Visceral Fat Area and Cardiometabolic Risk: The Kardiovize Study.

Running Title: Visceral Fat and Cardiometabolic Risk

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Abstract.

Background: Visceral fat is associated with adiposity-based cardiometabolic complications and may complement predictive assessment by body mass index. The standard method to measure visceral fat is computed tomography, but bioimpedance measurement allows estimation of visceral fat area (VFA) in an easy and low-cost manner. However, a validated cut-off value for VFA by bioimpedance that is associated with elevated cardiometabolic risk is lacking.

Aim: To determine cut-off values of VFA measured via bioimpedance that are associated with increased cardiometabolic risk in a specific European population.

Methods: Data on 25-64 years old subjects from a random cross-sectional Czech population-based sample from 2013-2014. Bioimpedance measurements for VFA were determined using InBody 370. Sex based Receiver Operating Characteristic (ROC) curves were used and the area under the curve (AUC), sensitivity, and specificity were calculated to determine the best cut-off values of VFA associated with cardiometabolic risk. The Cardiometabolic Disease Staging System (CMDS) was used to classify cardiometabolic risk: Stage 1 – one or two metabolic syndrome (MetS) components, without impaired fasting glucose (IFG); Stage 2 – MetS or IFG; Stage 3 – MetS with IFG; and Stage 4 – type 2 diabetes and/or cardiovascular disease.

Results: 2052 participants, (54.5 % females, median age 49 years) were included. Median VFA (inter-quartile range) were 82.2 cm^2 (54.8) in men and 89.8 cm^2 (55.6) in women. In men and women, the AUCs were Stage 1: 0.509 (p=0.652) and 0.624 (p<0.001); Stage 2: 0.628 (p<0.001) and 0.715 (p<0.001); Stage 3: 0.780 (p<0.001) and 0.788 (p<0.001); Stage 4: 0.647 (p<0.001) and 0.572 (p=0.002), respectively.The best VFA cut-offs associated with CMDS Stage 1 in men and women were 71 cm^2 (sensitivity=0.654; specificity=0.427) and 83 cm^2 (sensitivity=0.705; specificity=0.556); Stage 2: 84 cm^2 (sensitivity=0.673; specificity=0.551) and 98 cm^2 (sensitivity=0.702; specificity=0.628); Stage 3: 90 cm^2 (sensitivity=0.886; specificity=0.605) and 109 cm^2 (sensitivity=0.755; specificity=0.704); Stage 4: 91 cm^2 (sensitivity=0.625; specificity=0.611) and 81cm^2 (sensitivity=0.695; specificity=0.448), respectively.

Conclusion: VFA is directly proportional to cardiometabolic risk. A cut-off value of VFA of 71 cm^2 in men and 83 cm^2 in women exhibited the earliest stage of cardiometabolic risk and the values of 90 cm^2 in men and 109 cm^2 in women showed the best sensitivity and specificity to detect subjects with CMDS. Prospective studies are required to assess the predictive value of these cut-offs and efficacy with VFA-guided prevention.

Introduction.

Body fat distribution is closely related to adiposity-based cardiometabolic complications including dyslipidaemia, insulin resistance, dysglycaemia, endothelial dysfunction, and elevated blood pressure,[1] and is considered a more sensitive marker to detect cardiometabolic risk than other anthropometric indicators, such as body mass index (BMI).[2-4] Computed tomography (CT) is the gold standard method to measure visceral fat area (VFA),[5] but this method is relatively expensive and exposes individuals to radiation. Bioelectrical impedance analysis (BIA) is an advantageous method to detect VFA due to its simplicity, quickness, low cost, high reliability, reproducibility, and non-invasiveness.[5] Measurement of VFA using BIA shows strong and positive correlations with values measured by CT.[6-9]

High amounts of visceral fat determined by VFA confers increased risk for adiposity-based complications.[10] To define high and normal values of VFA, multiple cut-offs have been determined using CT measurement, ranging from 82 cm^2 to 140 cm^2, with variations according to gender, ethnicity, and criteria used to define the thresholds of cardiometabolic risk.[11-16] The purpose of this study is to determine VFA cut-offs using BIA in both genders in a European population with direct correlation to a validated cardiometabolic staging system based on risk. The data were analysed from the Kardiovize study, a population-based evaluation of a representative sample of adults in Brno, Czech Republic. The Cardiometabolic Disease Staging System (CMDS)[17] was used to classify cardiometabolic risk.

Methods.

Design and population.

The Kardiovize study is a cross-sectional population-based study, evaluating health of adult population in Brno, the second-largest city in the Czech Republic, with 373,327 residents.[18]

Sampling and Recruitment.

Survey sampling was done in January 2013 with technical assistance from the health insurance companies. A random age – and sex-stratified sample of 6377 permanent residents from Brno aged 25-64 years s was selected and health insurance companies mailed invitation letters to selected individuals with a description of the study ensuring confidentiality., The overall

achieved response rate was 33.9%. No information on non-respondents was available.[18] For

this analysis, subjects with type 1 diabetes or missing information were excluded (see Figure 1

for flow chart describing study analytical sample).

