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Comparing the metabolic signatures of obesity defined by waist circumference, waist-hip ratio, or BMI

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Abstract

Objective: Measuring obesity is crucial for assessing health risks and developing effective prevention and treatment strategies. The most common methods used to measure obesity include BMI, waist circumference, and waist-hip ratio. This study aimed to determine the metabolic signatures associated with each measure of obesity in the Qatari population.

Methods: Metabolomics profiling was conducted to identify, quantify, and characterize metabolites in serum samples from the study participants. Inverse rank normalization, principal component analysis, and orthogonal partial least square-discriminant analysis were used to analyze the metabolomics data.

Results: This study revealed significant differences in metabolites associated with obesity based on different measurements. In men, phosphatidylcholine and phosphatidylethanolamine metabolites were significantly enriched in individuals classified as having obesity based on the waist-hip ratio. In women, significant changes were observed in leucine, isoleucine, and valine metabolism metabolites. Unique metabolites were found in the different categorization groups that could serve as biomarkers for assessing many obesity-related disorders.

Conclusions: This study identified unique metabolic signatures associated with obesity based on different measurements in the Qatari population. These findings contribute to a better understanding of the molecular pathways involved in obesity and may have implications for developing personalized prevention and treatment strategies.

INTRODUCTION

Obesity is defined as the excessive or abnormal accumulation of fat or adipose tissue in the body that impairs health via its association with the risk of developing diabetes mellitus, cardiovascular disease (CVD), hypertension, and hyperlipidemia [1]. Measuring obesity is important for assessing health risks and developing effective prevention and treatment strategies. There are various methods to measure obesity, each with its own strengths and limitations [2].

The most common method is the body mass index (BMI), which is a measure of body fat based on height and weight: weight in kilograms divided by height in meters squared [3]. A BMI of 30 or higher

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is considered obesity, and it is associated with an increased risk of metabolic syndrome [4]. Other methods include waist circumference (WC) and the waist-hip ratio (WHR). WC is a simple method to assess abdominal adiposity, also known as visceral obesity, that is easy to standardize and apply [5]. A WC greater than or equal to 94 cm for men and greater than or equal to 80 cm for women is often used as a criterion to identify central or abdominal obesity [6]. WHR considers body fat distribution [7]. WHR is obtained by dividing the WC by the hip circumference using the same units of measurement for both [8]. The World Health Organization defines abdominal obesity as a WHR above 0.90 for the male population and above 0.85 for the female population [9]. A study by Bener et al. assessed the best cutoffs of the three categories (BMI, WC, and WHR) in the Qatari population and found that the obesity criteria with the highest sensitivity and specificity in the male population were BMI ≥ 28, WC ≥ 99.5 cm, and WHR ≥ 0.9, whereas in the female population they were BMI ≥ 28.4, WC ≥ 91 cm, and WHR ≥ 0.88 [2].

Metabolomics is a powerful tool for studying the metabolic alterations associated with obesity and its complications. It is the comprehensive analysis of small molecules (metabolites) in biological samples, such as blood, urine, or tissue, that reflect the organism's metabolic state [10, 11].

Several studies have investigated the metabolic signatures of obesity by comparing BMI, WC, and WHR measurements in different populations [12, 13]. These studies have identified metabolic signatures associated with obesity, cancer risk, insulin resistance, and type 2 diabetes. Metabolomics has the potential to be used as a diagnostic tool for these conditions [14].

In this study, we aimed to determine the metabolic signatures associated with each population with obesity using the three different criteria: BMI, WC, and WHR. The hypothesis was that unique metabolites associated with each of these sets of criteria could indicate the molecular pathways that are associated with each individual obesity measure. Determining these unique metabolic signatures would help in the selection of optimal obesity measures for studying different obesity-associated comorbidities.

Study Importance

What is already known?

- Although different obesity measures exist and their links to various health risks are established, the specific metabolic signatures unique to each measurement remain unknown.

What does this study add?

- This study highlights the crucial role of gut microbiota and their metabolites in obesity, guiding future research toward antiobesity therapies targeting the gut microbiome. Our findings carry notable implications for personalized medicine, especially in the Persian Gulf. By offering insights into optimal obesity measurement tools and tailored cutoffs for the Qatari population, we aim to enhance understanding of obesity and its metabolic effects in the region.

How might these results change the direction of research or the focus of clinical practice?

- This study advocates personalized obesity management, considering gender differences and appropriate measurement tool selection for specific health concerns. It highlights the gut microbiota's potential, opening avenues for research on mechanisms, treatment, and innovative diagnostics. These insights promise to enhance health care, aiding tailored interventions and management strategies. However, limitations such as generalizability and the study's observational nature call for further longitudinal studies.

METHODS

Data source and study participants

This study gathered information from people using Qatar Biobank (QBB). The QBB database contains detailed information about Qatari nationals and long-term residents (those living in Qatar for 15 or more years) who are 18 years old and older. It includes basic personal details and health information such as BMI, blood pressure, and blood test results, as well as information about diabetes history, medications, and metabolomics data on 1000 different metabolites. All these measurements were performed at the Hamad Medical Corporation's central laboratory, which is certified by the College of American Pathologists. This research was approved by QBB's Institutional Review Boards (QF-QBB-RES-ACC-00125). As illustrated in Figure 1, patients were categorized based on age (20–40 years), sex ($n = 665$ women and $n = 779$ men), and specific BMI, WC, and WHR criteria derived from the Bener et al. study on Qatari adults and stratified by gender [2]. For the male group, this included BMI ≥ 28, WC ≥ 99.5 cm, and WHR ≥ 0.9, whereas for the female group, the criteria were BMI ≥ 28.4, WC ≥ 91 cm, and WHR ≥ 0.88.

