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The Association Between Detailed Obesity Measurements and Peripheral Neuropathy in Persons With Diabetes

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ABSTRACT

Background: Obesity increases the risk of diabetic peripheral neuropathy (DPN). However, past studies have typically assessed obesity using anthropometric measurements. Our primary aim determined associations between detailed obesity measurements, DPN, and painful DPN (pDPN). Our secondary aim compared the discriminatory capabilities of these measurements.

Methods: We performed a cross-sectional study of persons with diabetes. Obesity was assessed using anthropometrics, bioelectrical impedance (BIA), abdominal MRIs (aMRI), and/or dual x-ray absorptiometry (DEXA). Obesity measurements were categorized as measuring general, central, or peripheral obesity, or the central-peripheral obesity ratio. DPN was defined as Michigan Neuropathy Screening Instrument questionnaire ≥ 4. Within this group, pDPN was defined as bilateral foot pain in the prior 3 months. Areas under receiver operating characteristic curves (AUC) determined discriminatory capabilities of obesity measurements for DPN, stratified by sex.

Results: We identified 7090 persons with diabetes that completed DPN assessments (mean age: 58.4, 39.6% female), of which 100.0% completed anthropometrics, 98.4% completed BIA, 3.9% completed aMRI, and 2.3% completed DEXA. 1271 (17.9%) had DPN with 28.1% experiencing pDPN. Logistic regression revealed 13/13 anthropometric, 27/29 BIA, 21/34 DEXA, and 8/14 aMRI measurements associated with DPN, but none associated with pDPN. For males, median AUCs for DPN were similar regardless of location (central: 0.88, 0.89, general: 0.89, peripheral: 0.88, central–peripheral ratio: 0.87), whereas for females, central obesity (0.92) had the largest AUC for DPN, followed by general (0.88), peripheral (0.84), and central–peripheral obesity ratio (0.78).

Conclusions: Obesity is associated with DPN, but not pDPN. For males, obesity distribution did not differentially discriminate DPN, whereas for females, central obesity best discriminated DPN.

1 | Introduction

Diabetic peripheral neuropathy (DPN) is a prevalent complication of type 1 and type 2 diabetes that inflicts substantial morbidity and mortality [1, 2]. DPN can be painful or painless. Painful DPN (pDPN) can occur in up to approximately 60% of persons with severe DPN [3, 4]. Several epidemiologic studies have established that obesity is an independent risk factor for DPN [5]. On the other hand, fewer studies have assessed the impact of obesity on pDPN, which generally fail to find a significant association [6, 7].

Our 2024 narrative review found that 27 of 28 studies that assessed associations between obesity and neuropathy used simple anthropometric measurements, such as body mass index (BMI), waist circumference, waist-hip circumference ratio, or waist-height ratio [8]. Although practical, anthropometric measurements cannot ascertain differences in fat mass versus fat-free mass (e.g., bone, water, and lean mass). Alternatively, bioelectrical impedance analysis (BIA), dual x-ray absorptiometry scans (DEXA), and abdominal magnetic resonance imaging (aMRI) can accurately quantify fat distribution. Only four studies have employed detailed assessments of body fat and have had mixed associations with DPN [9–12]. Specifically, studies in Korea ($n=65$) and Qatar ($n=332$) found that worsened BIA or DEXA measurements including fat mass, fat percentage, and visceral adipose tissue (VAT) volume, associated with increased odds of DPN [9, 12]. In contrast, studies of adults from China ($n=488$ and $n=2494$) found higher visceral fat area was associated with smaller DPN likelihood [10, 11].

However, we did not identify any studies that directly compared head-to-head the discriminatory capability of obesity measurements assessed by anthropometrics, BIA, DEXA, and/or MRI for DPN or pDPN. Additionally, we identified only four studies that directly compared the discriminatory capability of different distributions of adipose tissues (e.g., general vs. central vs. peripheral obesity) for DPN. Our previous study of adults with obesity ($n=138$) found that anthropometric measurements of central obesity were more discriminatory for neuropathy than general or peripheral obesity measurements. Alternatively, studies in Germany ($n=513$) [13], Denmark ($n=5249$) [14], and the United Kingdom (UK) ($n=30{,}541$) [15] found central and general obesity to be similarly associated with DPN. No study has assessed whether there are sex-specific associations between the adipose tissue distribution and DPN, which may be important given that there are sex differences in body fat distribution [16, 17]. Thus, more evidence is needed to definitively determine whether detailed obesity assessments and/or distributions provide additional understanding of the likelihood of DPN and pDPN, and whether the relationship differs by sex.

In the present study, we determined the association between detailed obesity measurements, DPN and pDPN in a large population of adults with diabetes from the UK. Additionally, we compared the discriminatory capability of general, central, peripheral and central-peripheral ratio obesity measurements for DPN and pDPN, stratified by sex. Lastly, we compared the discriminatory capability of obesity measurements made using anthropometric measurements, BIA, DEXA, and aMRI, stratified by sex, to determine which assessment offers the best insight into DPN likelihood.

2 | Methods

2.1 | Population and Study Design

We performed a cross-sectional study of adults enrolled in the UK Biobank with type 1 or type 2 diabetes [Data-Field: 120007] who completed DPN phenotyping.

2.2 | Metabolic Risk Factors and Comorbidities

Participants completed assessments of hemoglobin A1c (HbA1c) (Data-Field: 30750), systolic blood pressure (SBP) (Data-Field: 4080), high-density lipoproteins (HDL) levels (Data-Field: 30760), and triglyceride levels (Data-Field: 30870). We determined the Charlson Comorbidity Index (CCI) using international classification of diseases diagnosis codes from inpatient hospitalization records (Data-Fields: 41270-41271).

2.3 | DPN

DPN was assessed using the Michigan Neuropathy Screening Instrument questionnaire (MNSIq) (Data-Fields: 120071-120085). MNSIq is a simple screening instrument of 15 questions total, including two that remain unscored and two in the reverse direction. MNSIq is scored by summing the number of "yes" responses to 13 questions and "no" responses to the two questions scored in reverse [18]. DPN was defined as MNSIq ≥ 4 [19]. MNSIq was part of the enhanced pain phenotyping data acquired in 2019, which was administered to a subset of UK Biobank participants potentially at risk of neuropathy (history of diabetes or cancer). Overall, MNSIq was completed by 26,194 out of the 335,587 UK Biobank participants who had consented for electronic follow-up and had active email addresses. Validation studies demonstrate MNSIq has strong discriminatory characteristics for both distal symmetric polyneuropathy and small fiber neuropathy [19–21].

2.4 | pDPN

We defined pDPN as those with DPN (e.g., MNSIq ≥ 4) who were troubled by pain or discomfort for more than 3 months (Data-Field: 120019) and reported bilateral pain in the feet during this time frame (Data-Field: 120032). Participants that reported having pain all over the body in the past 3 months were considered to have generalized pain, and not pDPN (Data-Field: 120021). As a sensitivity analysis, we also defined pDPN using the Douleur Neuropathique 4 (DN4) scale (Data-Field: 120046-120052) using the validated cutoff of DN4 ≥ 4 [22, 23].

2.5 | Obesity Measurements

Anthropometric assessments included assessments of BMI (Data-Field: 21001), weight (Data-Field: 21002), height (Data-Field: 50), waist circumference (Data-Field: 48), and hip circumference (Data-Field: 49).

BIA was assessed using the Tanita BC418MA body composition analyzer (Category ID: 100009). BIA estimates impedance, predicts total mass, fat-free mass, fat mass, and the fat percentage of the total mass, in the arms, legs, trunk, and whole body. BIA also estimates the basal metabolic rate.