Data Collection.

Face-to-face health interviews were performed by trained nurses and physicians masked

to study hypothesis at the International Clinical Research Center (ICRC) of the St Anne's

University Hospital (FNUSA) in Brno, using the web-based research electronic data capture

(REDCap).[19] The questionnaire included demographics, socioeconomic status, cardiovascular

risk behaviours, smoking status, medical history, and mental health. Laboratory analyses were

performed on 12-hour fasting whole blood samples using a Modular SWA P800 analyser

(Roche, Basel, Switzerland), total cholesterol, triglycerides, glucose, and creatinine were

analysed by the enzymatic colorimetric method (Roche Diagnostics GmbH, Mannheim,

Germany), high-density lipoprotein cholesterol (HDL-c) was analysed with the homogeneous

method for direct measurement without precipitation (Sekisui Medical, Hachimantai, Japan).

Urinary albumin was analysed by immunoturbidimetry (Roche Diagnostics GmbH, Mannheim,

Germany) in a punctual morning urine sample, and the urinary albumin/creatinine ratio was

calculated. Blood pressure was measured with the patient alone using an automated office

measurement device (BpTRU, model BPM 200; Bp TRU Medical Devices Ltd., Canada).

Anthropometric assessment included height, weight, and waist circumference. Weight and body

composition analyses were performed using a scale with bioelectrical impedance analysis

capabilities (InBody 370; BIOSPACE Co., Ltd., Korea). The ankle-brachial index (ABI) was

calculated as the ratio of the highest registered measurements of the ankle and brachial blood

pressures. Ankle and brachial pressures were measured with patients lying in the supine

position. ABI was measured using VaSera VS-1500N devise (Fukuda Denshi Co., Ltd., Japan).

To measure intima-media thickness (IMT) ultrasound measurements were obtained with the

ESAOTE MyLabClassC ultrasound (ESAOTE S.p.A, Genova, Italy) using the LA523 4-13MHz

linear transducer. Both left and right common carotid arteries were measured at 1 cm proximal

to their bifurcation. Evaluation of the IMT was performed by semi-automated ESAOTE

MyLabClassC software using patented methods of analysing RF data from the B-mode

images.[18]

Variables definition.

Cardiometabolic risk was defined according to the Cardiometabolic Disease Staging System (CMDS)[17](Supplementary Table 1). Cardiometabolic risk factors were as follows: (1) abnormal adiposity distribution defined as increased abdominal obesity by waist circumference ≥ 94 cm in men and ≥ 80 cm in women for European population[20]; (2) increased blood pressure defined as systolic blood pressure ≥ 130mmHg and/or diastolic blood pressure ≥85 mmHg or on antihypertensive medication; (3) low HDL-c defined as HDL-c <1.0 mmol/L in men and <1.3 mmol/L in woman; (4) high triglycerides defined as triglycerides ≥1.7 mmol/l or on medication. Study subjects were classified according to the presence of cardiometabolic risk factors as Stage 0 when no presence of metabolic syndrome components were identifiable; Stage 1 when one or two of the risk factors were present, Stage 2 when three of the risk factors were present or with the presence of prediabetes defined as a fasting glucose between 5.6 to 6.9 mmol/L; Stage 3 when metabolic syndrome and prediabetes were present; Stage 4 when subject had diagnosed type 2 diabetes (T2D) and/or vascular disease. T2D was defined as self-report of T2D or fasting glucose ≥ 7 mmol/L or on anti-diabetic therapy. Vascular disease was defined as the presence of any of the following: (1) self-report of ischemic heart disease, stroke, or claudication; (2) presence of peripheral artery disease, defined as those subjects with an ankle-brachial index <0.9; (3) carotid IMT thickness increased, defined as those subjects with 0.9mm or more of the maximum measured value of IMT on both carotids; (4) chronic kidney disease, defined as those with a glomerular filtration rate (GFR) < 60 ml/min/173m2; (5) microalbuminuria defined as albumin-to-creatinine ratio (ACR) between 30 to 300 (μg albumin/mg creatinine) and macroalbuminuria as ACR > 300 (μg albumin/mg creatinine).[21]

Ethics Approval.

Study protocol complied with the Helsinki declaration and all participants signed the informed consent. The Kardiovize was approved by the ethics committee of St Anne's University Hospital, Brno, Czech Republic.

Statistical analysis.

Analyses were performed using the SPSS software (SPSS, version 23.0, Armonk, NY: IBM Corp.). The normality of continuous variables was assessed using Kolmogorov-Smirnov

test. As the data were not normally distributed, median and Mann Whitney test were used to evaluate sex differences in continuous variables. Proportions were presented as percentages and Pearson Chi-square test were used for evaluation of sex differences in categorical variables. Spearman correlation analysis between VFA and other variables was performed. The area under the curve (AUC) of the Receiver Operating Characteristic (ROC) Curves were used. AUC was assessed to evaluate the performance of VFA to detect cardiometabolic complications. The values of sensitivity, representing true positive rate, and specificity representing true negative rate were calculated. The highest value of the sum of sensitivity plus specificity, in favour of sensitivity, was used to determine the cut-off values to detect CMDS.

