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ORIGINAL ARTICLE

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Traditional and novel cardiometabolic risk markers across strata of body mass index in young adults

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Abstract

Background: Cardiometabolic risk increases with increasing body mass index (BMI). The exact mechanism is poorly understood, and traditional risk assessment of young adults with obesity has shown to be ineffective. Greater knowledge about potential new effective biomarkers and the use of advanced cardiac imaging for risk assessment in young adults is, therefore, necessary.

Objective: This study aims to explore traditional and novel cardiometabolic risk markers across strata of BMI in young adults.

Methods: Participants ($N = 264$, 50% women, age 28–30 years) were invited from an ongoing cohort study, based on BMI and sex. BMI-strata were: BMI <25, 25–30, >30 kg/m^2, representing normal weight (NW), overweight (OW), and obesity (OB). Participants underwent cardiac computed tomography to detect coronary artery calcification, measures of body composition, blood pressure measurements, and a comprehensive panel of circulating cardiometabolic risk markers.

Results: No significant coronary artery calcifications were detected in this study. Minor differences in median levels of traditional risk markers were detected across BMI-strata, for example, total cholesterol (men- NW: 4.7 (4.3–5.1) and OB: 4.8 (4.2–5.6) mmol/L, $p = 0.58$; women- NW: 4.3 (3.9–4.8) and OB: 4.7 (4.2–5.3) mmol/L, $p = 0.016$), whereas substantial differences were seen in markers of inflammation and glucose metabolism, for example, high sensitive CRP (men- NW: 0.6 (0.3–1.1) and OB: 2.8 (1.5–4.0) mg/L, $p < 0.001$; women- NW: 0.7 (0.3–1.7) and OB: 4.0 (2.2–7.8) mg/L, $p < 0.001$) and insulin (men- NW: 47.0 (35.0–59.0) and OB: 113.5 (72.0–151.0) pmol/L, $p < 0.001$; women- NW: 44.0 (35.0–60.0) and OB: 84.5 (60.0–126.0) pmol/L, $p < 0.001$).

Conclusion: In young adults, obesity is associated with an early onset insulin resistance and inflammatory response prior to development of coronary artery calcification and deterioration of lipid profiles.

KEYWORDS
body mass index, cardiovascular risk, inflammation, obesity, risk management

1 | INTRODUCTION

Obesity, physical inactivity, and diabetes mellitus are known risk factors for cardiovascular diseases (CVD). The prevalence rates for these risk factors continue to show a global increase.[1,2] Furthermore, age-specific analyses of prevalence and incidence for CVD suggest an increasing trend among individuals aged <55 years.[3–5] This is a major health concern as CVD is already the main cause of death in most developed countries.[6] Knowledge about which risk markers are present in young adulthood, and potentially could be incorporated into early risk assessment for CVD, is warranted to identify young individuals at high risk and to tailor effective strategies for CVD prevention.[7]

Due to the low chronological age and the slowly developing nature of CVD, most young individuals are currently classified as low risk according to established algorithms for CVD risk assessment involving traditional risk markers such as age, dyslipidemia, smoking, and hypertension.[8,9]

In addition to traditional risk markers, novel circulating biomarkers and coronary artery calcium score (CACS), evaluated by computed tomography (CT), have been suggested as potential refinements of the risk assessment.[10–13] For example, novel inflammatory biomarkers, most extensively high-sensitive CRP (hs-CRP) and various interleukins, are being evaluated both as risk markers and as mediators of disease progression, yet few studies have evaluated this in young adults and no specific anti-inflammatory treatment has been established.[14–23] Regarding CACS, little is known about the occurrence of CT positive plaques in young adults and CACS is currently not recommended in asymptomatic individuals.[7]

The aim of this study was to explore traditional and novel cardiometabolic risk markers across strata of sex and body mass index (BMI) in individuals aged 28–30 years. It was hypothesized that obesity was associated with increased values of circulating biomarkers, and that coronary artery calcification was more prevalent in young adults with obesity as compared to individuals with normal weight.

2 | MATERIALS AND METHODS

2.1 | Study population and overall design of the study

A flowchart of the sample selection is shown in Figure 1. The study participants were included from the ongoing West Jutland Cohort Study ($N = 3681$). The overall design and purpose of this study has been described elsewhere.[24,25] In brief, the West Jutland Cohort Study consists of all individuals born in 1989, living in a specific geographical area of Western Denmark in 2004. Participants filled in questionnaires at age 15 and at three follow-up time points (age 18, 21, and 28). At the latest follow-up, the participants were asked to indicate interest in a health examination. If interest was indicated, respondents were stratified into one of three BMI-groups of normal weight, overweight, and obesity (BMI < 25 kg/m^2, 25–30 kg/m^2, and >30 kg/m^2) based on the latest self-reported height and weight. The participants were randomly sampled within their sex- and BMI-group and contacted through the nationally required electronic mailbox. A reminder was sent out to individuals not responding to the first invitation. Five consecutive waves of invitations were used, to obtain similar numbers in each sex- and BMI-group, until a total of 264 participants were included. Individuals with congenital heart disease, active cancer disease, severe claustrophobia, weight > 300 kg or who had not responded to both the initial and the latest questionnaire were excluded. Pregnant participants were included but investigated after giving birth (Figure 1). All data were linked to the unique personal identification number (CPR-number), assigned to all Danish citizens at birth and subsequently stored in the Danish Civil Registration System, to supplement the results with existing data from Danish registries.

2.2 | Assessing cardiovascular risk

The health examinations were performed from April 2018 to December 2019. All examinations were conducted in the morning and the participants were asked to avoid hard physical exercise, smoking, and more than two units of alcohol the day before and on the day of examination as well as to be fasting.

2.3 | Computed tomography of the heart

CACS was computed from ECG-gated cardiac CT scan (Toshiba Aquilion One, 320 slice CT scanner, Canon, Japan) using a standard clinical scan (120 keV and adjusted mAs). CACS was measured with the scoring system previously described by Agatston et al.[26] The system is semiautomatic and image analysis was blinded from all clinical information and evaluated by a trained physician. Additionally, an experienced CT cardiologist examined 15% randomly selected images, and 8% with uncertain primary evaluation.