DEXA scans were completed using the GE-Lunar iDXA instrument (Category ID: 124). DEXA estimates fat, lean, bone, and total mass, as well as the fat percentage of the total mass, in the android, arm, gynoid, leg, trunk, and whole body. DEXA also estimates the VAT mass and volume.

aMRI was performed using Siemens 1.5T MAGNETOM Aera (Category ID: 149). Body composition estimates were made using the AMRA software. aMRI estimates fat, fat-free, and muscle volumes.

Based on these values, we calculated a number of additional indices [24, 25], that are described in more detail in Supporting Information. In total, we included 13 anthropometric, 29 BIA, 38 DEXA, and 15 aMRI-derived obesity measurements which are displayed in Table 2.

2.6 | Adipose Tissue Distribution

Obesity measurements were categorized as measuring general obesity, central obesity, peripheral obesity, or the central-peripheral obesity ratio (Table 3). General obesity included whole body measurements. Central obesity included trunk, abdomen, waist, or android measurements. Peripheral obesity included arm, hip, gynoid, or leg measurements. Central-peripheral obesity ratio measurements were those that included a ratio of central and peripheral obesity measurements.

2.7 | Statistical Analysis

Our primary analysis determined associations between obesity measurements and DPN and with pDPN. Our secondary analysis compared the discriminatory capability of obesity measurements with DPN. Given the small number of participants that completed DEXA and aMRI, the analysis of the association between DEXA and aMRI derived obesity measurements and DPN was considered exploratory. Further, given the small number of participants with DPN that completed DEXA and aMRI, we were unable to determine the associations between these measurements and pDPN.

Descriptive statistics summarized demographic and socioeconomic characteristics, stratified by the presence of DPN and pDPN.

Logistic regression models determined associations between obesity measurements and DPN, adjusted for age, sex, height, CCI, HbA1c, SBP, HDL, and triglyceride levels. We fit separate models for each individual obesity measurement. Among participants with DPN, we fit additional logistic models to determine associations between each obesity measurement separately and pDPN (versus painless DPN), adjusted for the same risk factors above. We performed Hosmer–Lemeshow tests to ensure each model was well calibrated. In the case of poor calibration, results were not reported. Multicollinearity was assessed using variance inflation factors (VIF): if a covariate was found to have VIF > 5, we removed the problematic covariate from the regression model. Change in pseudo-R^2 correlation coefficients with and without each obesity measurement was used to assess variable importance. Available case analysis managed missing data when determining associations between obesity measurements and DPN. Given the number of obesity measurements, we calculated Benjamini–Hochberg corrected p values for each odds ratio (OR).

Among participants that completed all obesity measurements, we fit logistic regression models for DPN, and determined discriminatory capability by calculating the area under the receiver operating characteristic curves (AUC). AUC differences of 0.10 were considered clinically significant. We used Delong's methods to calculate 95% CI for each AUC, which were compared using Delong's paired test. We also calculated AUC for each obesity measurement stratified by sex, to determine whether obesity measurements differentially discriminate DPN between male and female participants. Analyses were completed using R.

3 | Results

We identified 26,194 participants in the UK Biobank that completed MNSIq, of whom 9446 (36.1%) had diabetes (Figure 1). Of the 9446 with diabetes, 7090 (75.1%) had complete data on age, sex, height, CCI, HbA1c, SBP, and HDL and triglyceride levels. Of the 7090 the mean (SD) age was 58.4 (7.1) years, 39.6% were female, and most participants reported having a British/Irish/White ethnic background (93.6%) (Table 1). Of the 7090 with complete data on these confounding variables, 7090 (100.0%) completed anthropometric measurements, 6973 (98.4%) completed BIA, 160 (2.3%) completed DEXA, and 276 (3.9%) completed aMRI. There were 126 (1.8%) participants that completed all obesity phenotyping. We found that 1271 (17.9%) had DPN, of which 357 (28.1%) had pDPN. Similarly, of those with DPN that completed DN4 ($n = 1202$), 263 (21.9%) had pDPN defined using DN4.

3.1 | Association of Individual Metabolic Risk Factors to DPN, Adjusted for Total Weight

We found sex (female, OR 0.76, 95% CI 0.66–0.86), HDL (unit = mmol/L, 0.63, 0.50–0.81), and SBP (unit = mmHg, 0.995, 0.992–0.999) associated with lower DPN odds. Additionally, HbA1c (unit = mmol/mol, 1.01, 1.01–1.02) and CCI (1.50, 1.39–1.62) were associated with higher DPN odds. Age, height, and triglycerides did not associate with DPN.

3.2 | Association of Individual Obesity Measurements to DPN

Using all available data, we found that 13 of 13 anthropometric, 27 of 29 BIA, 21 of 34 DEXA, and 8 of 14 aMRI obesity measurements significantly associated with DPN, adjusted for confounders(Table 2; Benjamini-Hochberg corrected p value < 0.05). Individual measurements with the highest variable importance were waist circumference to height ratio (pseudo-R^2 change: 0.015), relative fat mass (0.015), and waist circumference (0.014) for anthropometric; fat-free arms and legs to BMI ratio (0.013), leg fat percentage (0.013), and arm fat percentage (0.012) for BIA; android fat mass (0.085), android total mass (0.084), and total fat percentage (0.082) for DEXA; and weight-to-muscle ratio (0.098), abdominal fat ratio (0.043), and muscle fat infiltration (0.040) for aMRI measurements.

3.3 | Discriminatory Capability of Obesity Measurements for DPN

The AUCs of obesity measurements ranged from 0.79–0.86 (Table 3), which were highest for the relative fat mass (anthropometric, 0.86, 0.74–0.97), body surface area (anthropometric,

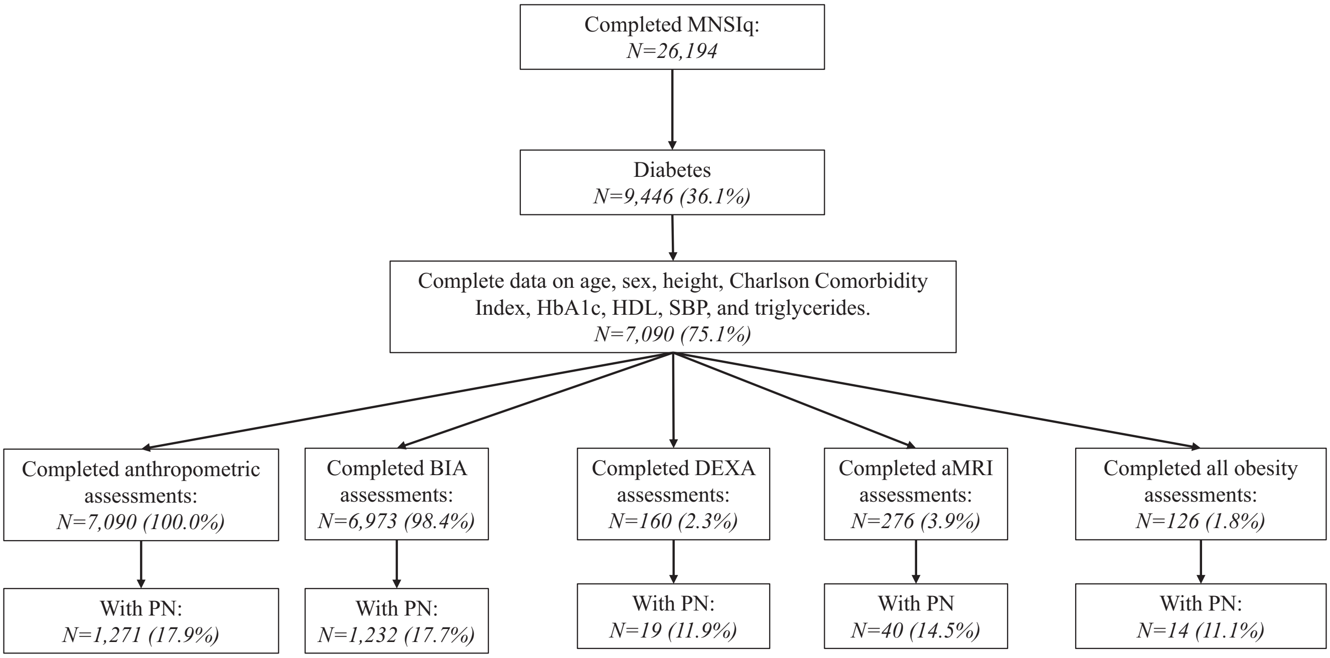

FIGURE 1 | Flow chart of participant inclusion. aMRI, abdominal magnetic resonance imaging; BIA, bioelectrical impedance analysis; DEXA, dual x-ray absorptiometry scans; DPN, diabetic peripheral neuropathy; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; MNSIq, Michigan neuropathy screening instrument questionnaire; SBP, systolic blood pressure.