Results.

Subject Characteristics

In total, 2052 participants were included in the analytical sample and 54.5% were women (Figure 1), the median (IQR) age was 49.0 (20) years, and the median (IQR) VFA was 86.6 (55.4) cm^2. Waist circumference, blood pressure, triglycerides, blood glucose, prevalence of T2D, and vascular diseases were higher in men than in women; VFA and HDL-c were higher in women than in men (Table 1).

Visceral Fat Area and Biological Risk Factors

VFA was significantly and positively correlated to age (r=0.294 in men and r=0.404 in women; p<0.001), waist circumference (r=0.872 in men and r=0.886 in women; p<0.001), systolic blood pressure (r=0.365 in men and r=0.0.391 in women; p<0.001), diastolic blood pressure (r=0.364 in men and r=0.300 in women; p<0.001), triglycerides (r=0.349 in men and r=0.383 in women; p<0.001), and fasting blood glucose (r=0.270 in men and r=0.305 in women; p<0.001), and negatively correlated to HDL-c (r=-0.348 in men and r=-0.311 in women, p<0.001) (Figure 2).

Visceral Fat Area and the Cardiometabolic Disease Staging System

The prevalence of CMDS were 24.2% Stage 0, 40.3% Stage 1, 12.6% Stage 2, 6.4% Stage 3, and 16.4% Stage 4 (Figure 3). The prevalence of Stage 0 and 1 were higher in women, whereas the prevalence of Stage 2 and 3 were higher in men. VFA was lowest in

subjects with Stage 0 and increased progressively until Stage 3 (Figure 4). VFA was higher in women than in men (p<0.001) in all CMDS stages, except in Stage 4.

Visceral Fat Area to detect Cardiometabolic Risk Factors

In men and women, the AUCs were for Stage 1: 0.509 (p=0.652) and 0.624 (p<0.001); Stage 2: 0.628 (p<0.001) and 0.715 (p<0.001); Stage 3: 0.780 (p<0.001) and 0.788 (p<0.001), Stage 4: 0.647 (p<0.001) and 0.572 (p=0.002), respectively (Figure 5). Similarly, the best VFA cut-offs associated with CMDS Stage 1 were 71 cm^2 (sensitivity=0.654; specificity=0.427) and 83 cm^2 (sensitivity=0.705; specificity=0.556); Stage 2: 84 cm^2 (sensitivity=0.673; specificity=0.551) and 98 cm^2 (sensitivity=0.702; specificity=0.628); Stage 3: 90 cm^2 (sensitivity=0.886; specificity=0.605) and 109 cm^2 (sensitivity=0.755; specificity=0.704); Stage 4: 91 cm^2 (sensitivity=0.625; specificity=0.611) and 81cm^2 (sensitivity=0.695; specificity=0.448), respectively.

Discussion.

This is the first analysis designed to determine cut-off values of VFA measured via BIA applying the CMDS and taking into account gender differences in a Central European population. VFA values were correlated to all the biological cardiometabolic risk factors, and the strongest positive correlation was with waist circumference. Despite men having lower VFA values compared to women, they had a higher prevalence of CMDS Stage 2 and Stage 3. Thus, men showed an increased risk at lower VFA values in comparison to women. A cut-off VFA value of 90 cm^2 in men and 109 cm^2 in women showed the best performance to detect subjects with CMDS 3 (metabolic syndrome and prediabetes) in both genders. The performance to detect other CMDS stages was poor.

In the only European study to date on the relevance of VFA with cardiometabolic risk,146 subjects in the U.K., including only men and using CT, had a cut-off value of VFA of 131 cm^2 related to two components of MetS.[11] This was higher than the cut-off value in the present study (90 cm^2 in men).[11] On the other hand, in the U.S. among caucasian Americans (N=835; 49% males, aged 18–74 years), the VFA cut-off values associated with cardiometabolic risk were 140 cm^2 in men and 141 cm^2 in women (higher than in the present study), and among African Americans (N=411; 24% males, aged 18–74 years), the values were 82 cm^2 in men and

97 cm^2 in women[16] (lower than in the present study). These differences may reflect ethnic heterogeneity in adipose dysfunction.[22] In two Japanese studies (N=1193; 65% males, aged 20–84 years[14] and N=12,443; 81% males, aged 19–88 years[15]), a cut-off value of VFA associated with cardiometabolic risk of 100 cm^2 was provided for both genders, and similar with a South Korean study (N=413; 42% males, aged 18–74 years), in which the cut-off value of VFA associated with cardiometabolic risk was 103.8 cm^2, also for both genders [12] In another South Korean study, (N=280; 34% males, aged 30–80 years), the VFA cut-off values were 136 cm^2 in men and 95 cm^2 in women.[13] These differences among various studies not only infer technical variations in VFA measurement, but also ethno-racial heterogeneity and potentially complex interactions between molecular and environmental drivers on adipose dysfunction.[22]