2.4 | Blood sample collection, handling, and biochemical analyses

Fasting blood samples were obtained on the day of examination. All blood samples were drawn from an antecubital vein and handled according to standard operating procedures. The plasma and serum were stored at −80°C until batch analysis after inclusion of all participants. Samples were analyzed on different bioanalytical platforms. Eight biomarkers (HDL-cholesterol (HDL-C), total cholesterol, triglycerides, insulin, glucose, HbA1c, high-sensitive CRP (hs-CRP), and fibrinogen) were analyzed at the central laboratory at Aarhus University Hospital (Denmark). Four biomarkers (interleukin-6 (IL-6), interferon-γ (IFN-γ), interleukin-1beta (IL-1β), and tumor necrosis factor α (TNF-α)) were measured using Meso Scale Diagnostics technology V-plex human pro-inflammatory panel 1 (Meso Scale Diagnostics, Rockville, Maryland) at BioXpedia (Aarhus, Denmark) and six proteins (coagulation factor 7 + 11, Vascular Cell Adhesion

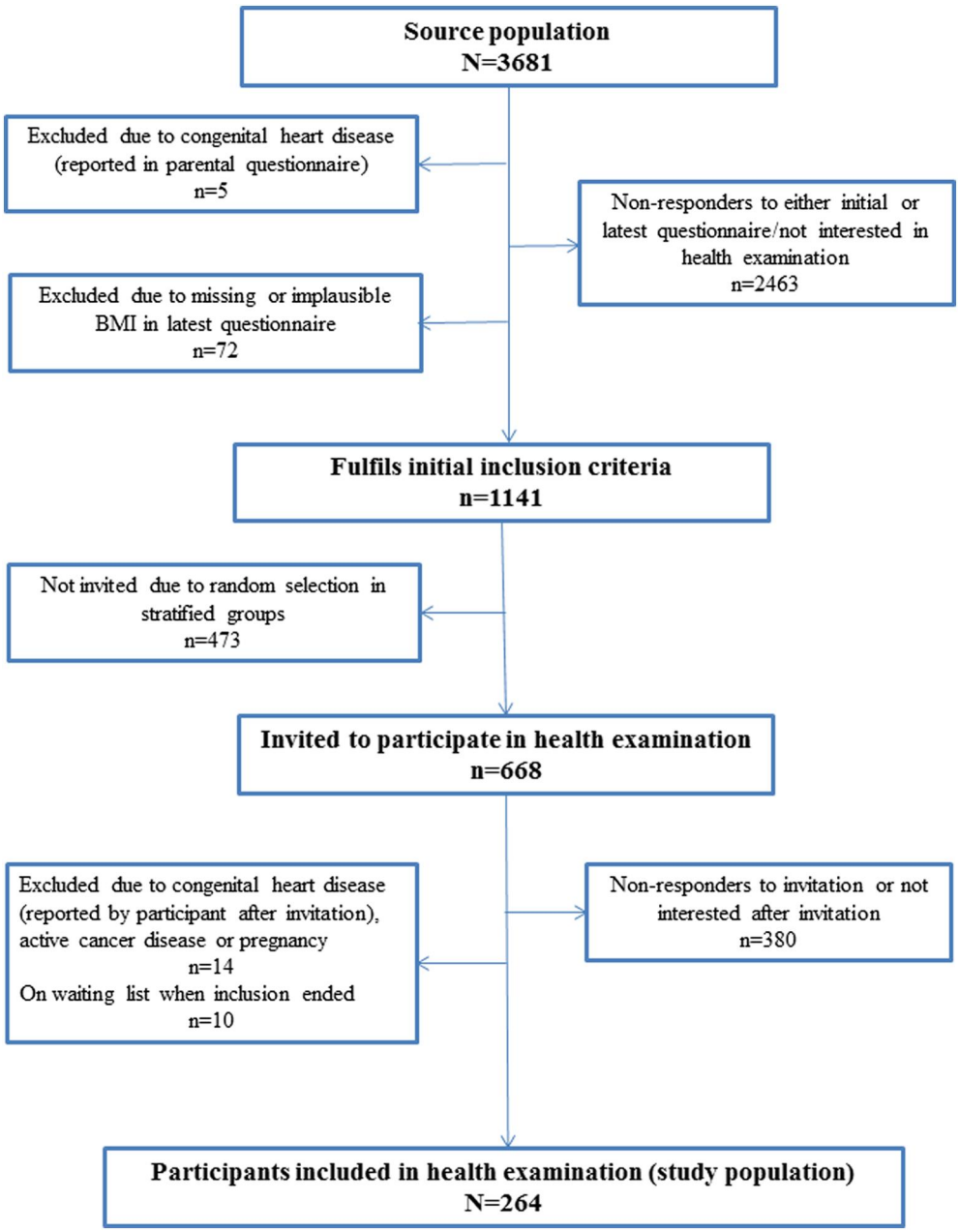

FIGURE 1 Flowchart of study population

Molecule 1 (VCAM-1), Intercellular Adhesion Molecule 1 (ICAM-1), L-selectin, and interleukin-7 receptor subunit alpha (IL7R-α)) were measured simultaneously using proximity extension assays from Olink (Olink Proteomics, Uppsala, Sweden) at BioXpedia (Aarhus, Denmark) using the protein panel CARDIOMETABOLIC (v.3603). Plasma LDL-cholesterol (LDL-C) was estimated by the Friedewald equation.[27]

2.5 | Measurements of weight, height, and waist circumference

Weight to the nearest 0.1 kg was measured using a calibrated electric scale with the participant wearing light clothes and no shoes. Standing height without shoes was recorded to the nearest 0.1 cm using a wall-mounted stadiometer. Waist (smallest circumference between the lower rib and iliac crest) circumference was measured in the horizontal plan using a narrow, nonelastic measuring tape after expiration.

2.6 | Bioelectrical impedance analysis

Whole-body measurements of body fat-percentage were obtained using a bioelectrical impedance analyzer (1500 MDD; 50 kHz, Bodystat, Isle of Man, United Kingdom) with skin surface electrodes located in pairs at the right wrist and ankle. Reliability of the

measurements was evaluated by three consecutive measurements in 5% of the participants. The mean difference from first to second and third measurement varied between 0 and 1%.

2.7 | Blood pressure measurements

Blood pressure was measured with a regularly calibrated automatic device. Mid-arm circumference was used to determine cuff-size. The cuff was applied in the sitting position and the participant was resting for 5 minutes before measurements. The participant was unable to see the monitor during measurements. Three measurements were recorded and the mean value of the last two readings was used to define diastolic and systolic blood pressures.