Metabolomics

Metabolomics profiling was conducted at Metabolon in Durham, North Carolina, following established protocols. The procedures involved the use of a Waters ACQUITY ultra-performance liquid chromatography (UPLC) and a Thermo Scientific Q-Exactive high-resolution/accurate mass spectrometer connected to a heated electrospray ionization (HESI-II) source and Orbitrap mass analyzer with a mass resolution of 35,000. A comprehensive explanation of the liquid chromatography–mass spectrometry methodology has been provided previously [15, 16]. Briefly, serum samples underwent methanol

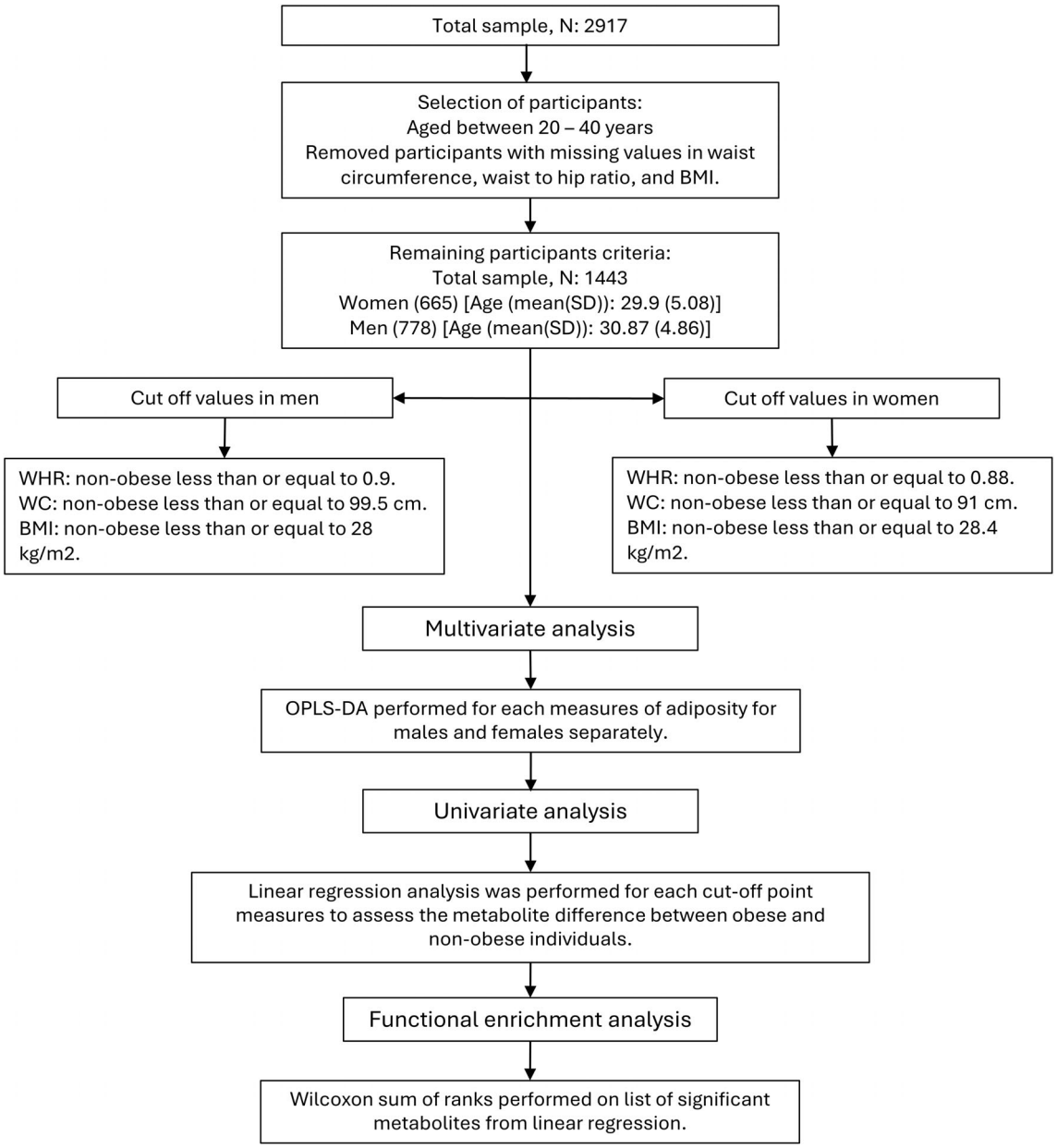

FIGURE 1 A schematic representation of study design. OPLS-DA, orthogonal partial least square-discriminant analysis; WC, waist circumference; WHR, waist-hip ratio.

extraction to eliminate the protein component. The resulting extract was divided into five segments: two were analyzed using distinct reverse-phase UPLC_tandem mass spectrometry (MS/MS) methods with positive ion mode electrospray ionization (ESI), one underwent analysis using reverse-phase UPLC_MS/MS with negative ion mode ESI, another was subjected to analysis through hydrophilic interaction chromatography/UPLC_MS/MS with negative ion mode ESI, and one sample was preserved as a backup. Following this, raw data were processed, peaks were identified, and quality control procedures were applied using Metabolon's hardware and software [17]. The compounds were identified by comparing them to entries in a library of either purified standards or recurring unknown substances. This library contained over 3300 commercially available purified standard compounds. For each compound, the library matches were scrutinized for every sample and adjusted when needed.

Statistical analysis

The metabolomics data underwent inverse rank normalization, and the analysis was conducted using SIMCA software (version 18.0.0). SIMCA is a flexible software for multivariate data analysis that utilizes advanced algorithms and interactive visual tools to investigate, analyze, and interpret intricate data sets. Various multivariate analyses were performed, encompassing unsupervised methods such as principal component analysis and supervised techniques such as

orthogonal partial least square-discriminant analysis. We employed R software (version 4.2.1) to carry out linear models for each metabolite. These models incorporated several confounding factors, including age, sex, BMI, and the first two principal components from principal component analysis. Subsequently, nominal p values were adjusted using the false discovery rate (FDR) method to account for multiple testing. An FDR < 0.05 was considered indicative of statistical significance. To further explore the data, we conducted functional enrichment analysis on the metabolite lists ordered by their p values from the linear models in this study. This analysis was performed using a one-way Wilcoxon rank sum test followed by the FDR multiple-testing correction method. The subpathways were previously characterized by Metabolon using a combination of Creative Proteomics technology, advanced bioinformatics tools, and databases to link identified metabolites to distinct metabolic pathways. Any subpathways with less than three significant matches were excluded from the analysis. Furthermore, the uniquely significantly modified metabolites with FDR ≤ 0.01 in each cutoff group were assessed for their association with obesity-related comorbidities such as CVD, diabetes, cancer, liver diseases, and kidney diseases through the Human Metabolome Database [18] and the literature.

RESULTS

General characteristics of study participants

A total of 1443 participants aged between 28 and 37 years were included (male, $n = 778$; female, $n = 665$). Obesity was defined using three measures of adiposity: BMI, WC, and WHR. Female participants had a greater BMI mean in the WC and WHR groups compared to the male participants in the same groups, whereas both BMI cutoff points showed similar means among both male and female participants.

Significantly higher levels of various health markers (blood pressure, liver profile, kidney profile, and lipid profile) using the WC, WHR, and BMI cutoff point measurements were identified in the male group and the female group (Tables 1 and 2).

