from 0.83 to 0.93.

Table I Sample Characteristics

	No Metabolic Syndrome		Metabolic Syndrome		Total	P
	Number	Percent	Number	Percent	Number	
Gender						
Male	2955	77.2	872	22.8	3827	<0.001
Female	3176	83.6	623	16.4	3799	
Total	6131.00	80.4	1495.00	19.6	7626	
High HbA1c						
<6.0%	6064.00	83.0	1238.00	17.0	7302.00	<0.001
≥6.0%	67	20.7	257	79.3	324	
Total	6131.00	80.4	1495.00	19.6	7626.00	
Low HDL-cholesterol						
No	5700	87.2	838	12.8	6538	<0.001
Yes	431	39.6	657	60.4	1088	
Total	6131.00	80.4	1495.00	19.6	7626.00	
High waist circumference						
No	4915	97.4	133	2.6	5048.00	<0.001
Yes	1216	47.2	1362	52.8	2578.00	
Total	6131	80.4	1495.	19.6	7626	
High systolic blood pressure						
No	4281	92.5	345	7.5	4626	<0.001
Yes	1850	61.7	1150	38.3	3000	
Total	6131	80.4	1495.	19.6	7626	
High diastolic blood pressure						
No	4911	87.6	694	12.4	5605	<0.001
Yes	1220	60.4	801	39.6	2021	
Total	6131	80.4	1495.	19.6	7626	
Hypertension						
No	4166	93.7	282	6.3	4448	<0.001
Yes	1965	61.8	1213	38.2	3178	
Total	6131	80.4	1495.	19.6	7626	
High serum triglycerides						
No	3776	98.0	76	2.0	3852	<0.001
Yes	2355	62.4	1419	37.6	3774	
Total	6131	80.4	1495	19.6	7626	
Father's social class at birth						
Non Manual	1886	86.2	303	13.8	2189	<0.001
Manual	4186	81.3	966	18.8	5152	
Total	6072	82.7	1269	17.3	7341	
Birthweight						
Q1- Low weight	1344	80.2	331	19.8	1675	0.138
Q2	1577	81.2	364	18.8	1941	
Q3	1448	81.3	334	18.7	1782	
Q4	1416	78.6	386	21.4	1802	
Total	5785	80.3	1415	19.7	7200	
Gestational age						
38 weeks or less	472	80.4	115	19.6	587	0.959
38 to 41 weeks	4168	80.7	997	19.3	5165	
42 weeks or more	624	80.3	153	19.7	777	
Total	5264		1265		6529	
Overcrowding						
≤1.5 person/room	4998	80.7	1192	19.3	6190	0.056

(Continued)

Table I (Continued).

	No Metabolic Syndrome		Metabolic Syndrome		Total	P
	Number	Percent	Number	Percent	Number	
>1.5 person/room	658	78.0	186	22.0	844	
Total	5656	80.4	1378	19.6	7034	
Parity						
Oldest child	1397	82.5	349	17.5	1746	0.869
2nd child	1407	82.7	336	17.3	1743	
3rd child or more	2952	82.7	722	17.3	3674	
Total	5756	82.7	1407	17.3	7163	
Mother's age at birth						
23years or less	1472	77.5	376	19.8	1900	0.002
24 to 27 years	1636	80.8	340	16.8	2026	
28 to 31 years	1308	82.0	265	16.6	1595	
32 years or more	1391	81.7	269	15.8	1703	
Total	5807	80.4	1417	19.6	7224	
Mother smoked during pregnancy						
No	3936	81.6	890	18.4	4826	0.002
Moderate smoker	833	78.3	231	21.7	1064	
Heavy smoker	648	78.8	174	21.2	822	
Variable smoker	323	75.5	105	24.5	428	
Total	5740	80.4	1400	19.6	7140	
Foetal distress						
No distress	5320	80.7	1276	19.3	6596	0.076
Yes distress	492	77.7	141	22.3	633	
Total	5812	80.4	1417	19.6	7229	
Breastfed						
No	1568	81.8	424	20.3	1992	0.050
Yes < 1 month	1285	82.3	305	19.2	1590	
Yes >1 month	2502	83.8	569	18.5	3071	
Total	5355	80.5	1298	19.5	6653	
Family history of diabetes						
Yes	115	71.0	47	29.0	162	0.002
No	5215	80.8	1243	19.2	6458	
Total	5330	80.5	1290	19.5	6620	
BMI at 7						
Underweight	3602	85.8	596	14.2	4198	<0.001
Normal	726	77.2	214	22.8	940	
Overweight	194	65.5	102	34.5	296	
Obese	92	74.2	32	25.8	124	
Total	4614	83	944	17	5558	
BMI at 16						
Underweight	1060	88.8	134	11.2	1194	<0.001
Normal	3222	80.0	803	20.0	4025	
Overweight	175	59.1	121	40.9	296	
Obese	22	51.2	21	48.8	43	
Total	4479	80.6	944	17	5558	
BMI at 23						
Underweight	275	95.2	14	4.8	289	<0.001
Normal	4434	84.4	818	15.6	5252	
Overweight	486	58.8	341	41.2	827	
Obese	45	33.1	91	66.9	136	

(Continued)

Table 1 (Continued).

	No Metabolic Syndrome		Metabolic Syndrome		Total	P
	Number	Percent	Number	Percent	Number	
Total	5240	80.6	1264	19.4	6504	
Social class at 23						
Non Manual	2827	83.6	556	16.4	3383	<0.001
Manual	2097	76.4	647	23.6	2744	
Total	4924	80.4	1203	19.6	6127	
Social class at 45						
Non Manual	3858	82.7	806	17.3	4664	<0.001
Manual	2046	77.1	606	22.9	2652	
Total	5904	80.7	1412	19.3	7316	
Alcohol consumption at 45						
Non-drinker	359	73.9	127	26.1	486	<0.001
1–2 drinks per day	2786	83.0	572	17.0	3358	
3–4 drinks per day	1611	80.8	384	19.2	1995	
5–6 drinks per day	820	79.2	215	20.8	1035	
≥7 drinks per day	541	74.0	190	26.0	731	
Total	6117	80.4	1488	19.6	7605	
Physical activity at 45						
Highly active	997	80.7	238	19.3	1235	0.454
Moderately active	790	80.2	195	19.8	985	
Not active	983	78.8	265	21.2	1248	
Total	2770	83.4	698	20.1	3468	
Smoking at 45						
Never smoked	2768	82.2	599	17.8	3367	<0.001
Ex/occ-smoker	1803	80.6	434	19.4	2237	
Current smoker	1374	77.1	407	22.9	1781	
Total	5945	80.5	1440	19.5	7385	
BMI at 45						
Underweight	38	97.4	1	2.6	39	<0.001
Normal	2550	98.0	52	2.0	2602	
Overweight	2662	84.9	475	15.1	3137	
Obese	833	46.9	942	53.1	1775	
Total	6083	82.8	1470	17.2	7553	

The sensitivity of the models is quite modest. While the majority of the models (6 out of 10) have sensitivity slightly above 50%, few (3) are not sensitive with values far less than 50%. One model (Model 8) has very good sensitivity of 72.62%. On the contrary, the models in this study are very specific in predicting MetS in midlife. Specificity ranges from 91.76% to 98.05%.

Similarly, positive predictive value (PPV) of the produced models is good. The values for PPV range from 62.92% to 78.45%. In the same vein, negative predictive value (NPV) of the models is very good with values ranging from 84.23% to 93.44%.

Models Calibration

The Hosmer-Lemeshow goodness-of-fit test was used in this analysis to assess the calibration of the models produced. The summary of the calibration (Hosmer-Lemeshow goodness-of-fit test) is provided in Table 13 above. From the table, it is clear that the majority (70%) of the models are well calibrated.