2.8 | Assessing lifestyle and parental history of cardiometabolic diseases

In addition to the questionnaires sent to the entire West Jutland Cohort, the 264 participants attending the health examination received a questionnaire concerning updated smoking status, medical history, and family occurrence of cardiometabolic diseases. Furthermore, parental cardiometabolic disease history from somatic public hospitals was obtained from Danish registries and combined with the questionnaire data. Parental disease history included diabetes (type 1 and 2) and CVD (ischemic heart disease, acute myocardial infarction, atherosclerosis, and stroke). Smoking was dichotomized into ever (former/current) or never smoker.

Information about physical activity was extracted from questionnaire data obtained at age 28. Based on the reported number of hours spent exercising each week, physical activity was divided into three categories of ≈0–0.5 h, ≈1–3 h, and ≥4 h.

2.9 | Statistical analysis

Statistical analyses were performed with the statistical software package Stata, version 16.0 and 16.1 (Stata Corporation, College Station, Texas, USA).

Nonfasting measurements of insulin and glucose were excluded from analyses. Participants with self-reported diabetes mellitus type 1 were excluded from insulin, glucose, and HbA1c analyses. Missing attendance to CT scan or answers to lifestyle questionnaires were excluded from analyses.

Normal distribution was visually evaluated by histograms and QQ plots and variance homogeneity was assessed by Bartlett's test. Due to skewness of the continuous data median values across BMI-strata for each sex were compared using Kruskal–Wallis test. Pearson's chi-squared test was used for categorical variables. Data are presented as median (interquartile range) for continuous variables and number (percentage) for categorical variables.

2.10 | Ethical considerations

The Danish Data Protection Agency, the Danish Medicines Board, and the National Committee on Health Research Ethics (no: 1-10-72-400-17) all approved the study. Participants signed a statement of consent prior to the health examination. The study complies with the Declaration of Helsinki.

3 | RESULTS

Seven participants had missing biomarker measurements due to technical issues, were not fasting at the time of blood collection, or had self-reported diabetes mellitus type 1. Nonattendance to the planned CT scan resulted in five missing results in this analysis and missing answers to the questionnaire regarding physical activity resulted in eight missing values.

The IL-1β measurements were below lower limit of quantification (0.646 pg/ml) in more than 98% of the samples and were, therefore, removed from the analysis.

3.1 | Sample characteristics

Table 1 summarizes sex- and BMI-stratified biomarker values and additional characteristics. A total of 264 (50% women, age 28–30 years) participants were included in the study. There were no differences across BMI-strata regarding self-reported physical activity. Men with obesity smoked more compared to men with normal weight but no statistical significant difference was observed across BMI-groups for women. Participants with overweight or obesity more often had parents with cardiometabolic diseases as compared to participants with normal weight.

As seen in Figure 2, body fat percentage (men: 17.0 (15.0–19.0), 20.1 (18.0–22.0), and 29.3 (26.1–32.6) %, $p < 0.001$; women: 25.9 (23.6–29.1), 34.1 (31.0–36.4), and 44.5 (39.3–46.0) %, $p < 0.001$) and waist circumference (men: 82.5 (79.0–87.0), 90.5 (87.0–96.0), and 110.0 (105.0–117.0) cm, $p < 0.001$; women: 73.5 (69.5–87.0), 85.0 (81.0–88.0), and 99.0 (93.0–107.0) cm, $p < 0.001$) varied across strata of sex and BMI.

3.2 | Coronary artery calcification

There was a low occurrence of coronary artery calcification detected by cardiac CT. No participant had a CACS > 5 and all men with overweight and obesity as well as all women had CACS = 0 (Table 1).

3.3 | Cardiovascular profile, men

As seen in Table 1, men with obesity had higher systolic (129 (122–136) vs. 123 (114–131) mmHg) and diastolic (81 (73–86) vs. 73 (66–78)

TABLE 1 Median biomarker values and additional characteristics by body mass index and sex

		Men			Women		
	N	Normal weight	Overweight	Obesity	Normal weight	Overweight	Obesity
Total	264	38 (29%)	58 (44%)	36 (27%)	40 (30%)	45 (34%)	47 (36%)
BMI (kg/m^2)	264	23.0 (22.0–24.1)	26.8 (26.0–28.1)	34.4 (32.0–37.2)	22.2 (20.7–23.5)	27.6 (26.2–28.6)	35.1 (32.5–37.9)
Lifestyle							
Smoking	264						
Never		29 (76%)	37 (64%)	19 (53%)*	32 (80%)	31 (69%)	30 (64%)
Ever		9 (24%)	21 (36%)	17 (47%)*	8 (20%)	14 (31%)	17 (36%)
Physical activity	256						
0–0.5 h/week		10 (27%)	13 (23%)	7 (22%)	7 (18%)	8 (18%)	13 (28%)
1–3 h/week		14 (38%)	23 (40%)	14 (44%)	22 (55%)	24 (55%)	26 (57%)
>4 h/week		13 (35%)	21 (37%)	11 (34%)	11 (28%)	12 (27%)	7 (15%)
Family disease							
Parental diabetic disease	264	0 (0%)	6 (10%)*	10 (28%)**	<5	6 (13%)	14 (30%)*
Parental cardiovascular disease	264	8 (21%)	14 (24%)	13 (36%)	7 (18%)	17 (38%)*	19 (40%)*
Cardiovascular							
CACS > 0	259	<5	0	0	0	0	0
Diastolic blood pressure mmHg	264	73 (66–78)	74 (69–80)	81 (73–86)**	73 (69–76)	74 (69–77)	77 (73–85)*
Systolic blood pressure (mmHg)	264	123 (114–131)	125 (120–132)	129 (122–136)*	112 (104–118)	113 (105–121)	116 (109–120)
Resting heart rate (beats/min)	264	62 (53–70)	60 (49–65)	64 (56–72)	62 (57–66)	61 (56–66)	66 (58–74)*
Total cholesterol (mmol/L)	264	4.7 (4.3–5.1)	4.6 (4.1–5.2)	4.8 (4.2–5.6)	4.3 (3.9–4.8)	4.6 (4.1–5.2)	4.7 (4.2–5.3)*
LDL-cholesterol (mmol/L)	263	2.8 (2.4–3.1)	2.8 (2.4–3.3)	3.0 (2.5–3.4)	2.3 (1.9–2.8)	2.7 (2.4–3.1)*	2.8 (2.4–3.2)**
Triglyceride (mmol/L)	264	0.9 (0.7–1.5)	1.1 (0.8–1.4)	1.4 (1.1–2.0)**	0.8 (0.7–1.0)	0.9 (0.7–1.1)	1.2 (0.9–1.6)**
HDL-cholesterol (mmol/L)	264	1.3 (1.2–1.6)	1.3 (1.1–1.5)	1.1 (1.0–1.2)**	1.6 (1.4–1.7)	1.4 (1.2–1.6)	1.3 (1.1–1.4)**
Coagulation factor 7 NPX	262	4.2 (4.0–4.4)	4.4 (4.0–4.5)	4.4 (4.1–4.8)*	4.4 (4.1–4.6)	4.4 (4.1–4.6)	4.5 (4.2–4.8)
Coagulation factor 11 NPX	262	6.9 (6.8–7.1)	7.0 (6.7–7.2)	7.2 (6.9–7.3)**	6.9 (6.8–7.2)	7.0 (6.9–7.2)	7.0 (6.9–7.3)
Metabolism							
Body fat-percentage (%)	263	17.0 (15.0–19.0)	20.1 (18.0–22.0)**	29.3 (26.1–32.6)**	25.9 (23.6–29.1)	34.1 (31.0–36.4)**	44.5 (39.3–46.0)**
Waist (cm)	264	82.5 (79.0–87.0)	90.5 (87.0–96.0)**	110.0(105.0–117.0)**	73.5 (69.5–78.0)	85.0 (81.0–88.0)**	99.0 (93.0–107.0)**
HbA1C (mmol/mol)	262	31.1 (29.6–32.8)	31.1 (29.9–33.1)	32.7 (31.4–35.0)*	30.3 (28.7–32.9)	31.4 (28.8–32.1)	32.3 (30.5–34.4)*
Insulin (pmol/L)	262	47.0 (35.0–59.0)	52.5 (42.0–66.0)*	113.5 (72.0–151.0)**	44.0 (35.0-60.0)	61.0 (42.0–83.0)*	84.5 (60.0–126.0)**
Glucose (mmol/L)	262	4.9 (4.6–5.2)	5.0 (4.7–5.3)	5.1 (4.8–5.5)*	4.5 (4.4–4.8)	4.7 (4.4–4.9)	4.9 (4.7–5.1)**