Multivariate analysis of metabolites differentiating obesity and nonobesity based on different cutoffs

A nontargeted metabolomics analysis of serum samples from the 1443 participants was applied to identify metabolites that differentiate men from women to reveal metabolic signatures of obesity associated with using different measurements. Orthogonal partial least square-discriminant analysis was performed in participants without obesity and in participants with obesity from among the male participant (Figure 2 and Figure S1) and female participant (Figure 3 and Figure S1) groups.

Figure 2 shows a scatter plot of these components, distinguishing the participants without obesity from those with obesity in a two-dimensional space representation. The loading plots highlight enriched pathways that significantly changed between male participants without obesity and participants with obesity, as predicted based on different cutoffs in the Qatari population. Specifically, the pathways involving phosphatidylcholine and phosphatidylethanolamine within WHR, as well as the long-chain monounsaturated fatty acid pathway within the context of WHR and BMI, significantly change with obesity.

The loading plots in Figure 3 reveal enriched pathways that exhibited significant differences between female participants without obesity and participants with obesity, as predicted based on various cutoffs within the Qatari population. In particular, the pathways involving leucine, isoleucine, and valine within the context of WC were significantly different in participants with obesity.

Significant metabolites associated with obesity in men and women using different measurements of obesity

The linear model revealed significant differences in metabolites between men and women according to WC, WHR, and BMI measures.

Among the significantly altered metabolic pathways, the phosphatidylcholine pathway was significantly overrepresented based on enrichment analysis of the nominally significant metabolites from the male comparisons ($p = 5.1 \times 10^{-5}$) and female ($p \leq 0.0011$) comparisons using the WHR (Table 3).

Common and unique metabolites associated with obesity using different obesity measurements

Figure 4 illustrates how these three measures of obesity (WC, WHR, BMI) cluster together in both men and women, revealing common and unique metabolites associated with each. In men, there were 36 unique metabolites associated with WC, 40 metabolites associated with WHR, and 32 metabolites associated with BMI. The predominant metabolite categories for these were lipids and amino acids, constituting 11.3%, 12.6%, and 10.1% of the total, respectively. In women, 37 metabolites were associated with WC, 5 metabolites with WHR, and 101 metabolites with BMI. The primary metabolite categories in women were lipids and xenobiotics, making up 12.3%, 1.7%, and a significant 33.4% of the total, respectively.

DISCUSSION

Obesity is a global health problem that affects millions of people and increases the risk of various chronic diseases. To accurately assess obesity and its metabolic implications, it is important to consider multiple measurements such as WC [19], WHR [20], and BMI [21]. Although BMI is a widely used metric for assessing weight status and identifying potential health risks associated with excess body weight, it does not differentiate between different types of obesity or

TABLE 1 General characteristics of male participants according to the three cutoff criteria.

	WC cutoff				WHR cutoff				BMI cutoff			
Variable	**Without obesity**	**With obesity**	***p* value**	**FDR**	**Without obesity**	**With obesity**	***p* value**	**FDR**	**Without obesity**	**With obesity**	***p* value**	**FDR**
n	597	181	—	—	555	223	—	—	437	341	—	—
Without diabetes/with diabetes (frequency)	566/31	15/24	—	—	53/21	189/34	—	—	416/21	307/34	—	—
Physical tests												
Age, y	31 (27–35)	32 (28–36)	0.003		30 (26–34)	33 (29–37)	<0.001		31 (27–35)	32 (28–35)	0.024	
BMI, kg/m^2	25.82 (23.3–28.25)	35.25 (32.58–38.86)	<0.001	<0.001	25.99 (23.18–29.05)	30.59 (27.92–34.95)	<0.001	<0.001	24.47 (22.7–26.28)	31.8 (29.46–35.71)	<0.001	<0.001
Sitting height, cm	91.1 (88.1–96.025)	92.6 (89.4–132.13)	0.056	0.101	91.3 (88.5–96.18)	91.7 (88.4–98.3)	0.307	0.423	91.1 (88.2–96.1)	91.8 (88.9–96.75)	0.255	0.331
Weight, kg	77 (69.7–85.2)	107.1 (96–119.2)	<0.001	<0.001	78.3 (69.75–88.9)	91.7 (81.6–106.7)	<0.001	<0.001	73.7 (67.2–79)	94.9 (88–108.9)	<0.001	<0.001
Waist size, cm	87 (80–92)	108 (103–115)	<0.001	<0.001	86 (79.5–92)	101 (95–111)	<0.001	<0.001	83 (78–88)	100 (94–109)	<0.001	<0.001
Hips size, cm	101 (96–106)	119 (112–127)	<0.001	<0.001	102 (96–108)	107 (102–116)	<0.001	<0.001	99 (94–102)	112 (106–119)	<0.001	<0.001
Waist-hip ratio	0.85 (0.81–0.89)	0.93 (0.89–0.97)	<0.001	<0.001	0.84 (0.81–0.87)	0.94 (0.92–0.97)	<0.001	<0.001	0.84 (0.81–0.88)	0.9 (0.86–0.94)	<0.001	<0.001
Left handgrip	40 (35–46)	40 (34–46)	0.572	0.647	40 (36–46)	40 (34–46)	0.196	0.302	40 (34–46)	40 (36–46)	0.093	0.145
Right handgrip	42 (38–49)	42 (38–49.25)	0.843	0.863	42 (38–50)	42 (36–48)	0.126	0.214	42 (38–48)	44 (39–50)	0.039	0.067
Blood pressure												
Average systolic blood pressure, mmHg	113 (107–120)	117 (109–123)	<0.001	0.001	113 (107–119)	117 (109–124)	<0.001	<0.001	112 (106–118)	117 (109–124)	<0.001	<0.001
Average diastolic blood pressure, mmHg	72 (66–77)	77 (71–82)	<0.001	<0.001	71 (65–77)	76 (70–82)	<0.001	<0.001	71 (65–76)	75 (70–81)	<0.001	<0.001
Average pulse rate, beats/min	66 (60–72)	71 (63–77)	<0.001	<0.001	66 (60–72)	70 (63–77.5)	<0.001	<0.001	65 (60–71)	69 (63–75)	<0.001	<0.001
Liver profile												
Bilirubin total, µmol/L	7.3 (5.5–10)	6.9 (5–9.2)	0.055	0.101	7.2 (5.5–10.2)	7 (5.275–9.225)	0.202	0.302	7.5 (5.6–10.525)	6.8 (5.2–9.3)	0.015	0.026
Albumin, g/L	47 (45–48)	45 (44–47)	<0.001	<0.001	47 (45–48)	46 (44–48)	0.412	0.543	47 (46–49)	46 (44–48)	<0.001	<0.001
Alkaline phosphatase, U/L	68 (58–80)	69.5 (58–81)	0.275	0.358	69 (57–80)	69 (59.5–82)	0.128	0.214	69 (58–79)	69 (58–81.25)	0.118	0.180
ALT (SGPT), U/L	22 (16–34)	33 (23–46)	<0.001	<0.001	22 (16–33)	33 (23–46)	<0.001	<0.001	21 (16–32)	30 (21–43)	<0.001	<0.001
AST (SGOT), U/L	19 (16–24)	22 (18–26)	<0.001	<0.001	19 (16–23)	22 (18–27)	<0.001	<0.001	19 (16–23)	21 (17–26)	<0.001	<0.001
GGT, U/L	21 (15–29)	28.5 (19.25–40.5)	0.001	0.004	20 (15–26)	35 (21.25–49.5)	<0.001	<0.001	20.5 (15–27.75)	26 (19–38)	0.001	0.003
Kidney profile												
Bicarbonate, mmol/L	27 (26–28)	26 (25–27)	<0.001	<0.001	27 (26–28)	26 (25–28)	<0.001	<0.001	27 (26–28)	26 (25–28)	<0.001	<0.001
Creatine kinase, U/L	113 (81–174)	120 (80–182)	0.821	0.851	115 (80.5–173)	113 (80.5–182)	0.835	0.941	108 (80–174)	120 (82–181)	0.676	0.735
Creatinine, µmol/L	77 (70–84)	74 (68–81)	0.001	0.003	77 (70–84)	74 (69–81)	0.054	0.111	77 (71–84)	75 (69–83)	0.004	0.009