The models that are poorly calibrated (Models 2, 4 and 8) consist of four, six and three predictors, respectively. Also, they all share a common predictor (father's social class at birth).

Table 2 Gender Differences in the Prevalence in the Individual Components of MetS

	Male		Female		Total	P
	Number	Percent	Number	Percent	Number	
High HbA1c						
<6.0%	3763	49.67	3814	50.33	7577	<0.001
≥6.0%	213	61.56	133	38.44	346	
Low HDL-cholesterol						
No	3551	48.41	3132	51.59	6683	<0.001
Yes	363	32.27	762	67.73	1125	
High waist circumference						
No	3115	51.39	2946	48.61	6061	<0.001
Yes	1514	46.76	1724	53.24	3238	
Hypertension						
No	1986	36.98	3385	63.02	5371	<0.001
Yes	2646	67.40	1280	32.60	3926	
High serum triglycerides						
No	1986	32.52	3385	67.48	5371	<0.001
Yes	2834	63.20	1650	36.80	4484	

Table 3 Model 1 (MetS Prediction Model Consisting of Gender, Father's Social Class at Birth and High Waist Circumference)

	Complete Cases			Multiple Imputation		
	Coeff.	(95% CI)	P	Coeff.	(95% CI)	P
Gender	-0.86	(-1.01, -0.71)	<0.001	-0.87	(-1.01, -0.72)	<0.001
Father's social class at birth	0.30	(0.14, 0.47)	<0.001	0.30	(0.13, 0.47)	0.001
High waist circumference	3.82	(3.62, 4.01)	<0.001	3.84	(3.62, 4.01)	<0.001

Table 4 Model 2 (MetS Prediction Model Consisting of Gender, Father's Social Class at Birth, High Waist Circumference and HbA1c ≥6.0)

	Complete Cases			Multiple Imputation		
	Coeff.	(95% CI)	P	Coeff.	(95% CI)	P
Gender	-0.81	(0.97, -0.66)	<0.001	-0.83	(-0.98, -0.68)	<0.001
Father's social class at birth	0.24	(0.06, 0.41)	0.007	0.24	(0.07, 0.42)	0.007
High waist circumference	3.95	(3.73, 4.16)	<0.001	3.98	(3.76, 4.20)	<0.001
HbA1c ≥6.0	3.41	(3.00, 3.81)	<0.001	3.33	(3.00, 3.72)	<0.001

Table 5 Model 3 (MetS Prediction Model Consisting of Gender, Father's Social Class at Birth, BMI at 7, HbA1c ≥6.0 and Low HDL-Cholesterol)

	Complete Cases			Multiple Imputation		
	Coeff.	(95% CI)	P	Coeff.	(95% CI)	P
Gender	-1.00	(1.15, -82)	<0.001	-1.00	(-1.14, -85)	<0.001
Father's social class at birth	0.28	(0.11, 0.45)	0.001	0.26	(0.11, 0.42)	0.001
BMI at 7	0.14	(0.11, 0.17)	<0.001	0.15	(0.12, 0.17)	<0.001
HbA1c ≥6.0	2.83	(2.48, 3.17)	<0.001	2.80	(2.50, 3.11)	<0.001
Low HDL-cholesterol	2.56	(2.37, 2.74)	<0.001	2.64	(2.47, 2.80)	<0.001

Table 6 Model 4 (MetS Prediction Model Consisting of Gender, Father's Social Class at Birth, BMI at 7, HbA1c ≥ 6.0 , Hypertension and Overcrowding)

	Complete Cases			Multiple Imputation		
	Coeff.	(95% CI)	P	Coeff.	(95% CI)	P
Gender	0.27	(0.10, 0.43)	0.001	0.26	(0.12, 0.40)	0.001
Father's social class at birth	0.34	(0.17, 0.52)	<0.001	0.30	(0.14, 0.46)	<0.001
BMI at 7	0.17	(0.14, 0.20)	<0.001	0.17	(0.14, 0.20)	<0.001
HbA1c ≥ 6.0	3.02	(2.64, 3.40)	<0.001	3.10	(2.78, 3.43)	<0.001
Hypertension	2.46	(2.28, 2.65)	<0.001	2.44	(2.28, 2.60)	<0.001
Overcrowding	0.26	(0.05, 0.47)	0.016	0.15	(0.07, 0.36)	0.181

Table 7 Model 5 (MetS Prediction Model Consisting of Gender, Father's Social Class at Birth, BMI at 7, Hypertension and HDL-Cholesterol)

	Complete Cases			Multiple Imputation		
	Coeff.	(95% CI)	P	Coeff.	(95% CI)	P
Gender	-0.32	(-.50, -0.13)	0.001	-0.35	(-.51, -0.19)	<0.001
Father's social class at birth	0.25	(0.06, 0.44)	0.009	0.21	(0.04, 0.38)	0.015
BMI at 7	0.19	(0.16, 0.22)	<0.001	0.19	(0.16, 0.22)	<0.001
Hypertension	3.74	(3.42, 4.06)	<0.001	3.78	(3.49, 4.07)	<0.001
Low HDL-cholesterol	4.07	(3.74, 4.40)	<0.001	4.21	(3.90, 4.51)	<0.001

Table 8 Model 6 (MetS Prediction Model Consisting of Gender, Father's Social Class at Birth, BMI at 7, HbA1c ≥ 6.0 , Hypertension, High Serum Triglycerides and Overcrowding)

	Complete Cases			Multiple Imputation		
	Coeff.	(95% CI)	P	Coeff.	(95% CI)	P
Gender	1.33	(1.11, 1.55)	<0.001	1.35	(1.16, 1.55)	<0.001
Father's social class at birth	0.20	(-0.0, 0.41)	0.054	0.18	(-0.01, 0.36)	0.063
BMI at 7	0.21	(0.17, 0.25)	<0.001	0.21	(0.18, 0.25)	<0.001
Hypertension	2.84	(2.61, 3.07)	<0.001	2.81	(2.61, 3.01)	<0.001
HbA1c ≥ 6.0	3.70	(3.19, 4.21)	<0.001	3.81	(3.37, 4.25)	<0.001
High serum triglycerides	4.14	(3.80, 4.48)	<0.001	4.16	(3.86, 4.47)	<0.001
Overcrowding	0.26	(0.01, 0.51)	0.041	0.91	(-.16, 0.34)	0.471

Table 9 Model 7 (MetS Prediction Model Consisting of Gender, Father's Social Class at Birth, BMI at 7, Hypertension and High Serum Triglycerides)

	Complete Cases			Multiple Imputation		
	Coef.	(95% CI)	P	Coef.	(95% CI)	P
Gender	1.22	(1.02, 1.43)	<0.001	1.20	(1.02, 1.39)	<0.001
Father's social class at birth	0.27	(0.07, 0.46)	0.007	0.25	(0.08, 0.43)	0.004
BMI at 7	0.21	(0.18, 0.25)	<0.001	0.22	(0.19, 0.26)	<0.001
Hypertension	2.70	(2.49, 2.92)	<0.001	2.64	(2.45, 2.82)	<0.001
High serum triglycerides	3.90	(3.56, 4.17)	<0.001	3.85	(3.58, 4.12)	<0.001

Table 10 Model 8 (MetS Prediction Model Consisting of Father's Social Class at Birth, High Waist Circumference and Hypertension)