0.86, 0.76–0.95), and trunk fat mass (BIA, 0.86, 0.75–0.96). There were no significant differences in discriminatory capability between the measurement with the top AUC (anthropometric, relative fat mass, 0.86) and the measurements with the lowest AUC (aMRI, fat-free muscle anterior thigh volume, 0.79, 0.64–0.93).

3.4 | Association of Metabolic Risk Factors to pDPN, Adjusted for Total Weight

Older age (unit = year, 1.03, 1.01–1.05) increased the odds of pDPN. Sex, height, CCI, and other metabolic factors did not associate with pDPN. Our sensitivity analysis revealed that only sex (male, 1.62, 1.19–2.20) was associated with pDPN.

3.5 | Association of Individual Obesity Measurements to pDPN

No anthropometric or BIA measurements were associated with pDPN (Table 2). Similarly, in a sensitivity analysis, we found that no obesity measurements were associated with pDPN defined using DN4.

3.6 | Discriminatory Capability of Obesity Measurements Based on the Adipose Tissue Distribution

Overall, median [25th percentile–75th percentile] AUCs were similar for general (0.83, 0.82–0.85), central (0.83, 0.82–0.84), and peripheral obesity (0.83, 0.80–0.84), and central-peripheral obesity ratio (0.80, 0.80–0.80) measurements (Figure 2A). Among male participants, median AUCs were similar for general (0.89, 0.87–0.90), central (0.88, 0.87–0.89), and peripheral (0.88, 0.87–0.89), and central-peripheral ratio (0.87, 0.86–0.87) obesity measurements. In contrast, among female participants, central obesity measurements (0.92, 0.86–0.97) had the best discriminatory capability, followed by general (0.88, 0.82–0.93), peripheral (0.84, 0.78–0.91), and central-peripheral ratio (0.78, 0.77–0.80) obesity measurements.

3.7 | Comparison of Discriminatory Capability of Obesity Measurements Based on Assessment Technique

Overall, obesity measurements had similar discriminatory capability for DPN regardless of the assessment tool with median [25th percentile–75th percentile] AUCs of 0.85 (0.82–0.85) for anthropometric, 0.83 (0.82–0.84) for BIA, 0.82 (0.80–0.84) for DEXA, and 0.82 (0.80–0.84) for aMRI measurements (Figure 2B). For male participants, obesity measurements from anthropometric (AUC = 0.89), BIA (0.89), DEXA (0.87), and aMRI (0.87) assessments all had similar discriminatory capability for DPN. In contrast, for female participants, aMRI (0.93, 0.84–0.97) had the best discriminatory capability, followed by DEXA (0.89, 0.75–0.94), anthropometric (0.88, 0.85–0.90), and BIA (0.82, 0.81–0.88) measurements.

4 | Discussion

In a large study of UK adults with diabetes, we found obesity, regardless of how it was measured, consistently and robustly increased the odds of DPN. In contrast, obesity measurements did not associate with pDPN odds. Among male participants, we found that adipose tissue distribution and assessment technique did not

TABLE 1 | Study population demographic characteristics and metabolic risk factors stratified by presence of DPN and pDPN.

Variable	Overall (*N* = 7090)	No DPN (*N* = 5819)	DPN (*N* = 1271)	DPN without pain (*N* = 914)	DPN with pain (*N* = 357)
Age, mean (SD)	58.35 (7.14)	58.34 (7.14)	58.35 (7.13)	57.96 (7.31)	59.35 (6.55)
Sex, Female, *N* (%)	2810 (39.63)	2269 (38.99)	541 (42.57)	407 (44.53)	134 (37.54)
Race, *N* (%)					
Asian	212 (2.99)	167 (2.87)	45 (3.54)	36 (3.94)	9 (2.52)
British/Irish/White	6635 (93.58)	5460 (93.83)	1175 (92.45)	833 (91.14)	342 (95.80)
Mixed race	55 (0.78)	45 (0.77)	10 (0.79)	10 (1.09)	0 (0.00)
Other	154 (2.17)	119 (2.05)	35 (2.75)	30 (3.28)	5 (1.40)
Missing	34 (0.48)	28 (0.48)	6 (0.47)	5 (0.55)	1 (0.28)
Overall health rating, *N* (%)					
Excellent	506 (7.14)	468 (8.04)	38 (2.99)	31 (3.39)	7 (1.96)
Good	3626 (51.14)	3212 (55.20)	414 (32.57)	305 (33.37)	109 (30.53)
Fair	2386 (33.65)	1843 (31.67)	543 (42.72)	370 (40.48)	173 (48.46)
Poor	556 (7.84)	282 (4.85)	274 (21.56)	206 (22.54)	68 (19.05)
Missing	16 (0.23)	14 (0.24)	2 (0.16)	2 (0.22)	0 (0.00)
Long-standing illness, disability or infirmity, *N* (%)	4299 (60.64)	3300 (56.71)	999 (78.60)	714 (78.12)	285 (79.83)
Missing	128 (1.81)	109 (1.87)	19 (1.50)	15 (1.64)	4 (1.12)
Waist circumference (cm), mean (SD)	101.37 (13.92)	100.47 (13.72)	105.47 (14.09)	105.16 (14.19)	106.27 (13.83)
Missing	2	1	1	1	0
Height (cm), mean (SD)	170.44 (9.33)	170.42 (9.18)	170.53 (9.98)	169.97 (9.86)	171.98 (10.17)
HbA1c (mmol/mol), mean (SD)	46.80 (11.56)	46.43 (11.11)	48.48 (13.33)	48.23 (13.11)	49.10 (13.86)
HDL (mmol/L), mean (SD)	1.23 (0.33)	1.25 (0.33)	1.18 (0.30)	1.18 (0.30)	1.18 (0.31)
Triglycerides (mmol/L), mean (SD)	2.24 (1.26)	2.22 (1.24)	2.37 (1.32)	2.34 (1.33)	2.44 (1.30)
SBP (mmHg), mean (SD)	141.93 (17.21)	142.13 (17.30)	140.97 (16.79)	140.70 (17.33)	141.67 (15.32)

Abbreviations: DPN, diabetic peripheral neuropathy; HbA1c, hemoglobin A1c; HDL, high-density lipoproteins; SBP, systolic blood pressure.

differ in discriminatory capability for DPN. Therefore, simpler anthropometric assessments of obesity are sufficient for determining DPN risk in males. However, among female participants, central obesity and aMRI technique had the best discriminatory capability for DPN. Thus, aMRI provides additional risk factor information for females, although this benefit must be weighed against the additional cost and inconvenience of this test.

We found that obesity measurements are robustly associated with DPN, even after adjusting for multiple statistical comparisons and DPN risk factors, including age, sex, height, hyperglycemia, CCI, and other metabolic risk factors. Thus, our finding adds to the growing body of evidence that obesity is an independent DPN risk factor [8]. In fact, obesity is such an important risk factor that almost all obesity measures are associated with DPN, regardless of modality or specific measure. Although not yet completely understood, preclinical studies have identified several emerging mechanisms linking obesity to DPN, including dyslipidemia, mitochondrial dysfunction, and inflammation [26, 27]. Thus, obesity is a target

TABLE 2 | Association between obesity measurements, DPN, and pDPN.