Visceral fat represents accumulation of fat in the intra-abdominal area, which leads to adipocyte dysfunction.[1,3,4] Dysfunctional adipose cells produce excessive free fatty acids and glycerol leading to insulin resistance. Increased demands on insulin-producing pancreatic β-cells gradually impair insulin secretion and lead to hyperglycaemia.[23,24] Insulin resistance further causes excessive secretion of proinflammatory atherosclerotic cytokines in adipose tissue, underproduction of anti-atherosclerotic adiponectin, and atherogenic changes in the lipoprotein profile, characterized by excessive postprandial chylomicronaemia, high triglycerides, and low HDL-c.[2,4,23,24] Moreover, insulin resistance is related to accumulation of ectopic lipid in the cardiomyocyte and endothelial dysfunction increasing blood pressure and atherosclerotic platelet adhesiveness.[24]

The main limitation is the cross-sectional design of the study, which does not allow for an evaluation of causality. The main strength of the study is the representativeness of this population-based sample and use of validated measurements and cardiometabolic risk assessment.

In conclusion, VFA is directly proportional to cardiometabolic risk factors defined by CMDS. A cut-off value of VFA of 71 cm^2 in men and 83 cm^2 in women exhibited the earliest stage of cardiometabolic risk and the values of 90 cm^2 in men and 109 cm^2 in women showed the best sensitivity and specificity to detect subjects with cardiometabolic risk. Prospective studies are required to assess the predictive value of these cut-offs and efficacy with VFA-guided prevention.

Acknowledgements

Conflict of Interest

None to declare.

Source of Funding

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Table 1 – Subject´s characteristics

	Total	Men	Women	p
N (%)	2052	933 (45.5 %)	1119 (54.5 %)	
Age (years)	49.0 (20)	48.0 (20)	49.0 (19)	0.013
Waist circumference (cm)	89.0 (21)	96.0 (16)	82.0 (18)	<0.001
Visceral fat area (cm^2)	86.6 (55.38)	82.8 (54.8)	89.8 (55.6)	0.001
Systolic Blood Pressure (mmHg)	118.8 (19.8)	121.4 (17.70)	115.8 (20.2)	<0.001
Diastolic Blood Pressure (mmHg)	79.5 (12.8)	82.2 (11.8)	77.2 (11.8)	<0.001
HDL-cholesterol (mmol/L)	1.48 (0.51)	1.30 (0.39)	1.65 (0.47)	<0.001
Fasting Triglycerides (mmol/L)	1.06 (0.80)	1.24 (0.96)	0.95 (0.67)	<0.001
Fasting blood glucose (mmol/L)	4.9 (0.70)	5.0 (0.98)	4.8 (0.70)	<0.001
Type 2 Diabetes %	5.0 (4.0 – 5.9)	6.9 (5.2 – 8.5)	3.3 (2.2 – 4.3)	<0.001
Vascular disease %	5.8 (4.7 – 6.8)	7.1 (5.4 – 8.7)	4.8 (3.5 – 6.0)	0.025

Continuous variables are median (interquartile range). Mann-Whitney test was used for difference in medians. Proportions are present as percent and 95% confidence intervals. Chi-square test was used for difference in proportions.

Table 2 – Sensitivity, specificity and sum of VFA cutoffs in identifying CMDS stage in men and women.

CMDS stage 1

Men				Women			
VFA (cm²)	Sensitivity	Specificity	Sum	VFA (cm²)	Sensitivity	Specificity	Sum
62.05	0.779	0.330	1.109	**83.55**	0.705	0.556	1.261
69.75	0.682	0.402	1.084	82.85	0.712	0.547	1.259
71.35	0.654	0.427	1.081	79.85	0.737	0.519	1.256
69.45	0.682	0.399	1.081	80.40	0.731	0.525	1.256
71.55	0.651	0.428	1.079	84.05	0.697	0.557	1.254
70.75	0.659	0.420	1.079	87.25	0.667	0.585	1.252

CMDS stage 2

Men				Women			
VFA (cm²)	Sensitivity	Specificity	Sum	VFA (cm²)	Sensitivity	Specificity	Sum
79.45	0.714	0.514	1.228	95.25	0.746	0.588	1.334
84.35	0.673	0.551	1.224	**98.35**	0.702	0.628	1.330
91.70	0.612	0.610	1.222	96.00	0.728	0.599	1.327
90.55	0.619	0.600	1.219	94.30	0.746	0.578	1.324
85.45	0.660	0.558	1.218	99.35	0.684	0.638	1.322
83.95	0.673	0.544	1.217	97.45	0.702	0.617	1.319

CMDS stage 3

Men				Women			
VFA (cm²)	Sensitivity	Specificity	Sum	VFA (cm²)	Sensitivity	Specificity	Sum
85.60	0.924	0.569	1.493	107.55	0.774	0.695	1.469
89.95	0.886	0.605	1.491	106.75	0.774	0.690	1.464
83.95	0.937	0.551	1.488	**109.05**	0.755	0.704	1.459
89.50	0.886	0.599	1.485	108.60	0.755	0.702	1.457
88.90	0.886	0.593	1.479	105.80	0.774	0.682	1.456
90.25	0.873	0.605	1.478	107.90	0.755	0.699	1.454