(Continues)

TABLE 1 (Continued)

		Men			Women		
	N	Normal weight	Overweight	Obesity	Normal weight	Overweight	Obesity
Inflammation							
High-sensitive CRP (mg/L)	264	0.6 (0.3–1.1)	0.7 (0.4–1.7)	2.8 (1.5–4.0)**	0.7 (0.3–1.7)	1.8 (0.9–3.7)**	4.0 (2.2–7.8)**
IL-6 (pg/ml)	264	0.3 (0.3–0.5)	0.4 (0.3–0.5)	0.6 (0.4–0.9)**	0.3 (0.2–0.4)	0.5 (0.3–0.8)**	0.8 (0.6–1.1)**
TNF-α (pg/ml)	264	2.6 (2.1–3.1)	2.5 (2.1–2.8)	2.6 (2.3–3.1)	2.2 (1.9–2.9)	2.5 (2.1–2.8)	2.7 (2.4–3.2)**
IFN-γ (pg/ml)	264	4.9 (3.3–7.0)	4.0 (3.1–7.6)	4.9 (3.2–6.2)	4.1 (3.2–6.3)	4.9 (3.5–7.7)	4.9 (3.4–7.9)
Fibrinogen (μmol/L)	263	7.0 (6.1–8.1)	7.4 (6.6–8.4)	8.9 (7.7–9.9)**	8.7 (7.4–9.3)	9.0 (8.1–9.9)	11.2 (9.3–12.6)**
ICAM1 NPX	262	6.4 (6.2–6.5)	6.4 (6.2–6.6)	6.5 (6.3–6.7)	6.3 (6.2–6.5)	6.4 (6.1–-6.5)	6.5 (6.4–6.7)**
VCAM1 NPX	262	4.7 (4.6–4.8)	4.7 (4.5–4.9)	4.7 (4.5–4.8)	4.8 (4.6–5.0)	4.6 (4.4–4.8)*	4.7 (4.5–4.9)
L-selectin NPX	262	9.2 (9.0–9.4)	9.2 (9.1–9.4)	9.2 (9.0–9.4)	9.2 (9.1–9.5)	9.2 (9.1–9.4)	9.3 (9.2–9.5)
IL7R NPX	262	2.2 (1.9–2.7)	2.2 (1.9–2.6)	2.1 (1.6–2.5)	2.2 (1.9–2.5)	2.0 (1.8–2.2)	1.8 (1.4–2.3)*

Note: Normal weight (BMI < 25 kg/m^2), overweight (BMI 25–30 kg/m^2), and obesity (BMI > 30 kg/m^2). Values are shown as median (interquartile range) for continuous data and number (percentage) for categorical variables.

Abbreviations: BMI, body mass index; CACS, coronary artery calcification score; ICAM1, intercellular adhesion molecule 1; IFN-γ, interferon-gamma; IL-6, interleukin 6; IL7R, interleukin-7 receptor subunit alpha; NPX, normalized protein expression values (arbitrary unit in Log 2 scale); TNF-α, tumor necrosis factor alpha; VCAM1, vascular cell adhesion molecule 1.