	Complete Cases			Multiple Imputation		
	Coeff.	(95% CI)	P	Coeff.	(95% CI)	P
Father's social class at birth	0.22	(0.02, 0.41)	0.027	0.21	(0.02, 0.41)	0.031
High waist circumference	3.97	(3.76, 4.18)	<0.001	3.98	(3.78, 4.19)	<0.001
Hypertension	2.57	(2.39, 2.75)	<0.001	2.57	(2.39, 2.74)	<0.001

Table 11 Model 9 (MetS Prediction Model Consisting of Gender, Father's Social Class at Birth, Family History of T2DM and High Waist Circumference)

	Complete Cases			Multiple Imputation		
	Coeff.	(95% CI)	P	Coeff.	(95% CI)	P
Gender	-0.84	(-0.99, -0.68)	<0.001	-0.87	(-1.02, -0.73)	<0.001
Father's social class at birth	0.30	(0.12, 0.48)	0.001	0.30	(0.13, 0.47)	0.001
Family history of T2DM	-0.63	(-1.09, -0.18)	0.007	0.55	(0.11, 0.98)	0.013
High waist circumference	3.77	(3.56, 3.97)	<0.001	3.84	(3.65, 4.04)	<0.001

Table 12 Model 10 (MetS Prediction Model Consisting of Gender, BMI at 23 and High Waist Circumference)

	Complete Cases			Multiple Imputation		
	Coeff.	(95% CI)	P	Coeff.	(95% CI)	P
Gender	-0.74	(-0.90, -0.58)	<0.001	-0.81	(0.95, -0.65)	<0.001
BMI at 23	0.07	(0.04, 0.09)	<0.001	0.07	(0.05, 0.10)	<0.001
High waist circumference	3.73	(3.51, 3.95)	<0.001	3.67	(3.47, 3.88)	<0.001

Selecting the Model with the Most Potentials to Be Useful

The pragmatic model selection criteria discussed earlier was applied to all the ten (10) models developed. Briefly, a model is selected if it is *accurate* (has discrimination above 0.70 and statistically significant calibration), *simple to use* (contains few predictors that may not be difficult to obtain in a routine clinical setting). In addition to the above, the model should contain no more than 2 adult predictors. Finally, the model should contain predictors that can improve equity in the prevention of MetS.³⁴

Based on the above, the Model 7 (MetS prediction model consisting of gender, father's social class at birth, BMI at 7 years, hypertension and high serum triglycerides) was selected. The model is accurate as it has excellent discrimination 0.91 (0.90, 0.92) and is well calibrated (Hosmer-Lemeshow 6.47, P 0.595). Similarly, Model 7 is relatively simple to use as it is composed of five (5) predictors that may not be difficult to obtain in routine practice. Finally, the model has two (2) predictors (father's social class at birth and BMI at 7) which could be used to address issues of equity in the wider prevention of MetS.

Adjusting for Potential Confounders

Table 14 shows the selected model (model 7) adjusted for potential confounders. Confounders were adjusted for sequentially, starting from those measured around birth (early life). All the predictors remained significant even after the adjustment except father's social class at birth which became less significant after the adjustments. However, the overall model remained significant and reported performance similar to the unadjusted model (see Figure 11).

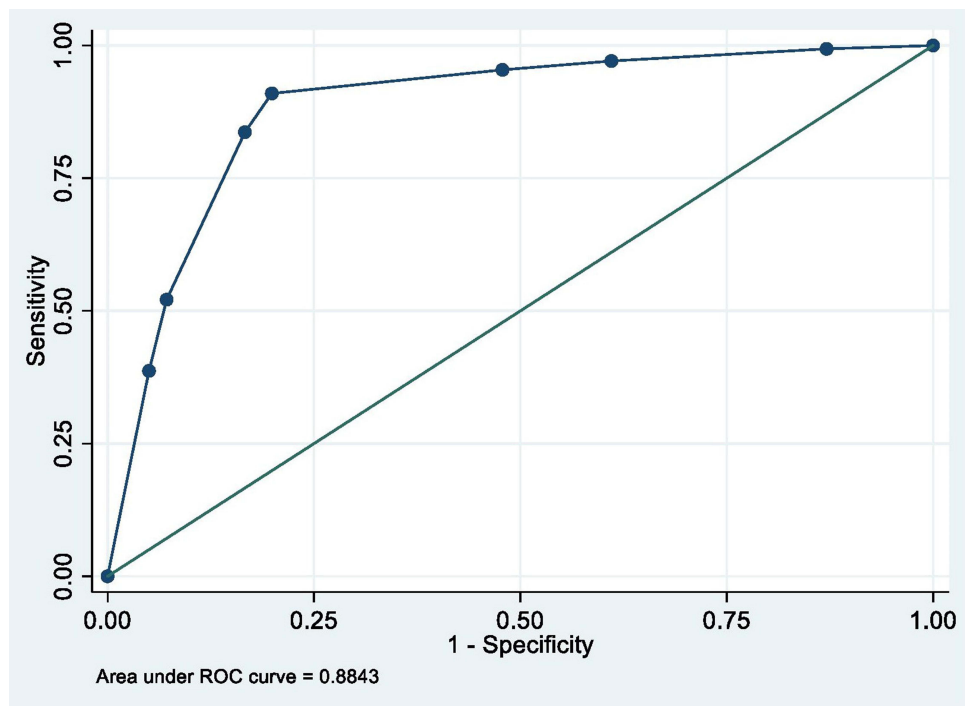


Figure 1 ROC curve of Model 1 (MetS prediction model consisting of gender, father's social class at birth and high waist circumference).

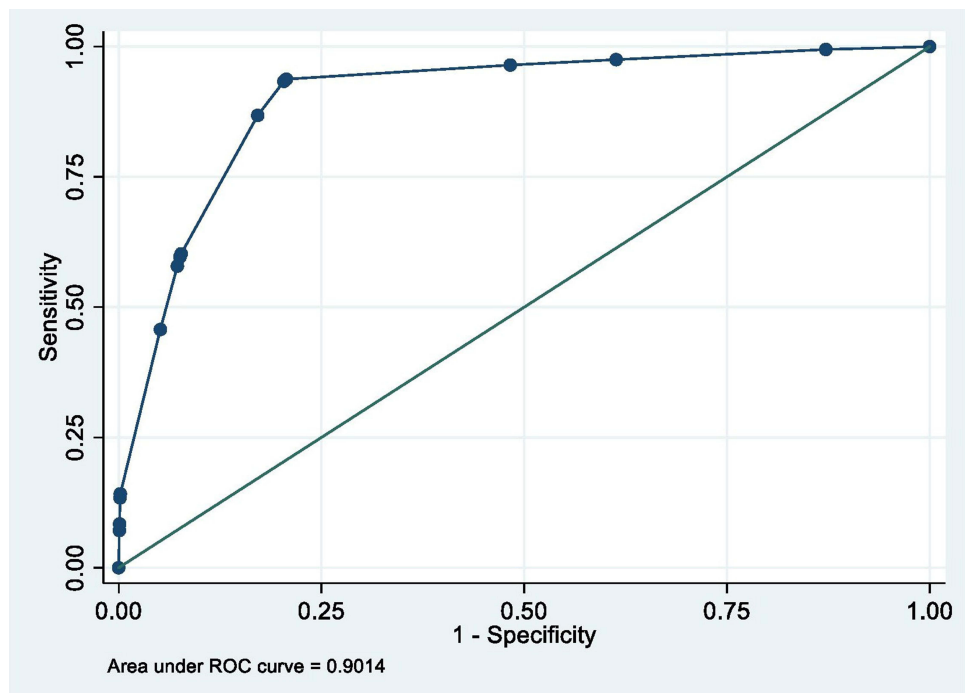


Figure 2 ROC curve of model 2 (MetS prediction model consisting of gender, father's social class at birth, high waist circumference and HbA1c ≥ 6.0).