TABLE 1 (Continued)

Variable	WC cutoff				WHR cutoff				BMI cutoff			
	Without obesity	With obesity	*p* value	FDR	Without obesity	With obesity	*p* value	FDR	Without obesity	With obesity	*p* value	FDR
Sodium, mmol/L	141 (140–142)	140 (139–142)	0.006	0.013	141 (140–142)	141 (139–142)	0.207	0.302	141 (140–142)	140 (139–142)	0.001	0.003
Urea, mmol/L	4.6 (4–5.4)	4.6 (3.8–5.5)	0.157	0.240	4.6 (4–5.4)	4.5 (3.85–5.5)	0.363	0.493	4.7 (4–5.4)	4.5 (3.8–5.2)	0.014	0.025
Uric acid, µmol/L	332 (295–380)	384 (339–433)	<0.001	<0.001	339 (295–382)	363 (318–424.5)	<0.001	<0.001	327 (288–368)	372 (327–423)	<0.001	<0.001
Blood sugar												
Glucose mmol/L	5 (4.7–5.36)	5.2 (4.9–5.7)	<0.001	<0.001	5 (4.7–5.345)	5.2 (4.9–5.7)	<0.001	<0.001	5 (4.7–5.33)	5.13 (4.8–5.64)	<0.001	<0.001
HbA1c, %	5.3 (5.1–5.5)	5.5 (5.2–5.8)	<0.001	<0.001	5.3 (5.1–5.5)	5.4 (5.1–5.8)	0.001	0.003	5.3 (5.1–5.5)	5.4 (5.1–5.7)	<0.001	0.001
Insulin, µU/mL	8.4 (6–15.1)	15.55 (10–26.175)	<0.001	<0.001	8.5 (5.95–16.15)	14.05 (9–22.88)	<0.001	<0.001	7.8 (5.3–14)	13.85 (8.6–22.83)	<0.001	<0.001
C-peptide ng/mL	2.06 (1.46–2.99)	3.11 (2.43–4.34)	<0.001	<0.001	2.04 (1.45–3.02)	2.9 (2.2–4.06)	<0.001	<0.001	1.88 (1.37–2.81)	2.73 (2.09–4.02)	<0.001	<0.001
Lipid profile												
Cholesterol total, mmol/L	4.8 (4.27–5.4)	4.98 (4.4–5.5)	0.232	0.306	4.7 (4.2–5.3)	5.08 (4.52–5.6)	0.001	0.002	4.8 (4.28–5.33)	4.93 (4.3–5.5)	0.227	0.314
HDL cholesterol, mmol/L	1.21 (1.02–1.42)	1.08 (0.9–1.24)	<0.001	<0.001	1.21 (1.03–1.44)	1.08 (0.93–1.25)	<0.001	<0.001	1.24 (1.04–1.45)	1.1 (0.95–1.27)	<0.001	<0.001
LDL cholesterol, calc mmol/L	3 (2.49–3.56)	3.02 (2.65–3.7)	0.186	0.261	2.96 (2.42–3.54)	3.12 (2.8–3.735)	0.001	0.003	3 (2.43–3.54)	3 (2.6025–3.66)	0.048	0.080
Triglycerides, mmol/L	1.1 (0.8–1.65)	1.4 (0.99–2.1)	<0.001	<0.001	1.1 (0.8–1.6)	1.49 (1–2.3)	<0.001	<0.001	1.1 (0.8–1.6)	1.3 (0.9–1.9)	<0.001	<0.001

Note: The results of the factors are presented as median (IQR).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FDR, false discovery rate; GGT, gamma-glutamyl transpeptidase; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; WC, waist circumference; WHR, waist-hip ratio.

TABLE 2 General characteristics of female participants according to the three cutoff criteria.