Variable	Logistic regression model: DPN (ref = No DPN)		Logistic regression model: PDPN (reference = DPN without pain)	
	N	OR (95% CI)	*N*	OR (95% CI)
Anthropometric measures				
Body Mass Index (unit = kg/m^2)	7081	1.05 (1.04, 1.06)[a]	1268	1.02 (0.9970, 1.04)
Body Roundness Index	7088	1.18 (1.14, 1.23)[a]	1270	1.02 (0.95, 1.09)
Body Shape Index (unit = 10 × m$^{(11/6)}$/kg$^{(2/3)}$)	7079	30.91 (7.07, 135.15)[a]	1267	0.04 (0.0021, 0.67)
Body surface area (unit = 10 × cm$^{(0.725)}$ × kg$^{(0.425)}$)	7081	1.21 (1.16, 1.26)[a]	1268	1.08 (0.99, 1.17)
Conicity Index (unit = 10 × m$^{(3/2)}$/kg$^{(1/2)}$)	7079	1.40 (1.29, 1.52)[a]	1267	0.90 (0.77, 1.06)
Estimated visceral Adipose Tissue Area (unit = cm^2)	7088	1.01 (1.01, 1.01)[a]	1270	1.0008 (0.9979, 1.0037)
Hip Circ. (unit = cm)	7090	1.02 (1.02, 1.03)[a]	1271	1.01 (0.9992, 1.02)
Log(Waist-height ratio)	7088	13.40 (7.97, 22.55)[a]	1270	1.37 (0.49, 3.84)
Log(Waist-hip ratio)	7088	20.30 (8.15, 50.52)[a]	1270	0.24 (0.04, 1.43)
Relative fat mass	7088	1.08 (1.06, 1.10)[a]	1270	1.01 (0.98, 1.04)
Waist circ. (unit = cm)	7088	1.03 (1.02, 1.03)[a]	1270	1.0026 (0.99, 1.01)
Weight (unit = kg)	7081	1.02 (1.01, 1.02)[a]	1268	1.01 (0.9989, 1.01)
Weight adj. waist circ. (unit = cm/kg$^{0.5}$)	7079	1.50 (1.36, 1.65)[a]	1267	0.88 (0.73, 1.07)
Bioelectrical impedance analysis				
Arm fat % (unit = %)	6967	1.02 (1.02, 1.03)[a]	1230	1.0076 (0.9985, 1.02)
Arm fat mass (unit = kg)	6967	1.16 (1.12, 1.20)[a]	1230	1.06 (0.99, 1.13)
Arm fat-free mass (unit = kg)	6967	1.23 (1.15, 1.32)[a]	1230	1.08 (0.95, 1.23)
Arm impedance (unit = ohm)	6971	0.9987 (0.9978, 0.9996)[a]	1232	0.9999 (0.9981, 1.0017)
Arm predicted mass (unit = kg)	6967	1.25 (1.16, 1.34)[a]	1230	1.09 (0.95, 1.25)
Basal metabolic rate (unit = kJ)	6973	1.0003 (1.0002, 1.0003)[a]	1232	1.0001 (0.99995, 1.0002)
Fat Mass Index (unit = kg/m^2)	6969	1.08 (1.06, 1.10)[a]	1232	1.03 (0.9992, 1.07)
Fat-Free Mass Index (unit = kg/m^2)	6970	1.10 (1.07, 1.13)[a]	1231	1.03 (0.97, 1.09)
Leg fat % (unit = %)	6972	1.02 (1.01, 1.02)[a,b]	1232	1.01 (0.9972, 1.01)[b]
Leg fat mass (unit = kg)	6972	1.07 (1.06, 1.09)[a]	1232	1.03 (1.0015, 1.07)
Leg fat-free mass (unit = kg)	6971	1.08 (1.05, 1.10)[a]	1232	1.02 (0.98, 1.07)
Leg impedance (unit = ohm)	6972	0.9984 (0.9974, 0.9993)[a]	1232	0.9998 (0.9981, 1.0016)
Leg predicted mass (unit = kg)	6971	1.08 (1.06, 1.11)[a]	1232	1.03 (0.98, 1.07)
Log(Arms+Legs/Total fat mass ratio)	6963	2.87 (1.33, 6.24)[a]	1230	2.18 (0.44, 10.82)
Log(Fat-free arms+Legs/Height ratio) (unit = log(kg/cm))	6967	5.57 (3.36, 9.23)[a]	1230	1.69 (0.63, 4.53)
Log(Fat-Free Arms+Legs/BMI Ratio) (unit = log(1/m^2))	6967	0.06 (0.04, 0.11)[a,b]	1230	0.50 (0.15, 1.66)[b]
Log(Legs/Total fat mass ratio)	6968	1.01 (0.53, 1.93)	1232	1.57 (0.44, 5.60)
Log(Trunk fat/Leg fat ratio)	6966	0.83 (0.57, 1.20)	1230	0.72 (0.33, 1.58)

(Continues)

TABLE 2 | (Continued)

Variable	Logistic regression model: DPN (ref = No DPN)		Logistic regression model: PDPN (reference = DPN without pain)	
	N	OR (95% CI)	*N*	OR (95% CI)
Log(Trunk fat-free/Leg fat-free ratio)	6964	0.15 (0.07, 0.32)[a]	1230	[c]
Log(Trunk/Total fat mass ratio)	6962	0.40 (0.19, 0.87)[a]	1230	0.40 (0.06, 2.52)
Trunk fat % (unit = %)	6966	1.04 (1.03, 1.05)[a]	1230	1.02 (0.996, 1.04)
Trunk fat mass (unit = kg)	6966	1.05 (1.04, 1.06)[a]	1230	1.02 (0.99, 1.04)
Trunk fat-free mass (unit = kg)	6964	1.06 (1.04, 1.09)[a]	1230	1.01 (0.97, 1.06)
Trunk predicted mass (unit = kg)	6964	1.07 (1.04, 1.09)[a]	1230	1.02 (0.97, 1.06)
Whole body fat % (unit = %)	6972	1.05 (1.04, 1.06)[a]	1232	1.02 (0.9991, 1.05)
Whole body fat mass (unit = kg)	6969	1.03 (1.02, 1.03)[a]	1232	1.01 (0.9989, 1.02)
Whole body fat-free mass (unit = kg)	6970	1.03 (1.02, 1.04)[a]	1231	1.01 (0.99, 1.03)
Whole body impedance (unit = ohm)	6972	0.9982 (0.9972, 0.9992)[a]	1232	1.0003 (0.9984, 1.0022)
Whole body water mass (unit = kg)	6973	1.05 (1.03, 1.06)[a]	1232	1.01 (0.99, 1.04)
Dual x-ray absorptiometry scans				
Android: %Fat of tissue (unit = %)	160	1.11 (1.02, 1.20)[a]	19	NR
Android: Fat mass (unit = kg)	160	1.89 (1.25, 2.86)[a]	19	NR
Android: Lean mass (unit = kg)	160	2.73 (1.0001, 7.44)	19	NR
Android: Total mass (unit = kg)	160	1.65 (1.19, 2.28)[a]	19	NR
Arms: %Fat of tissue (unit = %)	160	1.11 (1.02, 1.20)[a]	19	NR
Arms: Fat mass (unit = kg)	160	1.71 (1.15, 2.53)[a]	19	NR
Arms: Lean mass (unit = kg)	160	2.13 (1.16, 3.90)[a]	19	NR
Arms: Total mass (unit = kg)	160	1.47 (1.13, 1.92)[a]	19	NR
Fat Mass Index (unit = kg/m^2)	160	1.22 (1.07, 1.40)[a]	19	NR
Fat-Free Mass Index (unit = kg/m^2)	160	1.31 (1.0019, 1.72)	19	NR
Gynoid: %Fat of tissue (unit = %)	160	[c]	19	NR
Gynoid: Fat mass (unit = kg)	160	1.42 (1.09, 1.85)[a]	19	NR
Gynoid: Lean mass (unit = kg)	160	1.52 (0.86, 2.69)	19	NR
Gynoid: Total mass (unit = kg)	160	1.29 (1.06, 1.57)[a]	19	NR
Lean Mass Index (unit = kg/m^2)	160	1.32 (0.9970, 1.75)	19	NR
Legs: %Fat of tissue (unit = %)	160	[c]	19	NR
Legs: Fat mass (unit = kg)	160	1.23 (1.06, 1.43)[a]	19	NR
Legs: Lean mass (unit = kg)	160	1.24 (0.99, 1.54)	19	NR
Legs: Total mass (unit = kg)	160	1.14 (1.03, 1.26)[a]	19	NR
Log(Android/Gynoid fat ratio)	160	3.47 (0.39, 31.25)	19	NR
Log(Arms+Legs/Total fat mass ratio)	160	1.01 (0.02, 43.64)	19	NR
Log(Lean Arms+Legs/BMI ratio) (unit = log(1/m^2))	160	[c]	19	NR
Log(Lean Arms+Legs/Height ratio) (unit = log(kg/cm))	160	98.48 (1.28, 7575.54)[a]	19	NR