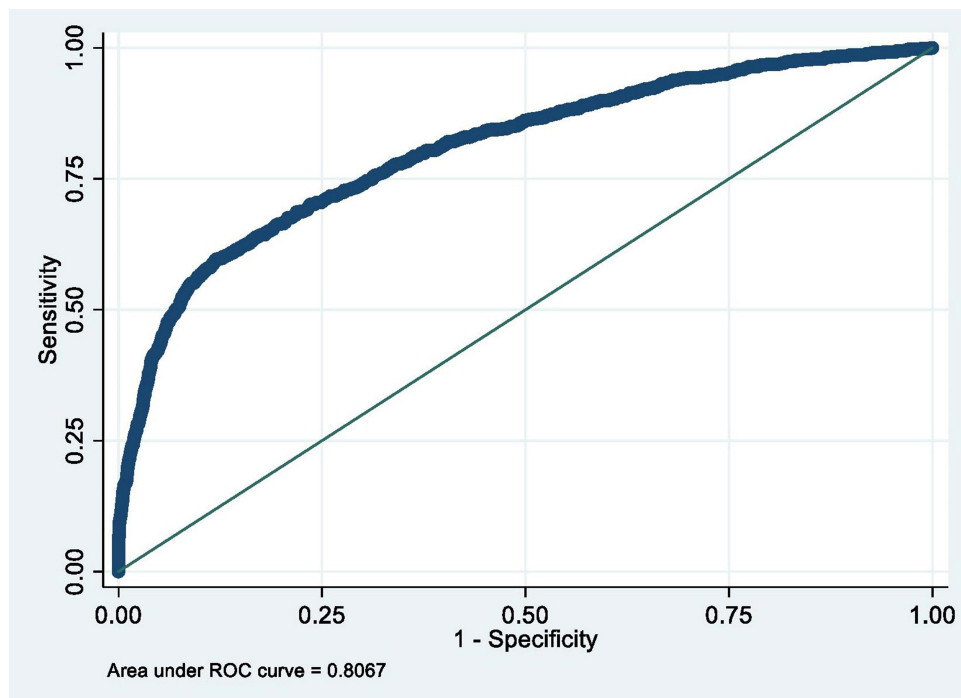


Figure 3 ROC curve of Model 3 (MetS prediction model consisting of gender, father's social class at birth, BMI at 7, HbA1c ≥ 6.0 and low HDL-cholesterol).

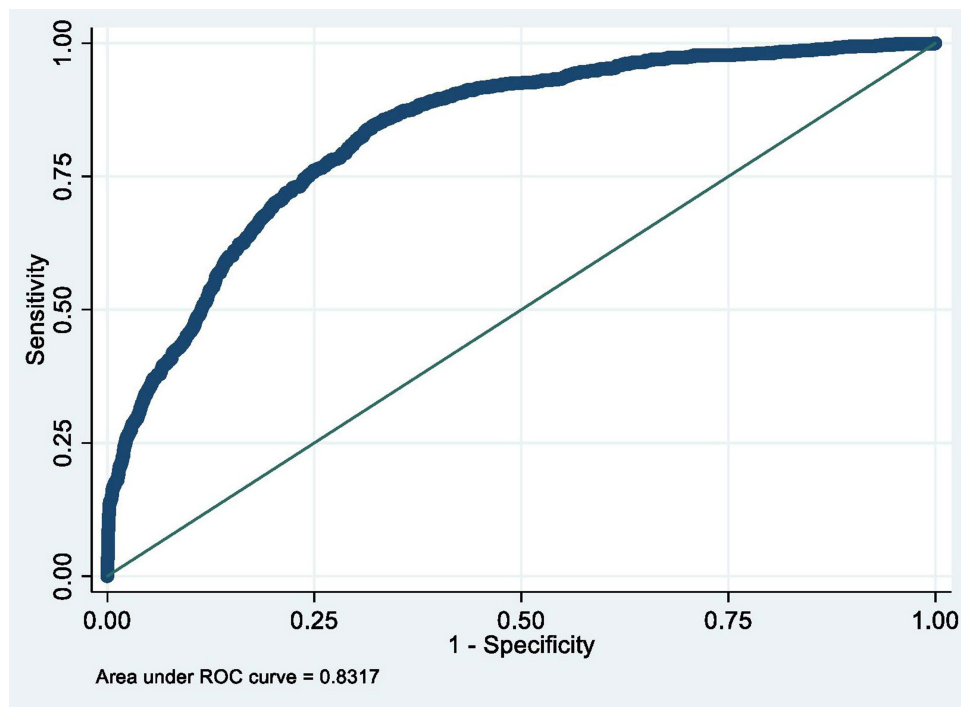


Figure 4 ROC curve of Model 4 (MetS prediction model consisting of gender, father's social class at birth, BMI at 7, HbA1c ≥ 6.0 , hypertension and overcrowding).

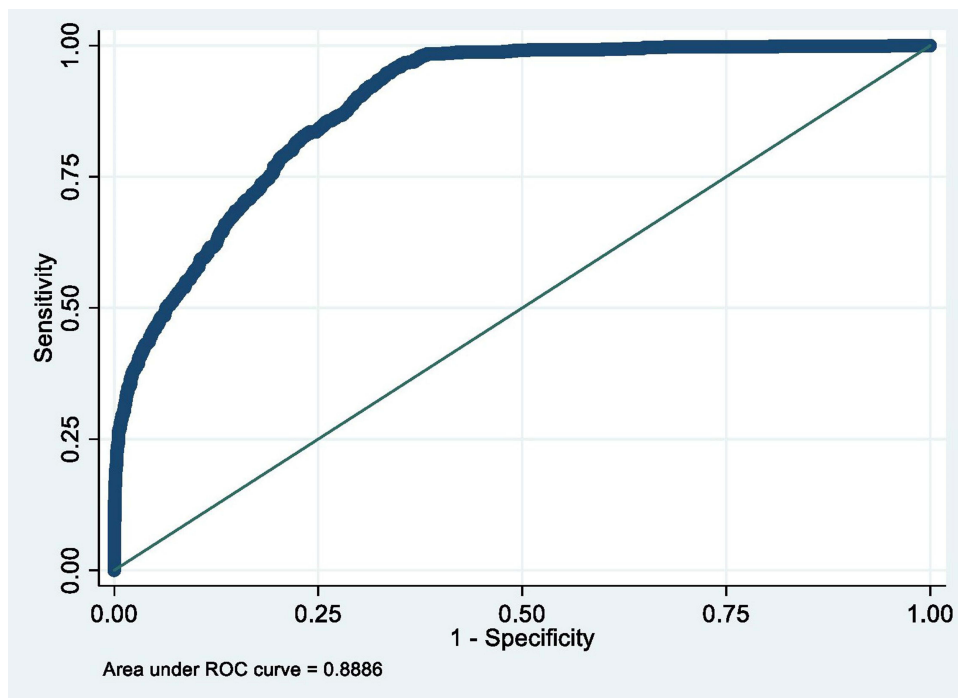


Figure 5 ROC curve of Model 5 (MetS prediction model consisting of gender, father's social class at birth, BMI at 7 and hypertension).