	WC cutoff				WHR cutoff				BMI cutoff			
Variable	Without obesity	With obesity	*p* value	FDR	Without obesity	With obesity	*p* value	FDR	Without obesity	With obesity	*p* value	FDR
n	555	110	—		638	27	—		408	257	—	—
Without diabetes/with diabetes (frequency)	537/18	94/16	—	—	611/27	20/7	—	—	401/7	230/27	—	—
Physical tests												
Age, y	29 (25–34)	33 (28–36)	<0.001		29 (26–34)	31 (28–35)	0.119		29 (25–33)	31 (28–36)	<0.001	
BMI, kg/m^2	25.4 (22.4–28.72)	35.7 (33.68–40.03)	<0.001	<0.001	26.38 (22.95–30.67)	35.17 (33.59–39.07)	<0.001	<0.001	23.86 (21.47–26)	33.08 (30.41–35.73)	<0.001	<0.001
Sitting height, cm	87.6 (83.2–133.2)	90.6 (84.43–134.53)	0.121	0.205	87.6 (83.3–133.4)	90 (84.5–133.65)	0.492	0.765	87.55 (83–133.525)	88.45 (84.08–133.3)	0.464	0.586
Weight, kg	63.8 (56.9–73.15)	92.55 (84.78–104.18)	<0.001	<0.001	66.35 (57.9–78.7)	88.1 (78.55–102.85)	<0.001	<0.001	59.9 (54.1–65.8)	83.8 (76.9–91.2)	<0.001	<0.001
Waist size, cm	76 (69.5–82)	98 (94–104.75)	<0.001	<0.001	78 (70–86)	104 (98–116.5)	<0.001	<0.001	73 (68–78)	89 (84–96)	<0.001	<0.001
Hips size, cm	102 (97–109)	121 (115–128)	<0.001	<0.001	104 (98–113)	115 (107.5–120.5)	0.001	0.007	99 (95–104)	115 (110–122)	<0.001	<0.001
Waist-hip ratio	0.73 (0.7–0.77)	0.82 (0.78–0.87)	<0.001	<0.001	0.74 (0.7–0.78)	0.91 (0.89–0.935)	<0.001	<0.001	0.73 (0.69–0.77)	0.77 (0.72–0.82)	<0.001	<0.001
Left handgrip	22 (18–26)	22 (20–28)	0.128	0.210	22 (18–26)	23 (19.5–29)	0.152	0.358	22 (18–26)	23 (20–28)	0.001	0.002
Right handgrip	24 (20–28)	26 (22–30)	0.465	0.578	24 (20–28)	26 (21.5–30)	0.286	0.540	24 (20–28)	26 (22–30)	0.004	0.011
Blood pressure												
Average systolic blood pressure, mmHg	101 (96–107)	109 (103–116)	<0.001	<0.001	102 (96–109)	107 (100.5–112.5)	0.077	0.204	100 (95–106)	106 (99–113)	<0.001	<0.001
Average diastolic blood pressure, mmHg	67 (62–72)	73.5 (67–79)	<0.001	<0.001	68 (63–73)	71 (66–77)	0.035	0.123	67 (62–71)	70 (64–77)	<0.001	0.001
Average pulse rate, beats/min	71 (65–77)	71 (66–78.75)	0.158	0.250	71 (65–77)	76 (66.5–78)	0.163	0.373	71 (65–77)	70 (64–78)	0.301	0.391
Liver profile												
Bilirubin total, µmol/L	5.7 (4–8)	5 (4–7)	0.378	0.496	5.4 (4–7.6)	6 (5–7.6)	0.239	0.495	6 (4–8)	5 (4–7)	0.012	0.024
Albumin, g/L	45 (43–46.5)	42 (41–44)	<0.001	<0.001	45 (43–46)	42 (41–45)	<0.001	0.001	45 (44–47)	43 (42–45)	<0.001	<0.001
Alkaline phosphatase, U/L	60 (51–72)	72 (60–88)	<0.001	<0.001	61 (51–74)	70 (55–95)	0.001	0.006	59 (50–70)	68 (56–81)	<0.001	<0.001
ALT (SGPT), U/L	12 (10–17)	16.5 (12–22)	<0.001	<0.001	13 (10–18)	18 (13–21.5)	0.052	0.161	12 (10–16)	14 (11–20)	<0.001	0.001
AST (SGOT), U/L	16 (13–18)	16 (13–19)	0.188	0.282	16 (13–18)	17 (13–21)	0.284	0.540	16 (13.75–18)	15 (13–18)	0.924	0.942
GGT, U/L	11 (8–14)	16 (13–27.5)	<0.001	<0.001	12 (9–15)	33 (14–78)	<0.001	<0.001	11 (8–13)	14 (10–21)	<0.001	<0.001
Kidney profile												
Bicarbonate, mmol/L	26 (24–27)	26 (24–27)	0.410	0.517	26 (24–27)	26 (24.5–27.5)	0.413	0.719	26 (24–27)	25 (24–27)	0.007	0.016
Creatine kinase, U/L	63 (49–86)	65 (50–82)	0.965	0.965	64 (49.5–86)	57 (43–71)	0.449	0.760	61 (48–83)	69 (51–89.5)	0.180	0.250
Creatinine, µmol/L	55 (50–61)	55 (51–61)	0.716	0.788	55 (51–61)	55 (50–62.5)	0.932	0.975	55 (50–60)	56 (51–61)	0.497	0.618

TABLE 2 (Continued)

Variable	WC cutoff				WHR cutoff				BMI cutoff			
	Without obesity	With obesity	*p* value	FDR	Without obesity	With obesity	*p* value	FDR	Without obesity	With obesity	*p* value	FDR
Total protein, g/L	73 (71–76)	72 (70–74)	0.001	0.003	73 (70–76)	72 (70–74)	0.331	0.600	74 (71–76)	72 (70–74)	<0.001	<0.001
Urea, mmol/L	3.7 (3.1–4.4)	3.7 (3.025–4.1)	0.123	0.205	3.7 (3.1–4.3)	3.3 (2.75–3.9)	0.043	0.139	3.7 (3–4.33)	3.7 (3.1–4.3)	0.432	0.553
Uric acid, µmol/L	233 (201–266)	280 (244.25–323.75)	<0.001	<0.001	238 (205–274.75)	268 (226.5–316)	0.007	0.030	227 (196.75–259)	263 (225–300)	<0.001	<0.001
Blood sugar												
Glucose, mmol/L	4.8 (4.5–5.1)	5.1 (4.7–5.6)	<0.001	<0.001	4.8 (4.5–5.1)	5.4 (4.8–6.3)	<0.001	<0.001	4.8 (4.5–5)	4.9 (4.7–5.3)	<0.001	0.001
HbA1c, %	5.2 (5–5.4)	5.5 (5.15–5.8)	<0.001	<0.001	5.2 (5–5.5)	5.4 (5.3–5.8)	0.004	0.017	5.2 (5–5.4)	5.4 (5.1–5.6)	<0.001	0.001
Insulin, µU/mL	7.95 (5–12.775)	15 (10–23)	<0.001	<0.001	8 (5.6–14)	17 (10–27)	<0.001	<0.001	7 (5–10.6)	12 (8–20)	<0.001	<0.001
C-peptide, ng/mL	1.77 (1.36–2.57)	3.04 (2.29–3.96)	<0.001	<0.001	1.89 (1.4–2.84)	2.94 (2.29–4.2)	<0.001	0.002	1.66 (1.29–2.37)	2.55 (1.89–3.71)	<0.001	<0.001
Lipid profile												
Cholesterol total, mmol/L	4.7 (4.19–5.2)	4.695 (4.35–5.2)	0.594	0.680	4.7 (4.2–5.2)	4.61 (4.26–4.96)	0.388	0.688	4.7 (4.17–5.17)	4.7 (4.27–5.2)	0.646	0.740
HDL cholesterol, mmol/L	1.55 (1.345–1.79)	1.21 (1.1–1.44)	<0.001	<0.001	1.495 (1.29–1.76)	1.21 (1.02–1.51)	<0.001	<0.001	1.6 (1.38–1.82)	1.34 (1.16–1.55)	<0.001	<0.001
LDL cholesterol, calc mmol/L	2.76 (2.07–3)	3 (2.49–3.12)	0.040	0.082	2.82 (2.1–3.04)	2.98 (2.45–3.01)	0.590	0.801	2.715 (2.03–3)	3 (2.32–3.16)	0.070	0.113
Triglycerides, mmol/L	0.8 (0.6–1.145)	1.225 (0.9–1.72)	<0.001	<0.001	0.87 (0.6–1.245)	1.2 (0.85–1.46)	0.061	0.181	0.8 (0.6–1.1)	1.08 (0.74–1.5)	<0.001	<0.001

Note: The results of the factors are presented as median (IQR).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FDR, false discovery rate; GGT, gamma-glutamyl transpeptidase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; WC, waist circumference; WHR, waist-hip ratio.