(Continues)

TABLE 2 | (Continued)

Variable	Logistic regression model: DPN (ref = No DPN)		Logistic regression model: PDPN (reference = DPN without pain)	
	N	OR (95% CI)	*N*	OR (95% CI)
Log(Legs/Total fat mass ratio)	160	1.12 (0.06, 22.11)	19	NR
Log(Trunk fat/Leg fat ratio)	160	1.27 (0.18, 9.14)	19	NR
Log(Trunk lean/Leg lean ratio)	160	0.06 (0.0002, 18.22)	19	NR
Log(Trunk/Total fat mass ratio)	160	10.33 (0.03, 3827.84)	19	NR
Total % Fat or tissue (unit = %)	160	[c]	19	NR
Total fat mass (unit = kg)	160	1.07 (1.03, 1.13)[a]	19	NR
Total lean mass (unit = kg)	160	1.10 (1.0025, 1.22)	19	NR
Total tissue mass (unit = kg)	160	1.05 (1.02, 1.09)[a]	19	NR
Trunk: %Fat of tissue (unit = %)	160	1.13 (1.03, 1.22)[a]	19	NR
Trunk: Fat mass (unit = kg)	160	1.12 (1.04, 1.21)[a]	19	NR
Trunk: Lean mass (unit = kg)	160	1.14 (0.95, 1.38)	19	NR
Trunk: Total mass (unit = kg)	160	1.09 (1.03, 1.16)[a]	19	NR
VAT Mass (unit = kg)	157	1.86 (1.08, 3.19)[a]	18	NR
VAT vol. (unit = cm^3)	157	1.0006 (1.0001, 1.0011)[a]	18	NR
VAT Vol. Index (unit = $10 \times kg/m^2$)	157	1.20 (1.03, 1.39)[a]	18	
Abdominal magnetic resonance imaging				
10P Liver PDFF (proton density fat fraction) (unit = %)	273	1.05 (0.9986, 1.10)	40	NR
Abdominal subcutaneous adipose tissue vol. (ASAT) (unit = L)	272	1.14 (1.03, 1.26)[a]	38	NR
Adipose tissue vol. (unit = L)	229	1.06 (1.01, 1.12)[a]	30	NR
Anterior thigh fat-free vol. (unit = L)	166	1.31 (0.49, 3.51)	21	NR
ASAST Vol Index (unit = L/m^2)	272	1.50 (1.12, 2.01)[a]	38	NR
Lean tissue vol. (unit = L)	229	1.02 (0.89, 1.17)	30	NR
Log(Abdominal fat ratio)	262	52.43 (2.85, 966.21)[a]	35	NR
Log(Weight-to-muscle ratio) (unit = log(kg/L))	264	458.28 (27.35, 7679.44)[a]	37	NR
Muscle fat infiltration (unit = %)	262	1.25 (1.08, 1.46)[a]	36	NR
Posterior thigh fat-free vol. (unit = L)	166	1.12 (0.64, 1.96)	21	NR
Thigh fat-free muscle vol. (unit = L)	264	[c]	37	NR
Total abdominal adipose tissue index (unit = L/m^2)	272	1.34 (1.09, 1.66)[a]	38	NR
Trunk fat vol. (unit = L)	175	1.11 (1.01, 1.23)[a]	22	NR
VAT vol. (unit = L)	272	1.16 (0.99, 1.36)	38	NR
VAT Vol. Index (unit = L/m^2)	272	1.61 (0.9985, 2.59)	38	NR

Abbreviations: CI, confidence interval; DPN, diabetic peripheral neuropathy; NR, not reported; OR, odds ratio; VAT, Visceral adipose tissue.
[a]Represents statistical significance based on a Benjamini-Hochberg corrected p value < 0.05.
[b]Indicates that sex was removed as a covariate from the model due to issues with multicollinearity (i.e., variance inflation factor > 5).
[c]Indicates lack of fit based on Hosmer-Lemeshow goodness of fit tests. These models were not reported.

TABLE 3 | Discriminatory capability of obesity measurements overall and stratified by sex.