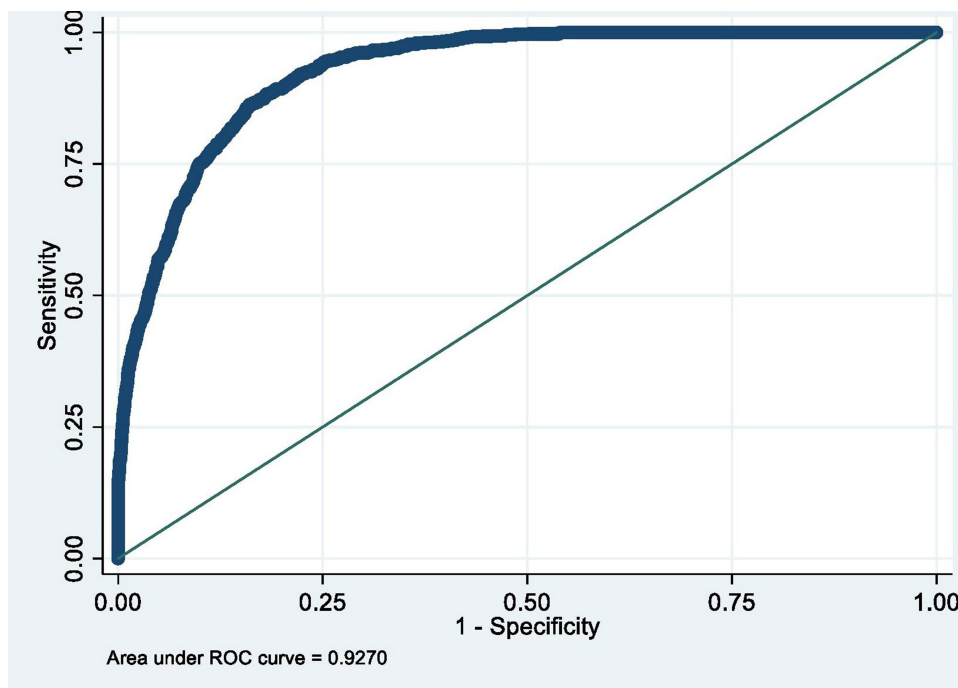


Figure 6 ROC curve of Model 6 (MetS prediction model consisting of gender, father's social class at birth, BMI at 7, HbA1c ≥ 6.0 , hypertension, high serum triglycerides and overcrowding).

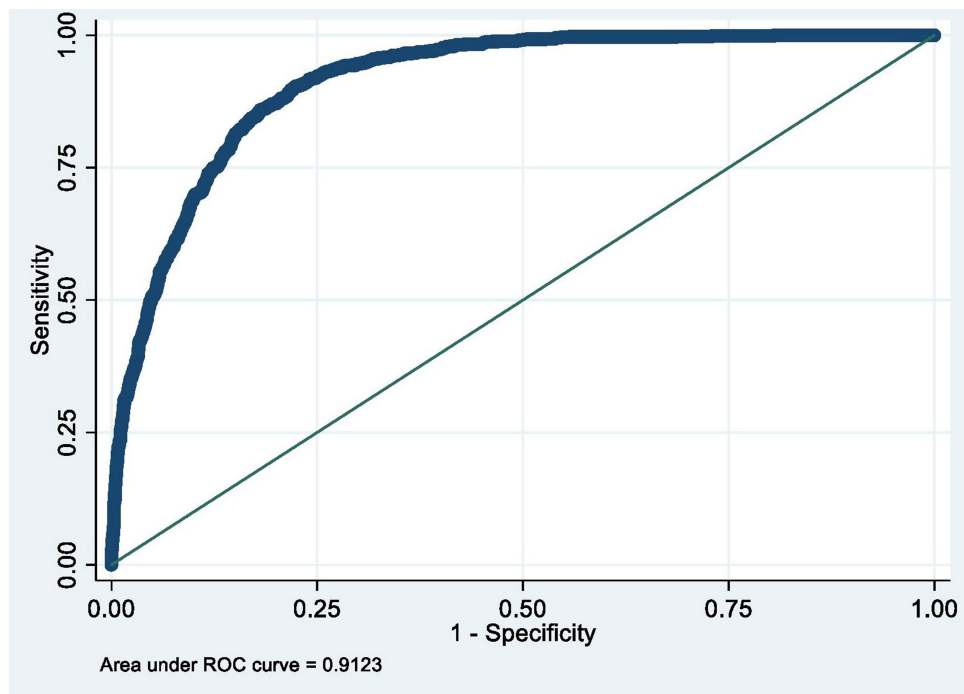


Figure 7 ROC curve of Model 7 (MetS prediction model consisting of gender, father's social class at birth, BMI at 7, hypertension and high serum triglycerides).

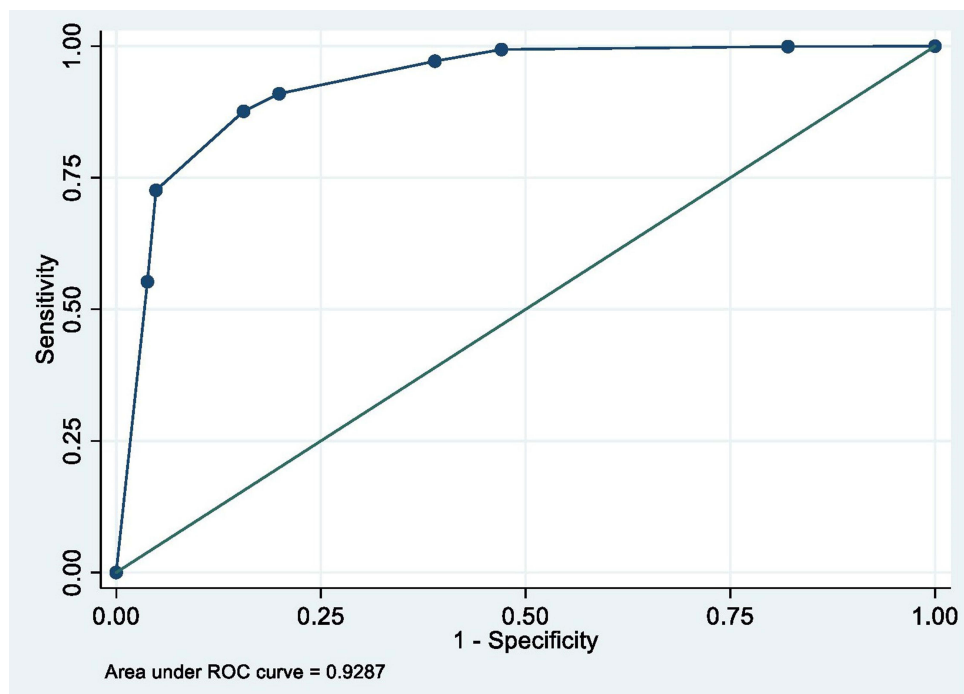


Figure 8 ROC curve of Model 8 (MetS prediction model consisting of father's social class at birth, high waist circumference and hypertension).