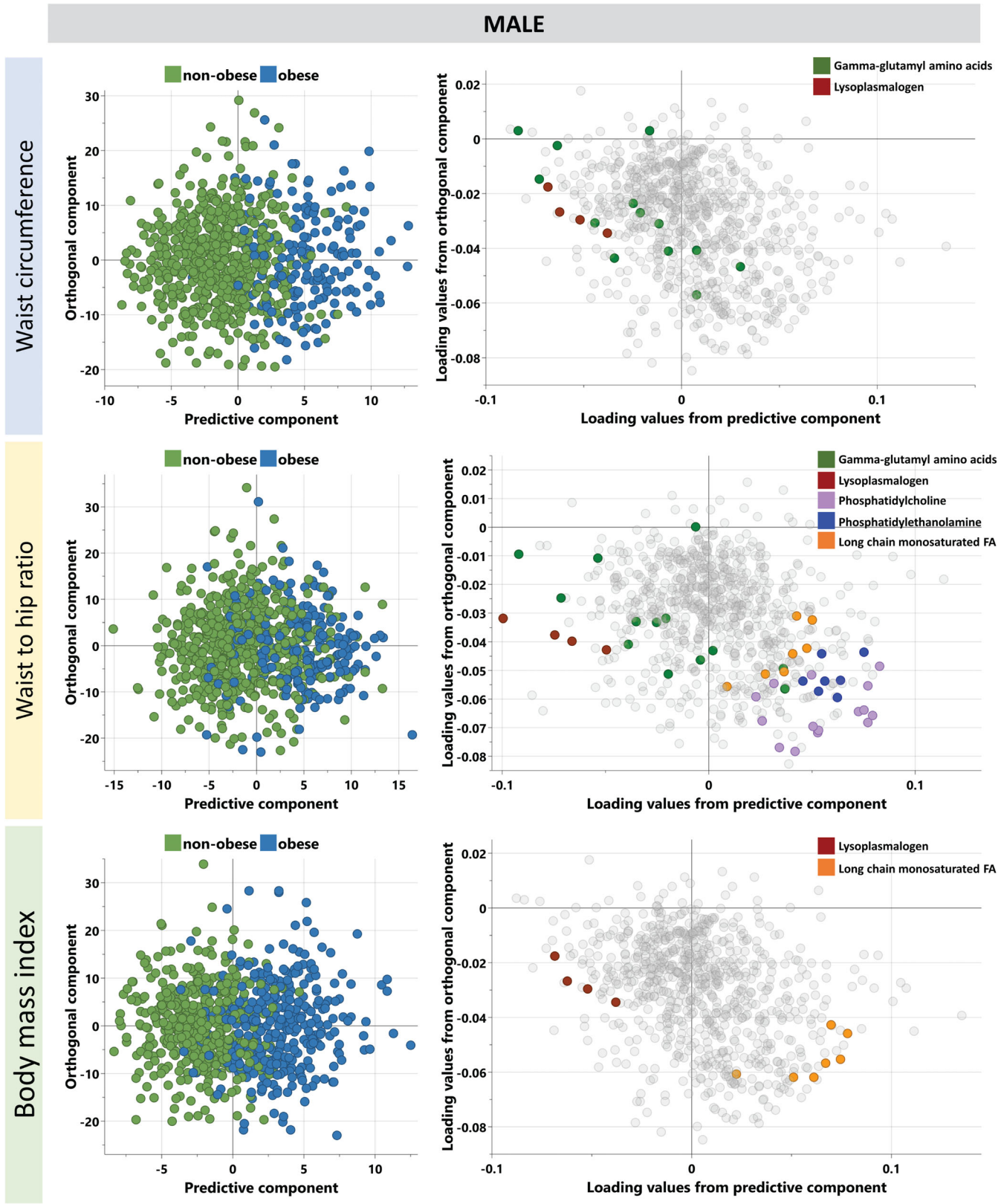

FIGURE 2 Scores and corresponding loading plots from orthogonal partial least square-discriminant analysis (OPLS-DA). Metabolic signatures between male participants with obesity and without obesity were predicted based on different cutoffs in the Qatari population. FA, fatty acid.