Variable	Adipose tissue distribution	Overall ($N = 126$)	Males ($N = 78$)	Females ($N = 48$)
		AUC (95% CI)	AUC (95% CI)	AUC (95% CI)
Anthropometric measures				
Relative fat mass	Central	0.86 (0.74, 0.97)	0.89 (0.77, 1.00)	0.92 (0.80, 1.00)
Body surface area (unit = $10 \times cm^{(0.725)} kg^{(0.425)}$)	General	0.86 (0.76, 0.95)	0.91 (0.81, 1.00)	0.89 (0.75, 1.00)
Weight (unit = kg)	General	0.85 (0.76, 0.95)	0.91 (0.81, 1.00)	0.89 (0.75, 1.00)
Log(waist-height ratio)	Central	0.85 (0.74, 0.97)	0.89 (0.76, 1.00)	0.92 (0.80, 1.00)
Body mass index (unit = kg/m^2)	General	0.85 (0.75, 0.95)	0.90 (0.80, 1.00)	0.88 (0.75, 1.00)
Waist circ. (unit = cm)	Central	0.85 (0.74, 0.96)	0.89 (0.77, 1.00)	0.90 (0.79, 1.00)
Body Roundness Index	Central	0.85 (0.74, 0.97)	0.89 (0.77, 1.00)	0.88 (0.74, 1.00)
Estimated visceral adipose tissue area (unit = cm^2)	Central	0.85 (0.74, 0.96)	0.89 (0.77, 1.00)	0.90 (0.79, 1.00)
Hip Circ. (unit = cm)	Peripheral	0.84 (0.75, 0.94)	0.88 (0.76, 1.00)	0.85 (0.67, 1.00)
Conicity Index (unit = $10 \times m^{(3/2)}/kg^{(1/2)}$)	General	0.82 (0.68, 0.95)	0.86 (0.75, 0.97)	0.85 (0.67, 1.00)
Weight Adj. Waist Circ. (unit = $cm/kg^{0.5}$)	Central	0.82 (0.68, 0.95)	0.86 (0.75, 0.97)	0.86 (0.68, 1.00)
Log(Waist-hip ratio)	Central-Peripheral Ratio	0.81 (0.68, 0.95)	0.87 (0.76, 0.98)	0.78 (0.53, 1.00)
Body Shape Index (unit = $10 \times m^{(11/6)}/kg^{(2/3)}$)	Central	0.80 (0.67, 0.93)	0.87 (0.77, 0.96)	0.75 (0.46, 1.00)
Bioelectrical impedance analysis				
Trunk fat mass (unit = kg)	Central	0.86 (0.75, 0.96)	0.89 (0.76, 1.00)	0.94 (0.86, 1.00)
Log(Fat-free arms+Legs/BMI ratio) (unit = $\log(1/m^2)$)	Peripheral	0.85 (0.73, 0.97)	0.87 (0.75, 1.00)	0.96 (0.89, 1.00)
Trunk fat % (unit = %)	Central	0.85 (0.74, 0.96)	0.89 (0.76, 1.00)	0.94 (0.86, 1.00)
Whole body fat mass (unit = kg)	General	0.85 (0.74, 0.95)	0.89 (0.76, 1.00)	0.88 (0.74, 1.00)
Whole body fat % (unit = %)	General	0.84 (0.73, 0.96)	0.89 (0.76, 1.00)	0.94 (0.87, 1.00)
Arm fat % (unit = %)	Peripheral	0.84 (0.74, 0.95)	0.89 (0.76, 1.00)	0.93 (0.84, 1.00)
Fat Mass Index (unit = kg/m^2)	General	0.84 (0.74, 0.95)	0.89 (0.77, 1.00)	0.88 (0.74, 1.00)
Leg fat mass (unit = kg)	Peripheral	0.84 (0.74, 0.94)	0.89 (0.77, 1.00)	0.86 (0.70, 1.00)
Fat-Free Mass Index (unit = kg/m^2)	General	0.84 (0.73, 0.94)	0.90 (0.82, 0.99)	0.82 (0.59, 1.00)
Leg fat % (unit = %)	Peripheral	0.84 (0.73, 0.95)	0.87 (0.75, 0.99)	0.92 (0.80, 1.00)
Log(Fat-free arms+Legs/Height ratio) (unit = log(kg/cm))	Peripheral	0.84 (0.73, 0.94)	0.91 (0.83, 0.99)	0.84 (0.63, 1.00)
Arm fat mass (unit = kg)	Peripheral	0.83 (0.73, 0.94)	0.89 (0.77, 1.00)	0.84 (0.66, 1.00)
Basal metabolic rate (unit = kJ)	General	0.83 (0.72, 0.94)	0.90 (0.82, 0.99)	0.84 (0.63, 1.00)
Leg predicted mass (unit = kg)	Peripheral	0.83 (0.72, 0.94)	0.90 (0.81, 0.99)	0.84 (0.63, 1.00)
Whole body water mass (unit = kg)	General	0.83 (0.72, 0.94)	0.90 (0.81, 0.98)	0.82 (0.59, 1.00)
Leg fat-free mass (unit = kg)	Peripheral	0.83 (0.72, 0.94)	0.90 (0.81, 0.99)	0.83 (0.62, 1.00)

(Continues)

Variable	Adipose tissue distribution	Overall (*N* = 126)	Males (*N* = 78)	Females (*N* = 48)
		AUC (95% CI)	AUC (95% CI)	AUC (95% CI)
Whole body fat-free mass (unit = kg)	General	0.83 (0.72, 0.94)	0.90 (0.81, 0.98)	0.82 (0.59, 1.00)
Trunk predicted mass (unit = kg)	Central	0.83 (0.71, 0.94)	0.89 (0.81, 0.98)	0.82 (0.57, 1.00)
Arm fat-free mass (unit = kg)	Peripheral	0.83 (0.71, 0.94)	0.91 (0.83, 0.98)	0.82 (0.55, 1.00)
Trunk fat-free mass (unit = kg)	Central	0.83 (0.71, 0.94)	0.89 (0.81, 0.98)	0.82 (0.56, 1.00)
Arm predicted mass (unit = kg)	Peripheral	0.82 (0.71, 0.94)	0.91 (0.83, 0.98)	0.82 (0.55, 1.00)
Log(Trunk fat-free/Leg fat-free ratio)	Central	0.82 (0.70, 0.93)	0.88 (0.78, 0.98)	0.77 (0.49, 1.00)
Whole body impedance (unit = ohm)	General	0.82 (0.69, 0.94)	0.89 (0.81, 0.98)	0.79 (0.48, 1.00)
Leg impedance (unit = ohm)	Peripheral	0.81 (0.69, 0.92)	0.88 (0.79, 0.98)	0.78 (0.52, 1.00)
Log(Trunk fat/Leg fat ratio)	Central-Peripheral Ratio	0.80 (0.67, 0.92)	0.87 (0.77, 0.96)	0.77 (0.48, 1.00)
Log(Legs/Total fat mass ratio)	Peripheral	0.80 (0.67, 0.92)	0.87 (0.77, 0.96)	0.81 (0.59, 1.00)
Log(Trunk/Total fat mass ratio)	Central	0.80 (0.67, 0.92)	0.87 (0.77, 0.96)	0.73 (0.37, 1.00)
Arm impedance (unit = ohm)	Peripheral	0.79 (0.66, 0.93)	0.89 (0.80, 0.98)	0.74 (0.38, 1.00)
Log(Arms+Legs/Total fat mass ratio)	Peripheral	0.79 (0.66, 0.93)	0.87 (0.78, 0.96)	0.73 (0.36, 1.00)
Dual x-ray absorptiometry scans				
Legs: %Fat of tissue (unit = %)	Peripheral	0.85 (0.75, 0.96)	0.86 (0.74, 0.98)	0.92 (0.82, 1.00)
Legs: Fat mass (unit = kg)	Peripheral	0.85 (0.75, 0.94)	0.88 (0.77, 0.98)	0.91 (0.81, 1.00)
Gynoid: %Fat of tissue (unit = %)	Peripheral	0.85 (0.74, 0.95)	0.87 (0.75, 0.99)	0.93 (0.84, 1.00)
Total % Fat or tissue (unit = %)	General	0.85 (0.74, 0.96)	0.87 (0.75, 0.99)	1.00 (1.00, 1.00)
Arms: %Fat of tissue (unit = %)	Peripheral	0.85 (0.74, 0.95)	0.86 (0.76, 0.97)	1.00 (1.00, 1.00)
Arms: Fat mass (unit = kg)	Peripheral	0.85 (0.75, 0.94)	0.87 (0.77, 0.98)	0.94 (0.84, 1.00)
Arms: Total mass (unit = kg)	Peripheral	0.84 (0.74, 0.95)	0.89 (0.80, 0.99)	0.91 (0.79, 1.00)
Log(Lean Arms+Legs/BMI ratio) (unit = log(1/m^2))	Peripheral	0.84 (0.73, 0.96)	0.87 (0.74, 0.99)	0.94 (0.87, 1.00)
Trunk: %Fat of tissue (unit = %)	Central	0.84 (0.73, 0.95)	0.87 (0.76, 0.99)	1.00 (1.00, 1.00)
Total fat mass (unit = kg)	General	0.84 (0.73, 0.94)	0.88 (0.77, 0.98)	0.93 (0.83, 1.00)
Gynoid: Fat mass (unit = kg)	Peripheral	0.84 (0.73, 0.94)	0.87 (0.76, 0.99)	0.86 (0.68, 1.00)
Android: %Fat of tissue (unit = %)	Central	0.84 (0.73, 0.95)	0.87 (0.75, 0.98)	0.97 (0.91, 1.00)
Fat Mass Index (unit = kg/m^2)	General	0.84 (0.73, 0.94)	0.87 (0.76, 0.99)	0.93 (0.83, 1.00)
Total tissue mass (unit = kg)	General	0.83 (0.72, 0.95)	0.89 (0.81, 0.98)	0.89 (0.75, 1.00)
Android: Fat mass (unit = kg)	Central	0.83 (0.72, 0.94)	0.87 (0.77, 0.98)	1.00 (1.00, 1.00)
Trunk: Fat mass (unit = kg)	Central	0.83 (0.72, 0.94)	0.88 (0.77, 0.98)	0.93 (0.84, 1.00)
Android: Total mass (unit = kg)	Central	0.83 (0.72, 0.94)	0.88 (0.78, 0.98)	0.97 (0.91, 1.00)
VAT Vol. Index (unit = 10 × kg/m^2)	Central	0.82 (0.71, 0.94)	0.87 (0.76, 0.97)	1.00 (1.00, 1.00)
Legs: Total mass (unit = kg)	Peripheral	0.82 (0.71, 0.94)	0.90 (0.82, 0.98)	0.89 (0.74, 1.00)
Gynoid: Total mass (unit = kg)	Peripheral	0.82 (0.71, 0.94)	0.88 (0.78, 0.99)	0.85 (0.66, 1.00)