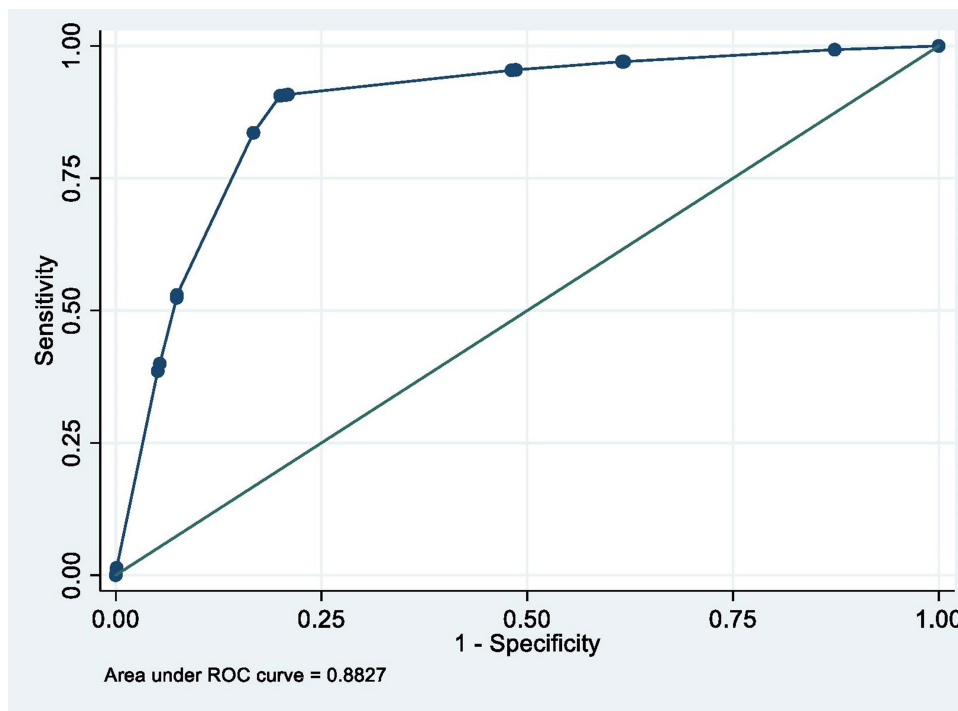


Figure 9 ROC curve of Model 9 (MetS prediction model consisting of gender, father's social class at birth, family history of T2DM and high waist circumference).

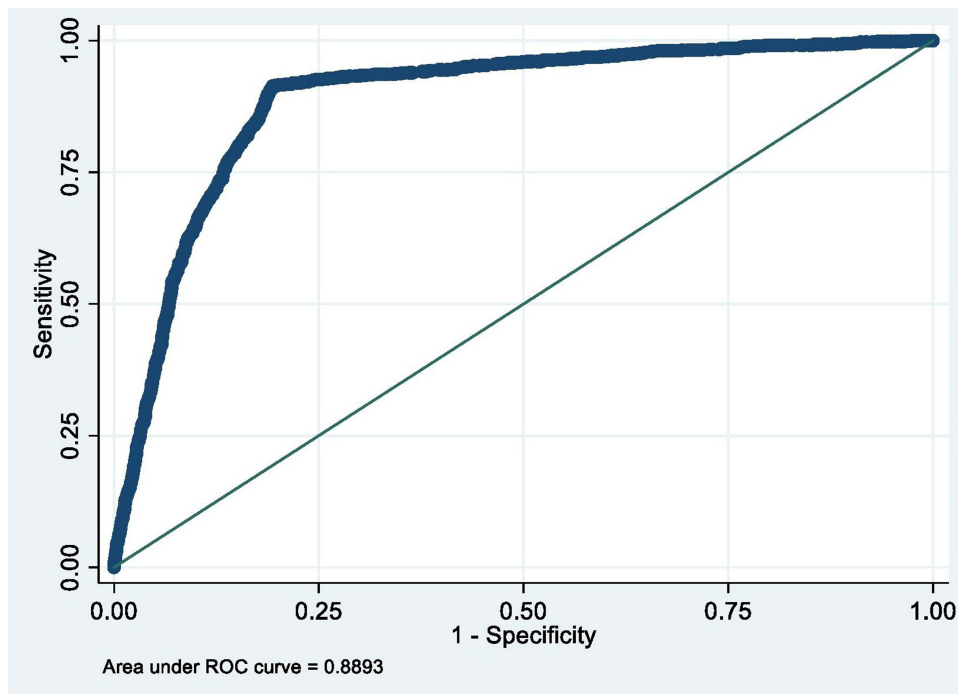


Figure 10 ROC curve of Model 10 (MetS prediction model consisting of gender, BMI at 23 and high waist circumference).

Table 13 Summary of the Performance Parameters of the Ten (10) MetS Models Developed

Model	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	AUROC (95% CI)	(Hosmer-Lemeshow) (P)
Model 1	52.12	92.85	63.99	88.83	0.88 (0.87, 0.89)	2.17 (0.825)
Model 2	57.89	92.77	66.11	90.03	0.90 (0.89, 0.91)	10.36 (0.066)
Model 3	41.27	95.63	69.86	86.91	0.81 (0.79, 0.82)	7.28 (0.507)
Model 4	25.64	97.73	73.55	84.23	0.83 (0.82, 0.84)	20.32 (0.010)
Model 5	35.27	98.05	81.58	86.07	0.89 (0.88, 0.90)	6.80 (0.559)
Model 6	57.12	94.92	73.42	90.00	0.93 (0.92, 0.93)	6.83 (0.555)
Model 7	57.11	93.24	67.44	89.86	0.91 (0.90, 0.92)	6.47 (0.595)
Model 8	72.62	95.14	78.45	93.44	0.93 (0.92, 0.94)	10.25 (0.036)
Model 9	52.95	92.56	63.35	89.01	0.88 (0.87, 0.89)	1.83 (0.935)
Model 10	57.99	91.76	62.92	90.05	0.89 (0.88, 0.90)	10.42 (0.237)

Table 14 Selected Model (Model 7) Adjusted for Confounders

	Model A	Model B	Model C
Gender	1.222***	1.263***	1.063***
Father's social class at birth	0.265**	0.202	-0.0102
BMI at 7	0.217***	0.221***	0.179***
Hypertension	2.705***	2.669***	2.689***
High serum triglycerides	3.865***	3.791***	3.959***
Mother's age at birth		-0.118**	-0.00551
Mother smoked during pregnancy		0.0249	0.0321
Parity		-0.0554	0.0697
Foetal distress		0.206	0.0540
Breastfed		-0.106*	-0.118
Smoking at 45			0.154
BMI at 45			0.0424
Alcohol consumption at 45			-0.0685
Physical activity at 45			0.0429

Notes: Model A: basic model. Model B: adjusting for early life confounders. Model C: adjusting for all confounders. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Internal Validity of the Selected Model (Model 7)

Table 15 shows the selected model (Model 7) applied on a random bootstrap sample. From the table, there is a slight variation between the coefficients and the respective 95% CI. However, the level of significance remained similar except for father's social class at birth which increased from 0.004 to 0.010.

Furthermore, the performance of the selected model (Model 7) applied on the bootstrap sample was assessed using ROC analyses and Hosmer-Lemeshow test. The findings did not differ significantly with those observed earlier on the main development data (see Table 16 and Figure 12). Therefore, the model is less likely to be overfitted to the developing data.