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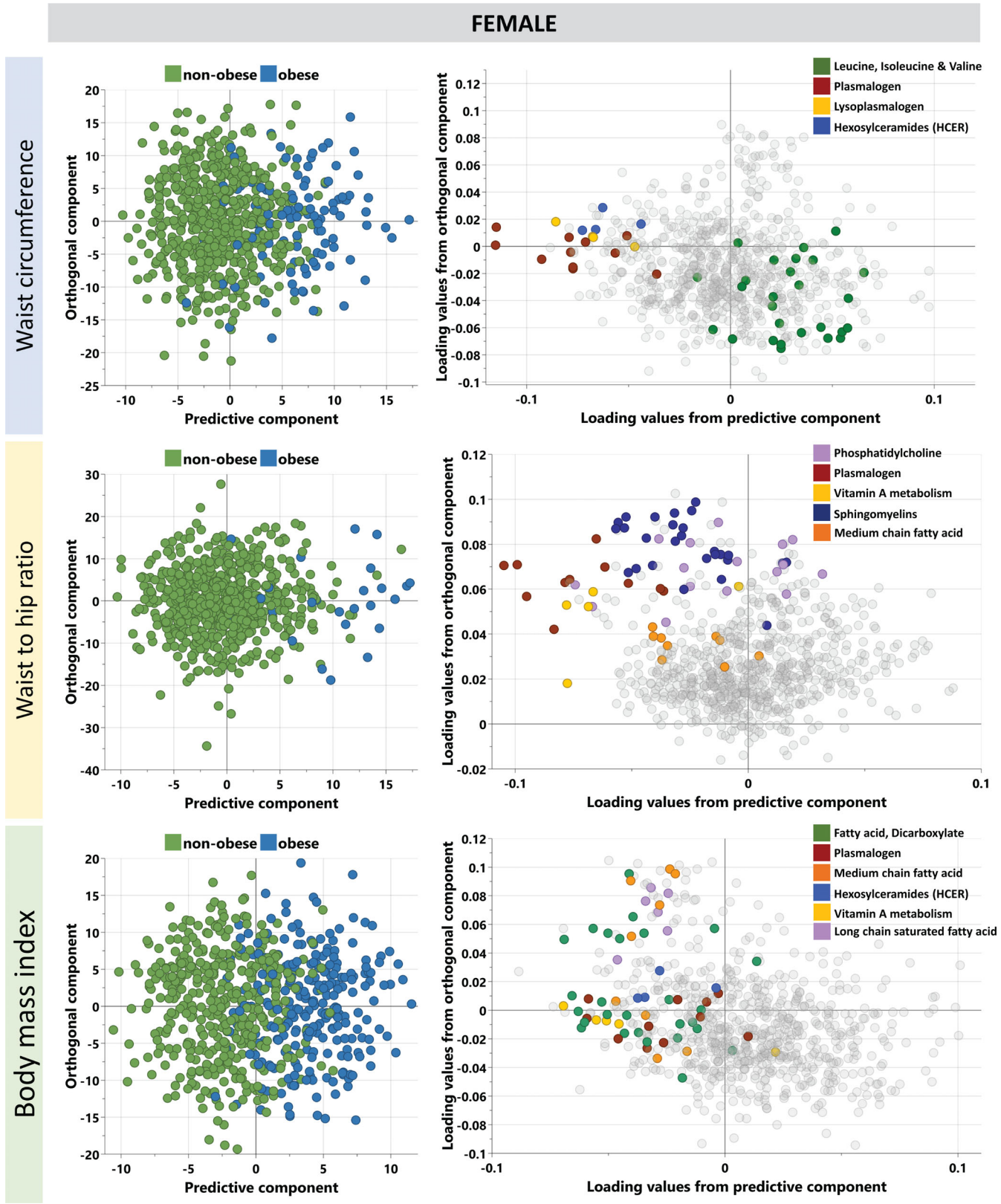

FIGURE 3 Scores and corresponding loading plots from orthogonal partial least square-discriminant analysis (OPLS-DA). Metabolic signatures between female participants with obesity and without obesity were predicted based on different cutoffs in the Qatari population.

TABLE 3 Significant pathways associated with obesity in male and female groups using different measurements of obesity.

	Subpathways	*p* value	FDR
Male			
WC	Lysoplasmalogen	0.0011	0.098
	Gamma-glutamyl amino acid	0.0019	0.098
WHR	PC	5.1×10^{-5}	0.005
	PE	0.0002	0.011
	Gamma-glutamyl amino acid	0.0006	0.020
	Lysoplasmalogen	0.0020	0.053
	Long-chain monounsaturated fatty acid	0.0038	0.079
BMI	Long-chain monounsaturated fatty acid	0.0007	0.051
	Lysoplasmalogen	0.0009	0.051
Female			
WC	Plasmalogen	5.9×10^{-6}	6.18×10^{-4}
	Leucine, isoleucine, and valine metabolism	0.0011	0.058
	Lysoplasmalogen	0.0034	0.090
	HCER	0.0034	0.090
WHR	Plasmalogen	6.09×10^{-7}	3.59×10^{-5}
	Sphingomyelins	7.04×10^{-7}	3.59×10^{-5}
	PC	0.0001	0.004
	Vitamin A metabolism	0.0013	0.034
	Medium-chain fatty acid	0.0026	0.053
BMI	Fatty acid, dicarboxylate	3.30×10^{-5}	0.004
	Medium-chain fatty acid	0.0005	0.025
	Plasmalogen	0.0021	0.063
	Long-chain saturated fatty acid	0.0026	0.063
	Vitamin A metabolism	0.0029	0.063
	HCER	0.0040	0.073

Note: Functional enrichment analysis of metabolites from linear regression ordered by *p* value using Wilcoxon rank sum test (in male and female groups). Significance was indicated by FDR < 0.1.

Abbreviations: FDR, false discovery rate; HCER, hexosylceramides; PC, phosphatidylcholine; PE, phosphatidylethanolamine; WC, waist circumference; WHR, waist-hip ratio.

distinguish between muscle mass and fat mass in individuals, which limits its specificity in certain cases. WC and WHR indicate a person's overall body fat content and offer insights into the distribution of fat throughout the body and the presence of abdominal obesity, which is associated with increased metabolic risk factors and health complications [20]. Metabolomics has the potential to be used as an approach to understanding the dynamics of metabolic processes involved in human obesity [22]. In this study, we aimed to assess the metabolomic signatures that are associated with the various definitions of obesity in male or female groups in order to identify the best categorization criterion for investigating obesity-related comorbidities.

Our identified metabolites were previously reported to be associated with various health outcomes in both male and female participants, such as CVD [23], diabetes risk [24], cancer risk [25], liver diseases [26], and kidney disease [27]. For CVD, WC and WHR emerged as superior metrics for the male group, whereas BMI proved most insightful for the female group. Diabetes, on the other hand, showed stronger links with WC in the male group and BMI in the female group, highlighting the varying roles of these measures across genders. Interestingly, WC or WHR in the male group and WC in the female group were identified as optimal for studying obesity-related cancer, whereas liver diseases exhibited complex associations with BMI in the male group and WHR or BMI in the female group. Finally, WC and WHR proved most informative for assessing kidney diseases in the male group and the female group, respectively (Tables S1–S5).

Overall, our results underscore the importance of considering gender and the most appropriate obesity parameter when investigating specific health outcomes. A single measure may not provide the complete picture, necessitating a nuanced approach to accurately understand the intricate interplay between obesity and its diverse health consequences.