(Continues)

Variable	Adipose tissue distribution	Overall ($N=126$)	Males ($N=78$)	Females ($N=48$)
		AUC (95% CI)	AUC (95% CI)	AUC (95% CI)
VAT mass (unit = kg)	Central	0.82 (0.71, 0.94)	0.87 (0.76, 0.97)	1.00 (1.00, 1.00)
VAT vol. (unit = cm^3)	Central	0.82 (0.71, 0.94)	0.87 (0.76, 0.97)	1.00 (1.00, 1.00)
Trunk: Total mass (unit = kg)	Central	0.82 (0.70, 0.94)	0.88 (0.78, 0.98)	0.88 (0.71, 1.00)
Arms: Lean mass (unit = kg)	Peripheral	0.81 (0.68, 0.94)	0.88 (0.78, 0.98)	0.80 (0.54, 1.00)
Log(Lean Arms+Legs/Height ratio) (unit = log(kg/cm))	Peripheral	0.80 (0.67, 0.94)	0.88 (0.77, 0.99)	0.78 (0.52, 1.00)
Android: Lean mass (unit = kg)	Central	0.80 (0.67, 0.93)	0.87 (0.78, 0.96)	0.75 (0.46, 1.00)
Fat-Free Mass Index (unit = kg/m^2)	General	0.80 (0.66, 0.94)	0.88 (0.79, 0.97)	0.75 (0.45, 1.00)
Lean Mass Index (unit = kg/m^2)	General	0.80 (0.66, 0.94)	0.87 (0.78, 0.97)	0.75 (0.45, 1.00)
Total lean mass (unit = kg)	General	0.80 (0.66, 0.94)	0.88 (0.78, 0.97)	0.74 (0.43, 1.00)
Log(Android/Gynoid fat ratio)	Central-Peripheral Ratio	0.80 (0.68, 0.92)	0.86 (0.75, 0.98)	0.84 (0.59, 1.00)
Log(Legs/Total fat mass ratio)	Peripheral	0.80 (0.67, 0.93)	0.86 (0.76, 0.96)	0.73 (0.34, 1.00)
Log(Arms+Legs/Total fat mass ratio)	Peripheral	0.80 (0.67, 0.92)	0.86 (0.75, 0.96)	0.73 (0.38, 1.00)
Log(Trunk lean/Leg lean ratio)	Central-Peripheral Ratio	0.80 (0.67, 0.92)	0.87 (0.76, 0.97)	0.80 (0.52, 1.00)
Trunk: Lean mass (unit = kg)	Central	0.80 (0.66, 0.93)	0.87 (0.78, 0.97)	0.74 (0.38, 1.00)
Log(Trunk fat/Leg fat ratio)	Central-Peripheral Ratio	0.79 (0.66, 0.93)	0.86 (0.75, 0.96)	0.74 (0.36, 1.00)
Legs: Lean mass (unit = kg)	Peripheral	0.79 (0.65, 0.93)	0.89 (0.79, 0.99)	0.74 (0.45, 1.00)
Gynoid: Lean mass (unit = kg)	Peripheral	0.79 (0.65, 0.93)	0.86 (0.76, 0.97)	0.76 (0.46, 1.00)
Log(Trunk/Total fat mass ratio)	Central	0.79 (0.66, 0.92)	0.86 (0.75, 0.97)	0.74 (0.38, 1.00)
Abdominal magnetic resonance imaging				
Log(Weight-to-muscle ratio) (unit = log(kg/L))	General	0.85 (0.74, 0.96)	0.87 (0.75, 0.99)	1.00 (1.00, 1.00)
Adipose tissue vol. (unit = L)	Central	0.84 (0.74, 0.95)	0.87 (0.76, 0.98)	0.93 (0.84, 1.00)
Trunk fat vol. (unit = L)	Central	0.84 (0.74, 0.94)	0.88 (0.77, 0.98)	0.98 (0.93, 1.00)
Abdominal subcutaneous adipose tissue vol. (ASAT) (unit = L)	Central	0.84 (0.74, 0.94)	0.88 (0.77, 0.98)	0.91 (0.75, 1.00)
Total abdominal adipose tissue index (unit = L/m^2)	Central	0.84 (0.73, 0.94)	0.88 (0.77, 0.98)	0.97 (0.91, 1.00)
ASAST Vol Index (unit = L/m^2)	Central	0.84 (0.73, 0.94)	0.88 (0.77, 0.99)	0.91 (0.75, 1.00)
Log(Abdominal fat ratio)	Central	0.83 (0.72, 0.95)	0.88 (0.77, 0.99)	0.97 (0.91, 1.00)
VAT Vol. Index (unit = L/m^2)	Central	0.82 (0.71, 0.94)	0.87 (0.77, 0.97)	1.00 (1.00, 1.00)
VAT vol. (unit = L)	Central	0.82 (0.70, 0.94)	0.88 (0.78, 0.97)	1.00 (1.00, 1.00)
10P Liver PDFF (proton density fat fraction) (unit = %)	General	0.82 (0.70, 0.94)	0.86 (0.74, 0.99)	0.94 (0.88, 1.00)
Muscle fat infiltration (unit = %)	General	0.81 (0.69, 0.93)	0.87 (0.78, 0.96)	0.93 (0.80, 1.00)
Lean tissue vol. (unit = L)	General	0.79 (0.66, 0.93)	0.87 (0.77, 0.96)	0.73 (0.37, 1.00)

(Continues)

TABLE 3 | (Continued)

Variable	Adipose tissue distribution	Overall (N = 126)	Males (N = 78)	Females (N = 48)
		AUC (95% CI)	AUC (95% CI)	AUC (95% CI)
Posterior thigh fat-free vol. (unit = L)	Peripheral	0.79 (0.65, 0.93)	0.87 (0.77, 0.97)	0.77 (0.42, 1.00)
Thigh fat-free muscle vol. (unit = L)	Peripheral	0.79 (0.64, 0.93)	0.87 (0.77, 0.98)	0.77 (0.45, 1.00)
Anterior thigh fat-free vol. (unit = L)	Peripheral	0.79 (0.64, 0.93)	0.88 (0.77, 0.98)	0.78 (0.47, 1.00)

Abbreviations: AUC, area under the receiver operating characteristics curve; CI, confidence interval.

to potentially prevent and/or reverse DPN. Indeed, recent observational studies indicate that weight loss may improve DPN outcomes. Specifically, two studies found that dietary-induced weight loss improves DPN, as measured by MNSIq [28, 29]. In addition, six small studies (*n* = 218 total) and a larger insurance claims-based study assessed DPN outcomes following surgical weight loss [30–35], with only one failing to find improved DPN outcomes [36]. The impact of pharmaceutical weight loss on DPN outcomes is quickly emerging. Randomized studies assessed the effect of topiramate (anticonvulsant with weight loss properties) [37](*n* = 132) and exenatide (glucagon-like peptide-1 receptor agonist) [38](*n* = 46) on DPN, but found modest weight loss (0.83 BMI and 1 kg weight reduction, respectively) and as a result, no change in DPN outcomes. Given the initial evidence for obesity-lowering therapies for preventing DPN, randomized studies are needed to identify the optimal modality, timing, and intensity of weight-loss interventions, to update standards of care accordingly.