Model Equation

The equation for the developed model (Model 7) is provided below:

$$\text{Logit} = -10.44 + 1.22 \times \text{Gender}(\text{female}) + 0.27 \times \text{Father's social class at birth} \\ (\text{Manual}) + 0.22 \times \text{BMI at 7}(\text{kg/m}^2) + 2.71 \times \text{Hypertension}(\text{mmHg}) + 3.87 \times \text{High serum} \\ \text{triglycerides}(\text{mg/dL}) \quad (1.0)$$

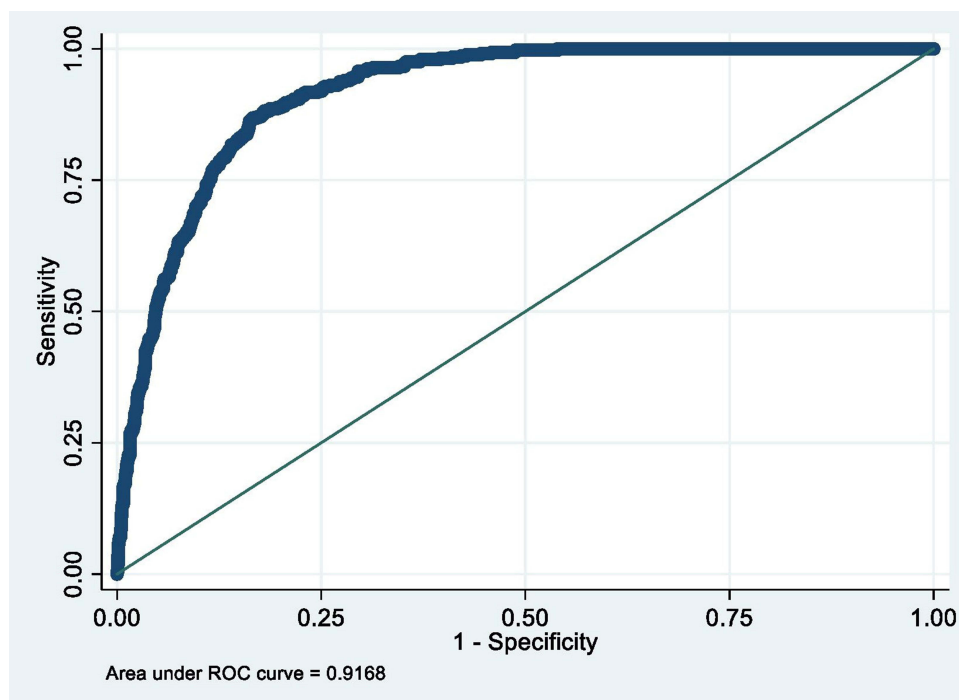


Figure 11 ROC of selected model after controlling for possible confounders.

Discussion

Main Findings

This analysis revealed that the prevalence of MetS in midlife is high, with males having higher risk as compared to females. Individuals with MetS are more likely to have higher levels of HbA1c and low HDL-cholesterol. Similarly, regarding the individual components of MetS, male cohort members are more likely to have higher levels of glycaemia (HbA1c), BP and serum triglycerides. In contrast, female cohort members have lower levels of HDL-cholesterol and higher levels of waist circumference. Furthermore, a total of ten (10) MetS risk prediction models were developed taking the life course approach. Out of these, one model (with most potential to be applied in practical setting) was selected after using the pragmatic criteria developed. The model has been shown to have good accuracy, is well calibrated and is free from overfitting (has good internal validity).

The prevalence of MetS is high and rising globally. The estimated global prevalence of MetS is nearly twenty-five per cent of the worldwide adult population.² Prevalence differs between countries, ethnicities, age groups and gender.^{2,35} A rough divide is observed between the more developed countries and developing countries with developed ones having a higher prevalence^{12,36,37} though this is not always the case.^{38,39} In this analysis, nearly one in five individuals have MetS. Although this is lower than the global average, it is in keeping with what was previously published.^{20,40–44}

A possible explanation of why the prevalence of MetS in this study is lower than the estimated global average could be due to the difference in the studied samples. The 1958 British birth cohort is 43/45 years old at the time of the

Table 15 Selected Model (Model 7) Applied on a Random Bootstrap Sample

	Coeff.	Bootstrap Standard Error	95% CI	P
Gender	1.22	0.11	(1.01, 1.43)	<0.001
Father's social class at birth	0.27	0.10	(0.06, 0.47)	0.010
BMI at 7	0.22	0.02	(0.18, 0.25)	<0.001
Hypertension	2.71	0.11	(2.50, 2.91)	<0.001
High serum triglycerides	3.90	0.15	(3.56, 4.17)	<0.001

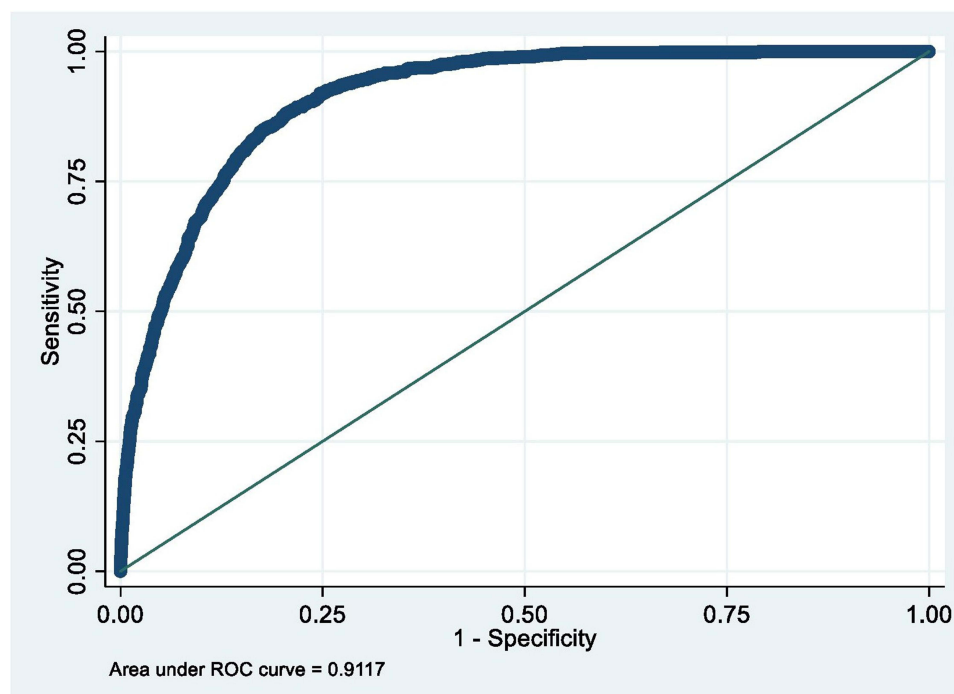
Table 16 Summary Performance of the Selected Model (Model 7) Applied on a Random Bootstrap Sample

Model	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	AUROC (95% CI)	(Hosmer-Lemeshow) (P)
Selected Model (Model 7)	57.11	93.24	67.44	89.86	0.91 (0.90, 0.92)	6.47 (0.595)

biomedical survey. Therefore, this study utilised relatively young individuals who are below the peak age of MetS prevalence.⁴⁵ However, recent studies are showing a rise in the prevalence of MetS in younger individuals.^{2,46} Similarly, this observed difference could be due to the criteria used in defining MetS (the NCEP-ATP III criteria). Certain criteria of MetS such as IDF are known to exaggerate the prevalence of MetS in some populations.^{2,46,47}

The overall aim of developing a risk prediction model is not just for it to be statistically significant, but, for it to work when applied in practice. For this to be achieved, it has to be accurate, generalisable and effective.³⁰ Clinical credibility of model focuses not only on the statistical significance of the constituent predictors, but, also on their clinical relevance, how easy they are to obtain, and the overall simplicity of the model.³⁰ Therefore, careful selection of predictors is necessary. The predictors used in this study are determined a priori from the literature. In addition, their clinical/ public health relevance and significance to the understanding of the life course origin of MetS was also considered. This is based on recommendations by experts in the field.⁴⁸⁻⁵⁰ However, this approach is not very popular in previous MetS studies. Therefore, in order for the MetS prediction discipline to progress to the next level, methods of predictor selection need to be improved by researchers. One of the ways this can be achieved is through collaboration between clinicians and statisticians to ensure predictors are included based on expert knowledge (literature) and clinical significance.^{48,49}

This analysis has shown that early life circumstances could have a significant effect on the individual's risk of MetS later in life. Also, it has revealed how these factors can be included in a risk model to predict MetS in midlife. A similar approach has been used in developing a popular CVD risk score (ASSIGN score).³⁴ This is an important finding because it highlights the relevance of wider determinants of health⁵¹ as a significant contributor to the rising burden of obesity and subsequent MetS.⁵² Therefore, for any genuine intervention aimed at MetS prevention to be successful, it needs to be