CMDS stage 4

Men				Women			
VFA (cm²)	Sensitivity	Specificity	Sum	VFA (cm²)	Sensitivity	Specificity	Sum
91.25	0.625	0.611	1.236	78.05	0.727	0.419	1.146
92.25	0.618	0.618	1.236	**81.50**	0.695	0.448	1.143
91.10	0.625	0.610	1.235	79.95	0.701	0.435	1.136
92.10	0.618	0.617	1.235	92.55	0.578	0.549	1.127
90.90	0.625	0.606	1.231	82.30	0.668	0.454	1.122
91.70	0.618	0.613	1.231	89.05	0.604	0.514	1.118

Abbreviations: CMDS – Cardiometabolic Disease Staging System. VFA – visceral fat area.
Bold values represent the cutoffs selected.

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│  Permanent residents of Brno city, age group 25-64 years │
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│           n=371 371 as of 31.12.2010                    │
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│       Random stratified sample (2013-2014)        │
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              │   Accepted invitation  │
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              ┌───────────────────────┐                    **Excluded participants**
              │  Enrolled in the study │
              │                        │              Participants with Type 1 Diabetes
              │        n=2160          │
              │                        │              Participants with missing values
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              │   Final sample for     │
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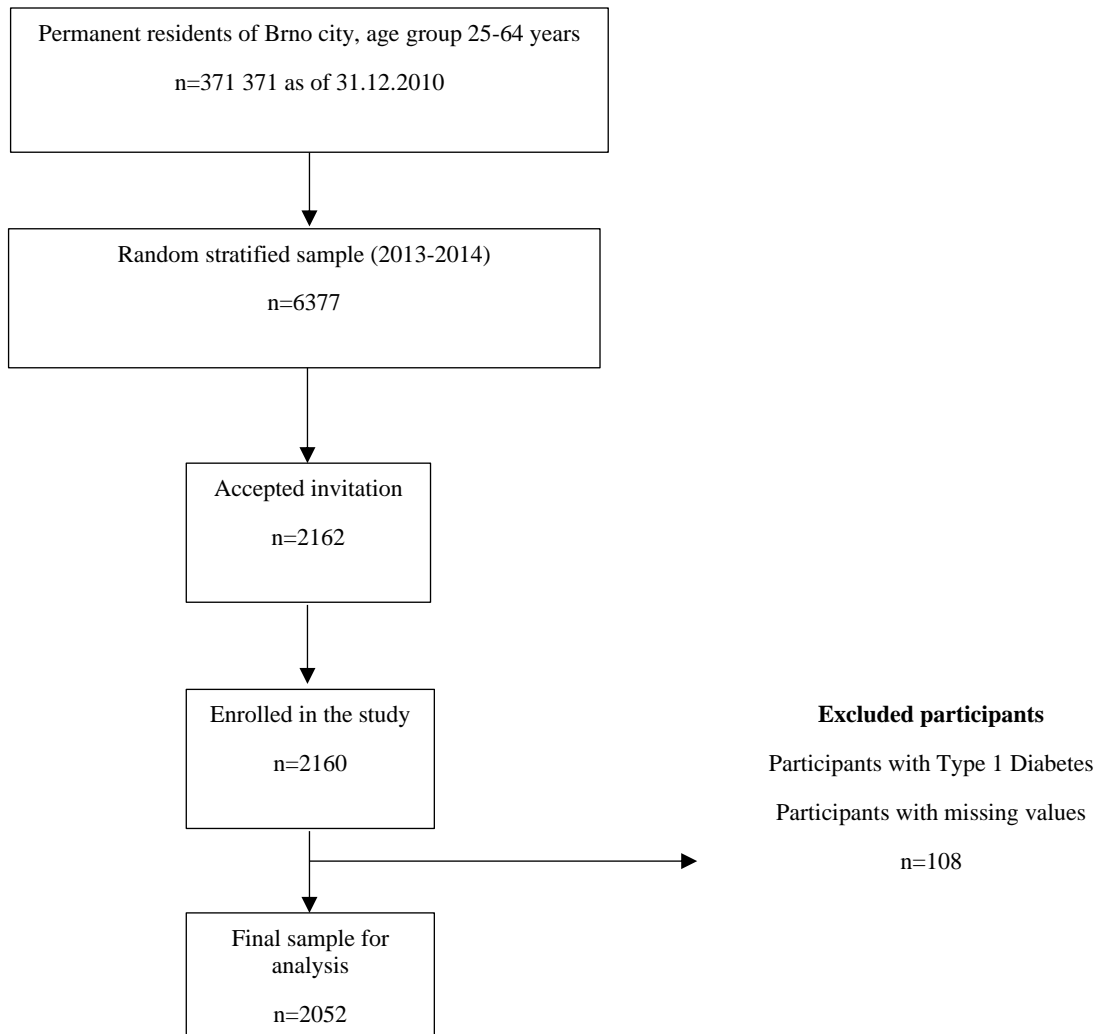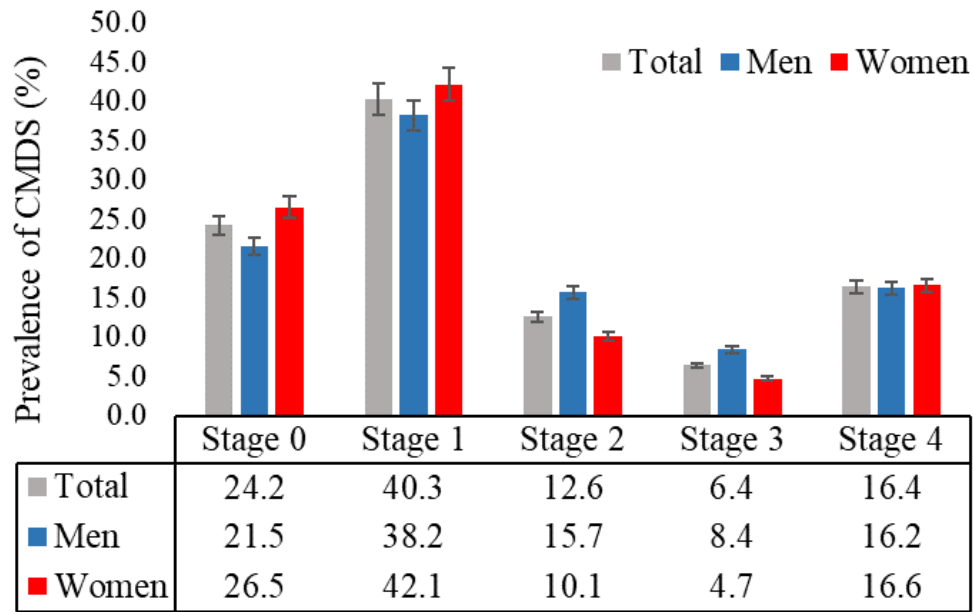
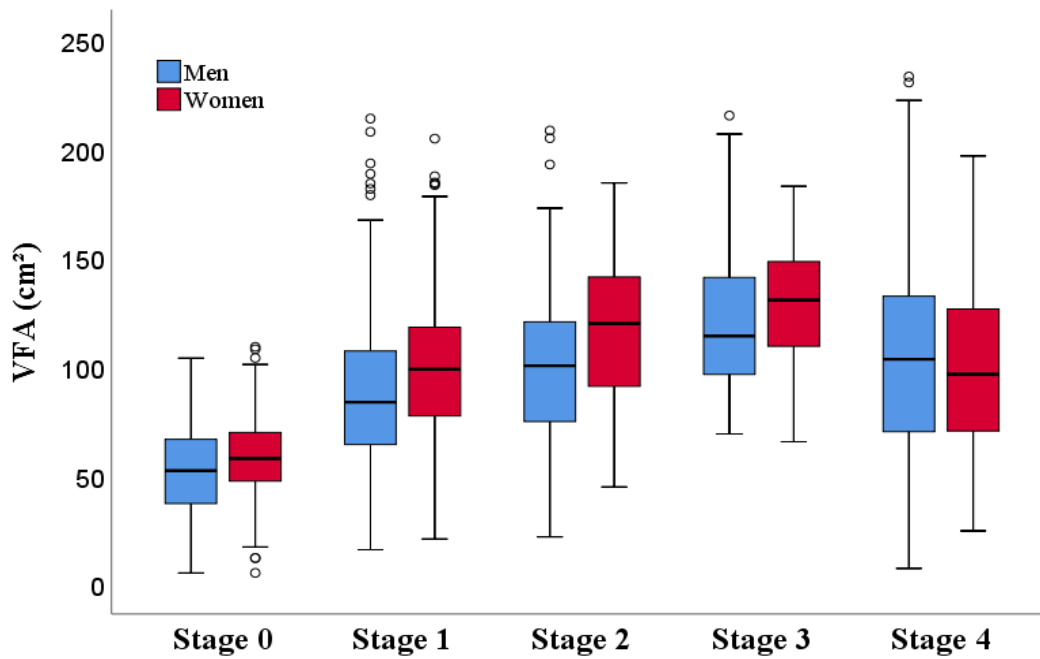**Figure 1:** Final sample for analysis
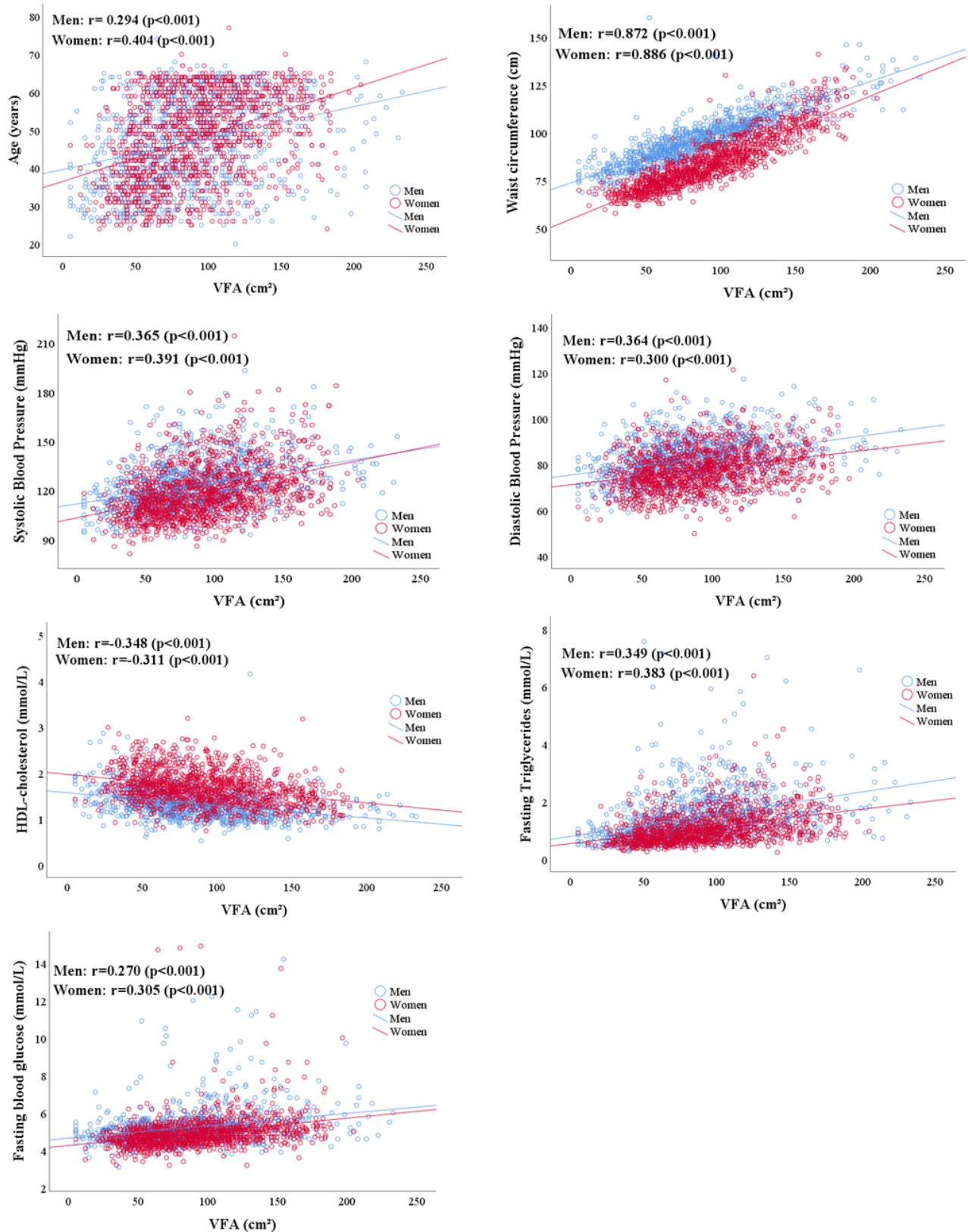
Figure 2: Correlation of Visceral fat area values and other variables – age, waist circumference, systolic blood pressure, diastolic blood pressure, HDL-cholesterol, fasting triglycerides, fasting blood glucose
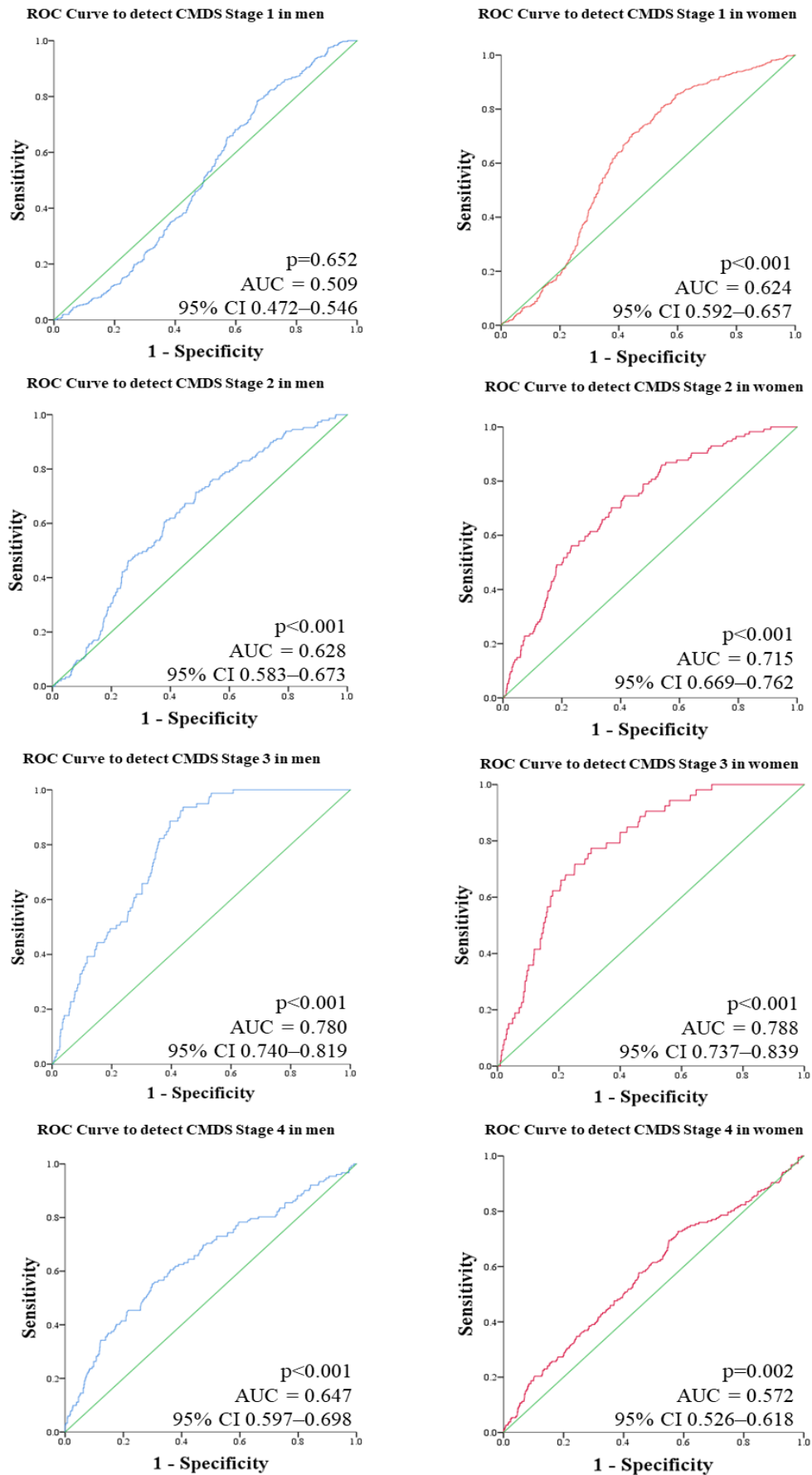
Figure 3: Prevalence of CMDS (%). Differences among gender categories using Chi-square test p<0.001