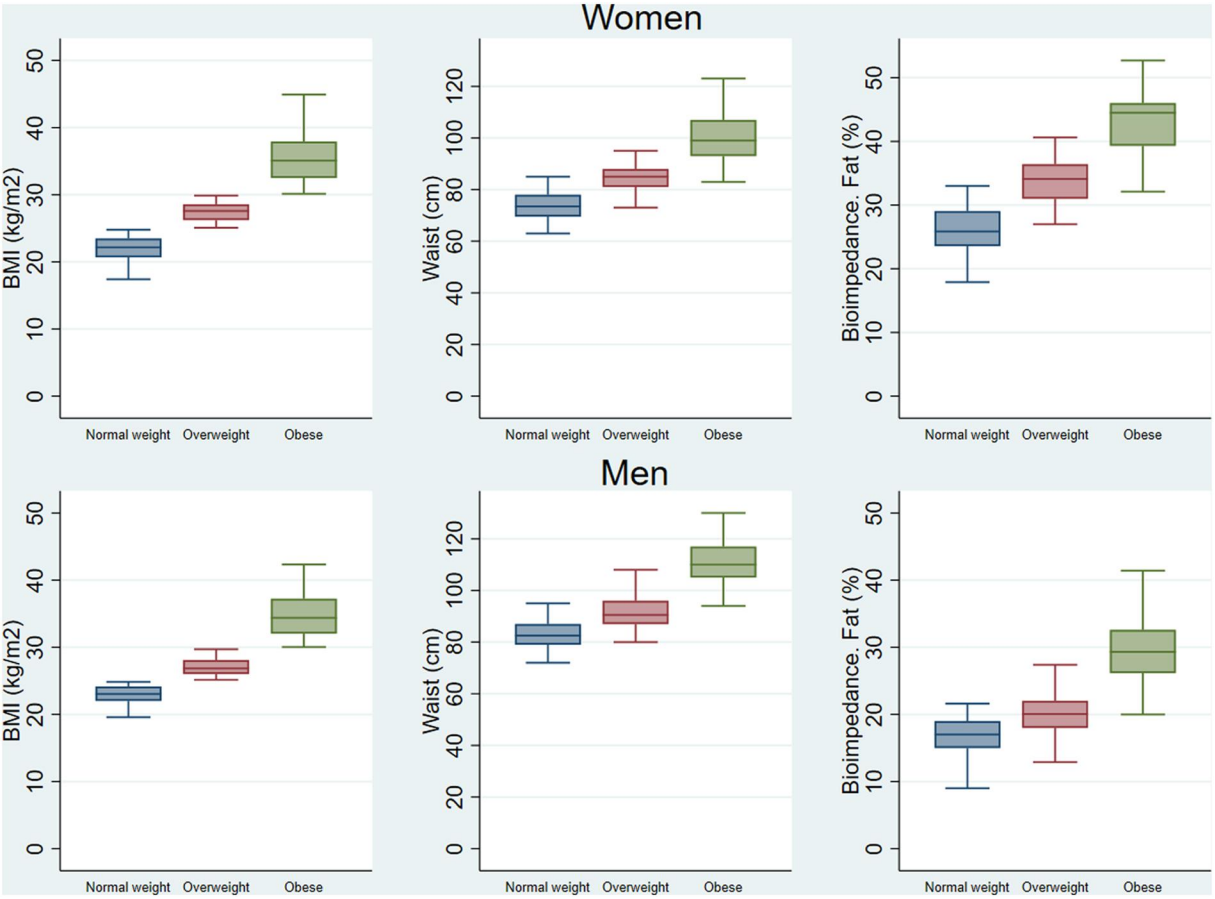

FIGURE 2 Body composition by body mass index (BMI) stratum and sex. Box plot bordered at the upper and lower quartiles of biomarker value. Whiskers extend from the most extreme values within 1.5*inter-quartile-range of the nearest quartile. Outside values excluded. All *p*-values for the overall comparison between BMI-groups are <0.001. *P*-values are conducted from Kruskal–Wallis test. Normal weight (BMI < 25 kg/m^2), overweight (BMI 25–30 kg/m^2), and obesity (BMI > 30 kg/m^2)

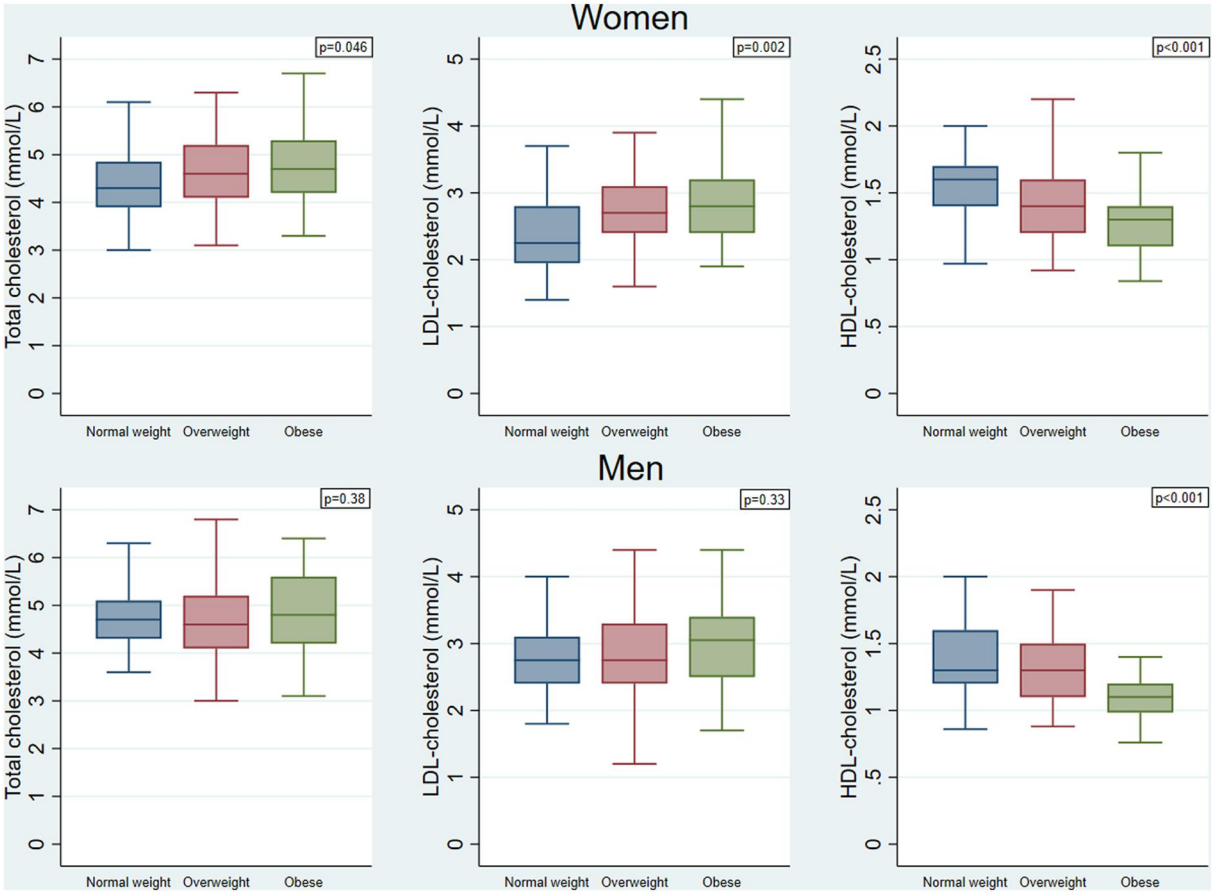

FIGURE 3 Selected biomarkers by body mass index stratum (BMI) and sex. Box plot bordered at the upper and lower quartiles of biomarker value. Whiskers extend from the most extreme values within 1.5*inter-quartile-range of the nearest quartile. Outside values excluded. *P*-values for the overall comparison between BMI-groups are conducted from Kruskal–Wallis test. Normal weight (BMI < 25 kg/m^2), overweight (BMI 25–30 kg/m^2), and obesity (BMI > 30 kg/m^2)