**Figure 12** ROC curve of selected model applied on a random bootstrap sample.

holistic and systematically address these factors at every stage of life.¹³ Indeed, for any intervention targeting one determinant of health to be effective, it has to address all the other determinants.⁵³

Discrimination is a statistical measure used in prediction models to distinguish individuals who will develop the outcome from those who will not.²⁸ The models developed in this analysis are well discriminated with AUROC ranging from 0.83 to 0.93; and the one selected having AUROC of 0.91 (95% CI 0.90, 0.92). Good discrimination is a common finding across the studies of MetS prediction models.^{20,36,54–60} Similarly, the models in this study have a relatively modest sensitivity. This is in keeping with what was reported in similar studies from Taiwan and Australia.^{61,62} On the contrary, other studies reported higher levels of sensitivity.^{20,54,55,57,59} The observed low sensitivity of the models could be due to the relatively low prevalence of MetS in the sample. It is well known that the prevalence of a disease has a direct relationship with the sensitivity of a prediction test.⁶¹ However, the sensitivity of a model is hardly used alone when deciding the diagnostic power of a model. Rather, it is determined by both sensitivity, specificity and the trade-off between them (AUROC).²⁸

Calibration assesses whether those categorised as having the outcome truly have it.²⁸ The Hosmer-Lemeshow test was used to assess calibration in this study. Majority (70%) of the models in this study are well calibrated. Also, the selected model is well calibrated. This is in keeping with what is obtained from previous studies of MetS.^{59,63} Noteworthy, most previous studies of MetS prediction models do not report calibration. Not reporting any measure of calibration is also a common problem across most NCD prediction studies.^{49,64–68}

Overfitting is one of the commonest flaws encountered in prediction model studies.^{50,69,70} Models often perform best in the data in which they are developed; thereby leading to an exaggeration of the findings.^{48–50} Furthermore, overfitting leads to models that cannot be applied beyond the sample which they are developed on.^{48–50} Bootstrapping was conducted on the model developed in this analysis to assess stability and overfitting. The findings remained significant, and no much difference was observed from the original model, indicating a good fit. However, the best way to assess overfitting is to apply the model on an entirely different sample from the one it is developed.⁷⁰ Therefore, this model will benefit from an external validation study.

Strengths and Weaknesses of the Analysis

One of the major strengths of this analysis is that variable selection, solely based on statistical significance, was avoided. The predictors are determined based on the literature, clinical/ public health relevance and importance to the understanding of the life course origin of MetS.^{48–50} The bootstrapping conducted to assess for stability and overfitting is another strength of this analysis.

However, this analysis has a number of limitations which should be considered. One of the methodological limitations of this analysis is the dichotomisation of variables. Majority of the variables used in this analysis are dichotomised. This could lead to a significant loss of information and statistical power to observe real associations.⁷⁰ However, dichotomisation is conducted in order to conform to the criteria used to define MetS (NCEP –ATP III),¹ which is binary in nature. Furthermore, the majority of the previous studies of MetS prediction used dichotomisation. Nevertheless, this could be improved in the future by not dichotomizing (retaining variables as continuous where necessary).

More so, the original NCEP-ATPIII criteria has been modified in this analysis in order to address the limitations of the cohort data. Hyperglycemia was defined as HbA1c $\geq 6.0\%$ because (FPG) was not collected in the data during the biomedical survey. Previous studies have used HbA1c as a marker of glycaemia.^{21,22} Also, due to limited information, individuals treated for high cholesterol, hypertension, or T2DM were not accounted for (not included) in the definition of MetS. Therefore, the definition of NCEP-ATP III criteria used in this analysis is a conservative one.

Although this analysis is conducted taking the life course approach, no attempt was made to establish the potential pathways through which MetS develops. This is beyond the scope of the study. Instead, the existing evidence was utilised and deemed sufficient in this regards. Furthermore, there is a possibility that some important variables, such as mother's BMI before pregnancy¹² may have been missed out in this analysis. The BMI pathway, especially through mother's BMI, is one of the currently held assumptions through which MetS is transmitted from parents to their offsprings.^{12,71} In the available dataset, the variable "maternal pre-pregnancy weight" is presented as grouped data. This makes it impossible to derive the individual mother's weight and subsequently compute the BMI.

Another limitation of this analysis is that only the father's social class at birth (occupation in 1958) was used in categorizing childhood socioeconomic position. A better approach would be to include the mother's social class at birth, compare the two and then select the one which is higher. The NCDS data lacks detailed information about the mother's social class at birth (occupation in 1958). However, father's social class has been used successfully in the past to denote childhood socioeconomic position in previous studies that used the NCDS data.¹²

The stepwise technique was used to build models in this study. Certain variables that fit well may have been missed by this technique.^{31,50} Also, the technique is criticised as it is prone to overfitting and overestimation of findings.^{50,72–74} However, several steps were taken to minimize the likelihood of overfitting/ overestimation in this analysis. Indeed, the biggest limitation of the stepwise technique is that of sample size; they tend to produce overfitted and spurious models if there are fewer data per variable. However, a large sample with an adequate event per variable is used in this analysis. Additionally, variables selection solely based on statistical significance was avoided. Finally, bootstrapping was conducted to test for internal validity/ overfitting, and no significant variations were observed between the findings. Nevertheless, the model developed will benefit from external validation study to assess whether its findings can be generalisable.

Missing data resulting from cohort attrition is among the major limitations of this study. Although this is partly addressed by the application of multiple imputations in the models. However, the application of multiple imputation relies on the assumption that the data is MAR (the missingness is dependent on the observed data but not the unobserved data), which is a hardly verifiable assumption. Therefore, there is a possibility that some of the data are MNAR. Including a large number of covariates in the multiple imputation is one way of limiting the impact of MNAR and thereby making the MAR assumption more credible.^{75,76} Also, age and socioeconomic status have been recognised as the leading causes of attrition in UK studies.^{77,78} In that regards, significant causes of missingness like socioeconomic status, demographic characteristics and behavioural/lifestyle variables were included in the multiple imputation conducted in this study. By so doing, it is assumed that any other unaccounted variable that is missing is MAR, since the known major causes of missingness have been accounted for. Moreover, no significant difference was observed between the results of this study (both complete cases and multiple imputation) when sensitivity analysis was conducted.

Another limitation of this study is the lack of representativeness of the sample, especially concerning ethnicity. The 1958 British birth cohort is predominantly white, which is a representation of the UK population in the 1950s. However, the contemporary UK population is ethnically diverse. More so, certain components of the MetS, such as waist circumference differ significantly between ethnicities.^{79,80} Therefore, the findings of this study in its current state might not be generalisable to the whole UK population. Similarly, the cohort members are relatively young (45 years) at the time the biomedical survey was conducted. This is below the peak age of MetS prevalence.⁴⁵ However, recent studies are showing a rise in the prevalence of MetS in younger individuals.^{2,46} Yet, caution should be applied while extrapolating the findings of this study to an older population.

Conclusion

We developed and validated a simple MetS risk prediction model in this study. The prevalence of MetS was observed to be high; approximately one in five participants has MetS with males being more at risk. Taking life course approach, it is possible to include early life factors to predict MetS in midlife. The developed model has been shown to be accurate and has good internal validity. Therefore, interventions targeting socioeconomic inequality could help in the wider prevention of MetS. However, the validity of the developed model needs to be further established in an external population.

Disclosure

The authors report no conflicts of interest in this work.

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