Figure 4: Visceral fat area (cm^2) values distribution according stages of CMDS by gender. Differences among gender categories using Kruskal-Wallis test p<0.001.

ROC Curve to detect CMDS Stage 1 in men

p=0.652
AUC = 0.509
95% CI 0.472–0.546

ROC Curve to detect CMDS Stage 1 in women

p<0.001
AUC = 0.624
95% CI 0.592–0.657

ROC Curve to detect CMDS Stage 2 in men

p<0.001
AUC = 0.628
95% CI 0.583–0.673

ROC Curve to detect CMDS Stage 2 in women

p<0.001
AUC = 0.715
95% CI 0.669–0.762

ROC Curve to detect CMDS Stage 3 in men

p<0.001
AUC = 0.780
95% CI 0.740–0.819

ROC Curve to detect CMDS Stage 3 in women

p<0.001
AUC = 0.788
95% CI 0.737–0.839

ROC Curve to detect CMDS Stage 4 in men

p<0.001
AUC = 0.647
95% CI 0.597–0.698

ROC Curve to detect CMDS Stage 4 in women

p=0.002
AUC = 0.572
95% CI 0.526–0.618

Figure 5: Receiver operating characteristic curves (ROC) for identifying visceral fat area cut-off values associated with cardiometabolic risk by gender.

Supplements

Supplementary Table 1 – CMDS stages[17]	
Stage	**Criteria**
Stage 0 No risk factors	No risk factors
Stage 1 One or Two Risk Factors	**One or two** of the following risk factors: **high WC** (≥ 94 cm in M ≥80 cm in W) **elevated BP** (SBP≥130mmHg and/or SBP ≥85 mmHg) or on medication **reduced serum HDL-c** (<1.0 mmol/L in M and <1.3 mmol/L in W) **elevated fasting serum triglycerides** ≥1.7 mmol/l or on medication
Stage 2 MS or Prediabetes	**MS based on three or more of four risk factors**: high WC, elevated BP, reduced HDL-c, elevated triglycerides **or** **IFG** (fasting glucose ≥5.6 mmol/L)
Stage 3 MS and Prediabetes	MS **and** IFG
Stage 4 T2DM and/or CVD	T2DM (fasting glucose >5.6 mmol/l or and anti-diabetic therapy) **And/or** CVD
Abbreviations: BP – blood pressure, CVD – Cardiovascular Disease, DBP – diastolic blood pressure, HDL-c – HDL-cholesterol, IFG – Impaired Fasting Glucose, M – men, SBP – systolic blood pressure, T2DM – Type 2 Diabetes Mellitus, W – women, WC – waist circumference,	