mmHg) blood pressures, higher levels of triglycerides (1.4 (1.1–2.0) vs. 0.9 (0.7–1.5) mmol/L), and lower levels of HDL-C (1.1 (1.0–1.2) vs. 1.3 (1.2–1.6) mmol/L) compared to participants with normal weight (Figures 3 and 4). On the contrary, total cholesterol (4.7, 4.6, and 4.8 mmol/L, $p = 0.38$) and LDL-C (2.8, 2.8, and 3.0 mmol/L, $p = 0.33$) were similar across BMI-strata (Figure 3).

3.4 | Cardiovascular profile, women

Table 1 also shows that higher systolic (116 (109–120) vs. 112 (104–118) mmHg) and diastolic (77 (73–85) vs. 73 (69–76) mmHg) blood pressures, higher levels of triglycerides (1.2 (0.9–1.6) vs. 0.8 (0.7–1.0) mmol/L), total cholesterol (4.7 (4.2–5.3) vs. 4.3 (3.9–4.8) mmol/L), and lower levels of HDL-C (1.3 (1.1–1.4) vs. 1.6 (1.4–1.7) mmol/L) were seen comparing women with obesity to women with normal weight (Figures 3 and 4). A similar tendency was seen comparing women with overweight to women with normal weight, though not reaching statistical significance. Furthermore, statistical significant higher levels of LDL-C were seen comparing women with obesity (2.8 (2.4–3.2) vs. 2.3 (1.9–2.8) mmol/L) and women with overweight (2.7 (2.4–3.1) vs. 2.3 (1.9–2.8) mmol/L) to women with normal weight but not comparing women with overweight to women with obesity ($p = 0.46$) (Figure 3).

3.5 | Metabolic profile, men and women

As can be seen in Table 1, the median level of HbA1c were higher among participants with obesity (men: 32.7 (31.4–35.0) vs. 31.1 (29.6–32.8) mmol/mol; women 32.3 (30.5–34.4) vs. 30.3 (28.7–32.9) mmol/mol) but not participants with overweight (men: 31.1 (29.9–33.1) vs. 31.1 (29.6–32.8) mmol/mol; women: 31.4 (28.8–32.1) vs. 30.3 (28.7–32.9) mmol/mol) compared to participants with normal weight. Furthermore, median insulin level was almost doubled among women with obesity and more than doubled among men with obesity compared to the groups with normal weight. A smaller but statistically significant difference in median insulin levels was also seen comparing participants with overweight to participants with normal weight in both sexes (Figure 4). Glucose levels were higher among participants with obesity (men: 5.1 (4.8–5.5) vs. 4.9 (4.6–5.2) mmol/L; women: 4.9