Interestingly, the majority of our identified metabolites are gut microbiota–related metabolites. Indeed, obesity is closely related to

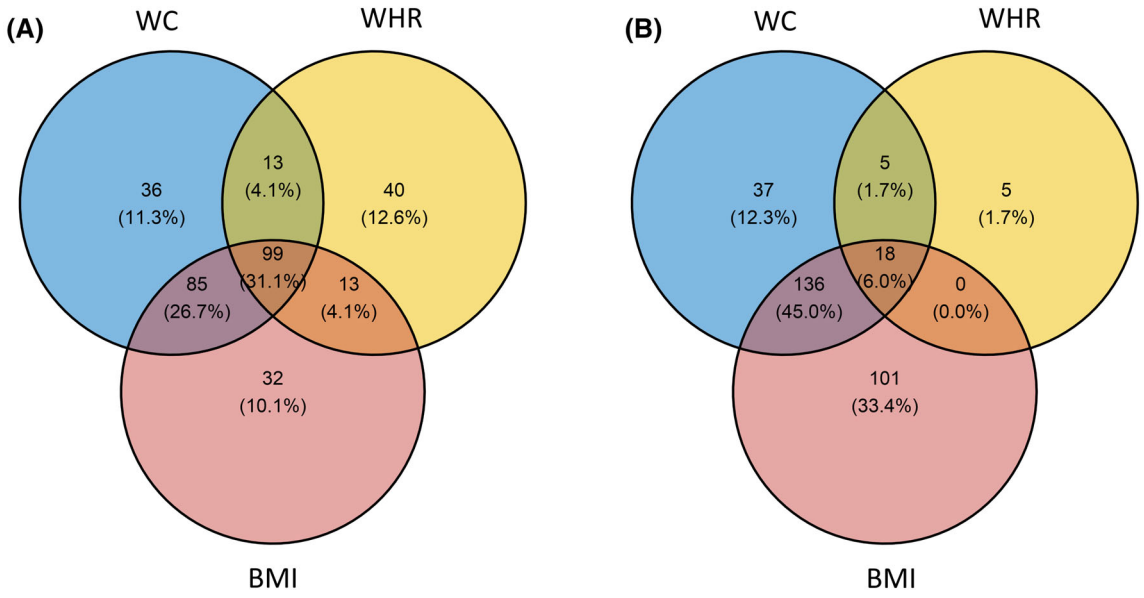

FIGURE 4 Venn diagram showing the FDR significant metabolites associated with obesity using different cutoff values in (A) men and (B) women. FDR, false discovery rate; WC, waist circumference; WHR, waist-hip ratio.

the gut microbiota [28], and studies have shown that an imbalance in the gut microbiome is a significant factor that contributes to obesity and the development of metabolic diseases [29]; moreover, microbiota management has emerged as a novel approach to treating obesity [30].

Our results showed that plasmalogens and lysoplasmalogens were significantly associated with participants without obesity in both genders and all three obesity categorization cutoffs. Plasmalogens are widespread in anaerobic bacteria [31]; recently, some members of the gut microbiota, including Bifidobacteria, Clostridia, and Bacteroides, have been shown to produce plasmalogens [32–34]. Moreover, plasmalogen-positive species have been shown to be enriched in the early-life human gut microbiome [35]. Additionally, research has shown that the consumption of postbiotics containing plasmalogens can provide various benefits in different contexts, such as obesity, type 2 diabetes, and cancer [36].

We hypothesize that gut-derived plasmalogens might contribute significantly to the plasmalogen pool in the host, thus playing an important role in human health. However, there is still relatively little information regarding the plasmalogen-producing bacteria in gut microbiota, and more research is needed to characterize the plasmalogen biosynthetic pathways and explore the therapeutic potential of targeting plasmalogens and lysoplasmalogens in the treatment of obesity-related diseases.

Our results also showed more gut microbiota–related lipid metabolites associated with different obesity measures, notably phosphatidylcholine, phosphatidylethanolamine, long-chain monounsaturated fatty acids, hexosylceramides, and sphingomyelins. The gut microbiota has been shown to promote significant alterations in the profile of glycerophospholipids, including phosphatidylcholine and phosphatidylethanolamines [37]. Additionally, long-chain fatty acids represent major constituents of the gut metabolome [38]. Moreover, the gut bacteria have been shown to produce sphingolipids, which enter the host metabolic pathways and impact ceramide levels [39].

In fact, the interplay between the gut microbiome and lipid homeostasis cannot be overstated, and it is relevant to the host physiology and metabolic diseases. By understanding the complex interactions between gut microbiota and lipid metabolism, the research community may develop new strategies for the prevention and treatment of obesity-related disorders.

Our results also showed other metabolites significantly associated with obesity measures and related to gut microbiota; they include 1-carboxyethylvaline, 1-carboxyethyltyrosine, pregnanediol-3-glucuronide, 3-phenylpropionate, indolepropionate, and glycolithocholate sulfate.

Strikingly, 3-phenylpropionate, indolepropionate, pregnanediol-3-glucuronide, and glycolithocholate sulfate, which are associated in our study with participants without obesity, were shown to predict higher microbiome diversity [40, 41], whereas 1-carboxyethylvaline and 1-carboxyethyltyrosine, which are associated in our study with participants with obesity, were shown to predict lower microbiome diversity [41]. However, the connection between microbiome diversity and obesity is highly contextual and complex and depends on many factors. Thus, further multiomics studies are needed to elucidate the properties of a healthy microbiome in the context of obesity.

Our findings are further corroborated by the significantly elevated levels of the liver enzyme gamma-glutamyl transpeptidase (GGT) that were found for all obesity measurements in male and female individuals with obesity when compared to their counterparts without obesity. There is evidence to suggest a link between GGT and gut microbiota, particularly in the context of metabolic syndrome. Recently, Sheng et al. showed that alterations of structural and functional gut microbiome were accompanied by elevated levels of GGT, which were characterized by increased levels of harmful bacteria [42].

Together with the existing literature, our results suggest a clear relationship between microbiome-related metabolites and obesity. However, there is still much to learn about how these metabolites contribute to the development or prevention of obesity.

This study holds some limitations, including that the data used in the study were obtained from QBB, which includes information from Qatari nationals and long-term residents. Therefore, the findings may not be generalizable to other populations. Additionally, the study focused on metabolic signatures and did not investigate other factors, such as lifestyle, diet, or genetic factors that may contribute to obesity. Moreover, the cross-sectional nature of the study limits its ability to validate the pathophysiological properties of the metabolites. Furthermore, this study was observational, which limits the nature of the relationship between the metabolites and the diseases to associations, which warrants future studies to validate the relationships. Finally, the WHR categorization in the female group yielded a low number of female participants who fulfilled the obesity definition. This limited the number of significantly altered metabolites in this category.

CONCLUSION

Our study corroborates the causal link between obesity and gut microbiota dysbiosis and highlights the importance of the microbiome as a new target for antiobesity therapies. This study may represent a step toward the understanding of the mechanisms by which variation of the microbiota and their metabolites can lead to obesity-related diseases. Future studies are warranted to comprehensively understand the role of these metabolites and the changes occurring in the gut microbiota in obesity, thus holding promise to create novel strategies that can be used to help treat this condition and related comorbidities.O

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CONFLICT OF INTEREST STATEMENT

The authors declared no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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