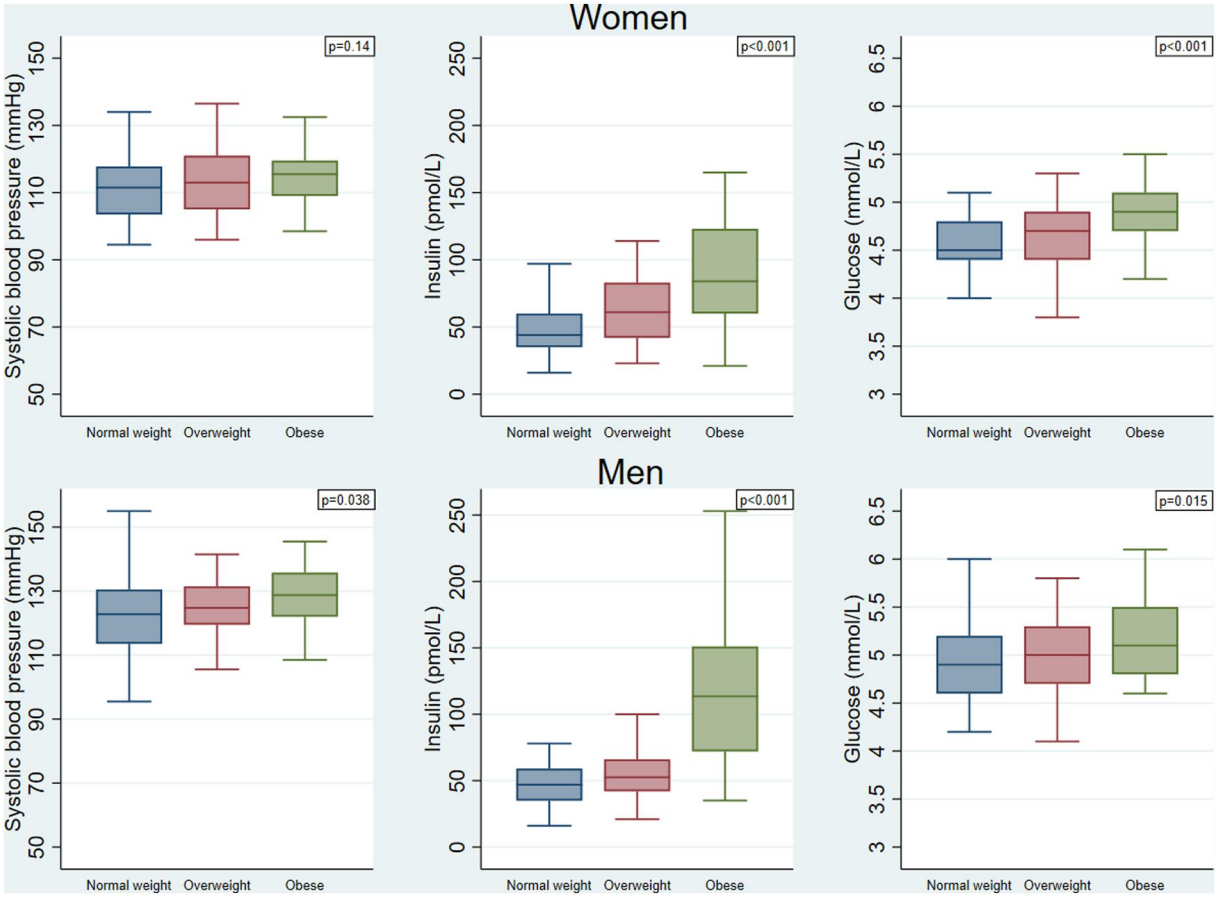

FIGURE 4 Selected biomarkers by body mass index (BMI) stratum and sex. Box plot bordered at the upper and lower quartiles of biomarker value. Whiskers extend from the most extreme values within 1.5*inter-quartile-range of the nearest quartile. Outside values excluded. *P*-values for the overall comparison between BMI-groups are conducted from Kruskal–Wallis test. Normal weight (BMI < 25 kg/m^2), overweight (BMI 25–30 kg/m^2), and obesity (BMI > 30 kg/m^2)

(4.7–5.1) vs. 4.5 (4.4–4.8) mmol/L) but not overweight of both sexes compared to participants with normal weight (Figure 4).

3.6 | Inflammatory profile, men and women

Differences in median levels of hs-CRP (men: >4-fold, women: almost 6-fold) and IL-6 (>2-fold for both sexes) were seen for participants with obesity compared to participants with normal weight (Table 1, Figure 5). Similarly, median levels of fibrinogen were higher comparing participants with obesity to participants with normal weight (men: 8.9 (7.7–9.9) vs. 7.0 (6.1–8.1) μmol/L; women: 11.2 (9.3–12.6) vs. 8.7 (7.4–9.3) μmol/L). On the contrary, no significant differences were observed in median levels of IFN-γ comparing participants with overweight (men: $p = 0.38$; women: $p = 0.21$) and obesity (men: $p = 0.52$; women: $p = 0.093$) to participants with normal weight. Women with obesity ($p < 0.001$), but not women with overweight ($p = 0.081$), men with overweight ($p = 0.42$) or men with obesity ($p = 0.67$) had higher median levels of TNF-α compared to the groups with normal weight.

4 | DISCUSSION

This study investigated a wide range of traditional and novel cardiometabolic risk markers in 264 young adults, aged 28–30 years, across strata of BMI and sex. The overall finding is that there was no clinically significant coronary artery calcification on cardiac CT scans in any of the participant strata. Furthermore, we found minor or insignificant differences across male BMI-groups in traditional risk markers like LDL-C and total cholesterol. As opposed to this, there were striking variations in other biomarkers related to glucose-metabolism and inflammation like insulin, hs-CRP, fibrinogen, and IL-6 across sex-stratified BMI-groups.

Knowledge on CACS in asymptomatic individuals below 30 years of age is scarce. One of the few studies to asses CACS in young adults is the CARDIA study.[28] In this follow-up study, 5115 participants (18–30 years at inclusion) were enrolled and followed. The study demonstrated a prevalence of CACS > 0 in 10% of participants at a mean age of 40.3 years and that any degree of plaque was associated with increased risk of coronary events over a mean follow-up period of 12.5 years. Furthermore, the study found progression of CAC over

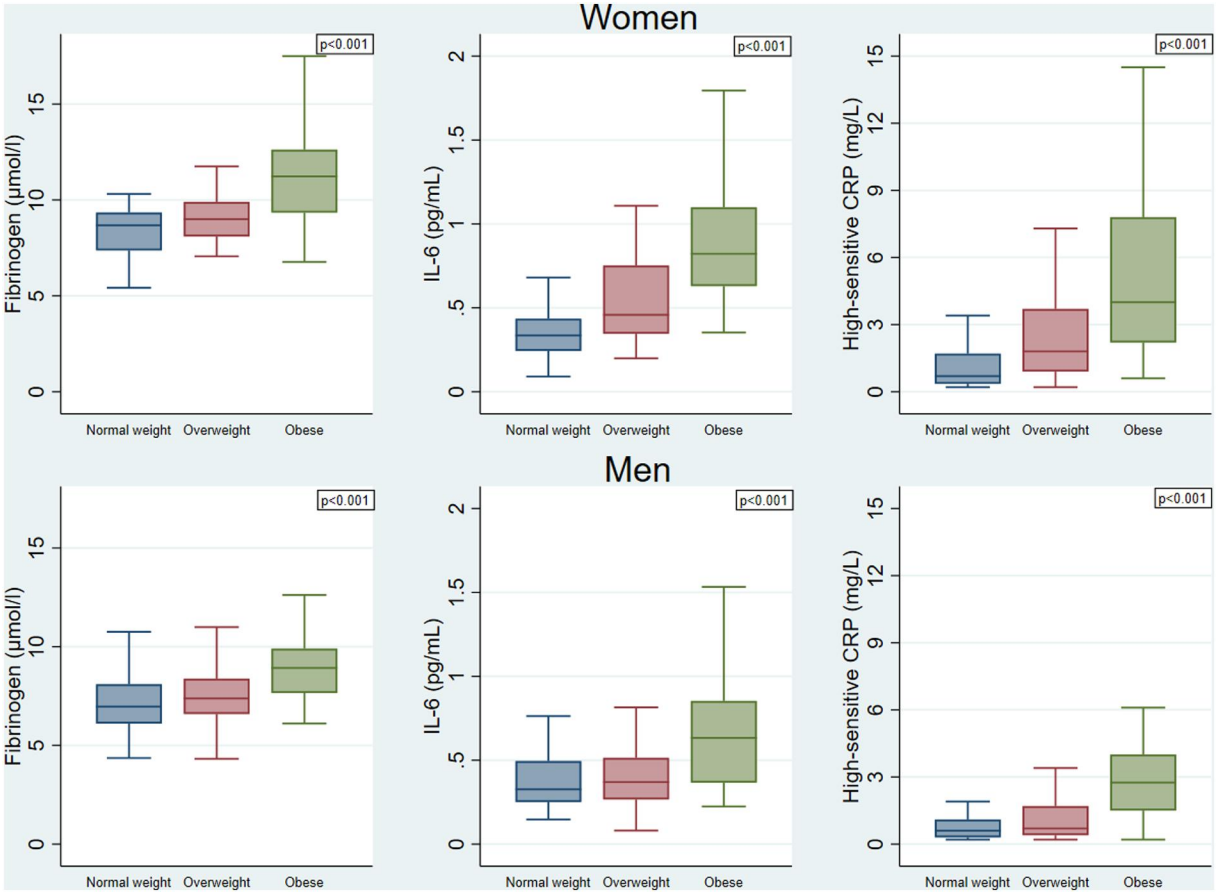

FIGURE 5 Selected biomarkers by body mass index (BMI) stratum and sex. Box plot bordered at the upper and lower quartiles of biomarker value. Whiskers extend from the most extreme values within 1.5*inter-quartile-range of the nearest quartile. Outside values excluded. *P*-values for the overall comparison between BMI-groups are conducted from Kruskal–Wallis test. Normal weight (BMI < 25 kg/m^2), overweight (BMI 25–30 kg/m^2), and obesity (BMI > 30 kg/m^2)

a 5-year period in 14.4% of middle-aged adults with CACS = 0 at the initial scan. Newly published studies from the CAC consortium, an ongoing multicenter study, demonstrated increased prevalence of CAC in individuals with overweight and obesity compared to individuals with normal weight, and an overall CAC prevalence of 21.8% in individuals aged 30–39 years.[29,30] The CAC consortium study population was asymptomatic; however, had clinical indications for CAC scoring, most often hyperlipidemia or a family history of CVD, which might explain the high occurrence of elevated CACS. The Bogalusa Heart study described the prevalence of fatty streaks and fibrous plaques in childhood and young adulthood by autopsy studies performed on individuals who had died from various causes, mostly accident or homicide.[31] The prevalence of fatty streaks was 85% at age 21–39 years and the prevalence of fibrous plaque lesions in the coronary arteries was 69% at age 26–39 years. Traditional cardiovascular risk factors such as BMI, lipids, and blood pressure were strongly associated with the amount of lesions. The Muscatine Study investigated a representative sample of a cohort from Iowa, and demonstrated increased carotid intima media thickness in adults aged 33–42 years with increased levels of total cholesterol in childhood and 21% with CAC at age 29–37.[32,33] Overall, it would be expected to find some degree of coronary calcification in the present study. CAC measured by CT is considered a reliable, noninvasive technique to evaluate coronary plaque burden associated with cardiovascular events.[34] It does, however, not evaluate noncalcified plaques or increased intima media thickness. Taken together with previous research, the findings seem to indicate that below 30 years of age only soft noncalcified plaques are evident, despite having a high-risk profile measured by multiple other parameters.

This study supports the association of higher levels of IL-6, fibrinogen, hs-CRP, and to some degree TNF-α with higher BMI. However, lowering of LDL-C is the primary aim of lipid-lowering therapy and only insignificant differences across male BMI-strata were seen in the current study. This emphasizes the question about the role of inflammation in CVD; inflammation could be causatively related to atherosclerosis or merely a risk marker which is not involved in the pathogenesis. The Jupiter trial evaluated apparently healthy individuals with low LDL-C but increased hs-CRP to see if vascular protection was achieved by statin treatment in the absence of hypercholesterolemia. The researchers found a reduction in both LDL-C and hs-CRP and a 44% reduction in all vascular events.[35] This does not answer the question on a causative role of inflammation as

reduced hs-CRP could potentially be secondary to reduced LDL-C. However, based on the overall high-risk profile of the groups with obesity in the present study, the findings support a more sophisticated risk assessment of young individuals including inflammatory markers, independently of levels of LDL-C and total cholesterol.

The observed more than twofold level of insulin in participants with obesity compared to participants with normal weight is striking, in particular in light of the normal levels of HbA1c. These findings indicate that abnormal insulin-desensitizing signals from target tissues has initiated but widespread impaired glucose homeostasis is not yet complete. Prior studies have furthermore shown that increased levels of TNF-α and IL-6 may be related to insulin resistance and this association, together with the association between hyperinsulinemia and CVD endpoints, need further investigation.[36,37]

4.1 | Limitations

The study is descriptive in nature and does not document any causal pathways between obesity and CVD risk. The biomarkers measured in this study can be both an antecedent and a consequence of each other. However, multiple and overlapping biomarkers involved in cardiovascular, metabolic, and inflammatory status were performed to strengthen the results. This study only investigated calcified lesions at the low dose CT scan. Supplementary noninvasive image modalities would be necessary to evaluate noncalcified plaques, intima media thickness, or pericardial fat depositions which could be of interest in this young population.

Epidemiological challenges concerning participation should also be mentioned. Responders to questionnaires generally have higher socioeconomic position and better health. A former study investigating the initial nonparticipation in the West Jutland Cohort study revealed that nonresponders were more likely to come from families with lower income and educational levels.[25] Further selection on most healthy individuals wanting to participate in a clinical examination is possible; however, this was accounted for by BMI-stratified inclusion and reliability of this selection was supported by measurements of body composition. Supplementary analyses (not shown) on self-reported lifestyle factors (smoking and physical activity), register based educational level at age 28, and parental cardiometabolic diseases revealed no statistically significant differences in sex- and BMI-stratified groups comparing study participants with nonparticipating responders to the latest questionnaire. Furthermore, the narrow age range of participants insure that no age effect can confound the variation in biomarker levels across BMI.

5 | CONCLUSION

In conclusion, increased BMI in young adults seems to be associated with only slightly increased levels of clinically used risk markers while several novel cardiometabolic biomarkers were markedly elevated. Cardiac CT detected no clinically significant coronary artery calcification in any of the participants. These findings support the hypothesis of an early onset insulin resistance and inflammatory response to obesity leading to increased cardiometabolic risk. CACS-screening in young, asymptomatic individuals does not seem justified based on these results but the findings hold promise that intervention at early age can precede formation of calcified plaques in the coronary arteries. A more sophisticated risk assessment, including novel cardiometabolic biomarkers, could be considered to improve preventive strategies of obesity-related CVD at this early stage.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Mia Klinkvort Kempel, Trine Nøhr Winding, Johan Hviid Andersen, and Morten Böttcher contributed to the conception and design of the work. All authors contributed to the acquisition and interpretation of data. Mia Klinkvort Kempel analyzed the data and drafted the manuscript. All critically revised the manuscript and gave final approval.

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