We found that although obesity increased DPN risk, among those with DPN, it was not associated with the likelihood of experiencing pDPN. Our findings are concordant with most prior studies that did not find an association between obesity and pDPN. Specifically, studies among persons with neuropathy in Denmark (*n* = 938), Europe (*n* = 276), UK (*n* = 191), United States (*n* = 1112), and Italy (*n* = 313) all found that obesity was not associated with pDPN [6, 7, 14, 39, 40]. In contrast, studies of persons with and without neuropathy in Belgium (*n* = 1111) and the Middle East (*n* = 3021) found that obesity increased pDPN likelihood versus no DPN; however, these studies did not determine the effects of obesity on painful versus painless DPN, limiting interpretation [41, 42]. Conversely, one United States study (*n* = 184) found that BMI correlated with pain among those with DPN [43]. Interestingly, we found that only older age was associated with the likelihood of pain. Thus, risk factors for pDPN remain elusive and deserve further investigation. Another possibility for the lack of associations between obesity measurements may be that our pDPN outcome included those with discomfort in the feet, and thus we might include participants with less severe pDPN. However, our secondary pDPN outcome measured using DN4, yielded similar results. Nonetheless, taken together, the current evidence indicates that obesity increases DPN likelihood, but once DPN develops, other factors may contribute to pain.

We found that measures of general, central, and peripheral obesity had similar discriminatory capability for DPN among male participants (AUCs = 0.87–0.89). Among female participants, we found clinically significant differences in discriminatory capability measurements across different obesity locations. Specifically, central obesity measurements had the highest discriminatory capability for DPN, followed by general, peripheral, and central-peripheral obesity. Thus, our results indicate that for females, assessments of central obesity are needed to accurately determine DPN risk, whereas for males, obesity, regardless of distribution, can accurately determine DPN risk. Four studies assessed differential associations between central and general obesity measurements with DPN. Our prior study compared the discriminatory capability of nine anthropometric measurements in 138 individuals with obesity [44]. We found that central obesity was more discriminatory of neuropathy compared to eight other general and peripheral measurements [44]. Since this study was performed in a predominantly female population (76%), the results agree with the current study, which also revealed that central obesity was more important than general obesity in females. Similarly, our overall results are aligned with the Danish Centre for Strategic Research in Type 2 Diabetes cohort (*n* = 5249), the Cooperative Health Research in the Region of Augsburg cohort (*n* = 513), and a UK Biobank study that found general (e.g., BMI) and central obesity (e.g., waist circumference, waist-height ratio, and waist-hip circumference ratio) similarly associated with neuropathy [13–15]. Abdominal fat has previously been found to be more metabolically impaired and pro-inflammatory compared to peripheral or subcutaneous fat [26, 45, 46]. Thus, it is possible that there are sex-specific differences in terms of how metabolically impaired the central fat is, which might drive the increased importance of central obesity for female participants. Alternatively, given the anthropometric differences between males and females [16, 17], there may be differences in terms of what degree of obesity results in increased DPN risk. However, additional studies are needed to confirm whether there exist sex-specific differences in the role adipose tissue distribution has on DPN likelihood and determine the underlying mechanisms resulting in these differences. We advocate using central obesity measurements, as these will provide the best assessment of DPN risk for both males and females.

In male participants, obesity measurements had similar discriminatory capability for DPN, regardless of assessment technique. Our findings are not completely surprising, given that prior studies found that simple anthropometric measurements provide good approximations of more complicated obesity indices. For example, approximately 75% of the variability in VAT volume can be explained by waist circumference alone [47]. Although anthropometric measurements are unable to distinguish between fat and lean mass, our results suggest that this perceived limitation is not relevant for quantifying DPN risk in males. On the other hand, anthropometric measurements have clear benefits in terms of healthcare costs, patient burden, and speed of assessment. Taken together, simple anthropometric assessments (e.g., waist circumference or BMI) should be the primary assessment

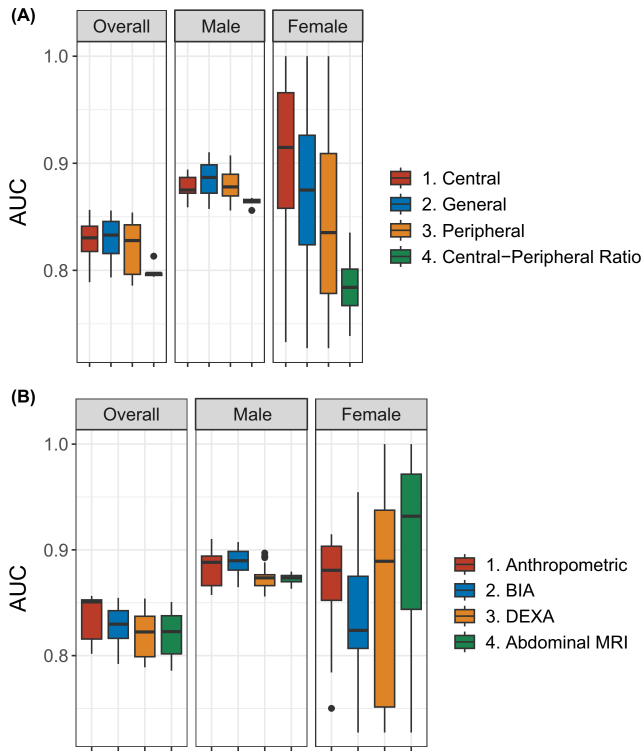

FIGURE 2 | Discriminatory capability of obesity measurements. Discriminatory capability of obesity measurements stratified by (A) distribution of adipose tissue and sex and (B) assessment tool and sex. Boxplots represent 25th percentile, median, and 75th percentile of data. Lines represent the median ± 1.5* inner quartile range. aMRI, abdominal magnetic resonance imaging; AUC, area under the receiver operating characteristics curve; BIA, bioelectrical impedance analysis; DEXA, dual x-ray absorptiometry scans.

used to ascertain DPN risk in males. However, in female participants, aMRI obesity measures had better discriminatory capability for DPN. aMRI better distinguishes between fat and lean mass and their relative distribution, indicating that these factors may be more important in female than male participants. Given the small number of participants with complete data on each obesity measurement, particularly when stratifying by sex, this result should be interpreted with some caution. However, if these findings are validated in another population, interventions designed to address central fat may be more effective in female than male participants. Either way, obesity intervention trials should stratify results by sex to see if important differences in neuropathy outcomes exist. Importantly, aMRI is more expensive and time-consuming than simple anthropometric measures; therefore, routine clinical use of these tests is likely not warranted until these measures change clinical management.

Strengths of our study include the substantial number of detailed obesity measurements and sample size with assessments of DPN, pain, anthropometric measures, and BIA. Limitations include the small number of participants that completed DEXA and aMRI, and small number of persons that completed all obesity measurements, particularly when stratifying by sex. Additionally, our study did not complete comprehensive DPN assessments, such as examination scales, nerve conduction studies, and/or skin biopsies. However, MNSIq, has acceptable discriminatory characteristics (AUC = 0.75–0.76) [20, 21] compared to a gold standard assessment of DPN. Our primary pDPN outcome allowed participants to report pain or discomfort, which may limit the specificity of our pDPN outcome or include those with less severe pDPN. Additionally our study was cross-sectional with data collected at different times. Therefore, future longitudinal studies are needed to further assess the relationship between obesity measures and neuropathy outcomes. Lastly, we did not distinguish between type 1 and type 2 diabetes. Thus, future work is needed to determine whether obesity measurements have differential associations with DPN between diabetes types.

To date, this was the largest study to assess the relationship between BIA, DEXA, aMRI, and DPN/pDPN, first to compare discriminatory characteristics for DPN across obesity measurements by different assessment techniques, and most robust assessment of the sex-specific relationship between adipose tissue distribution and DPN. We found that 69 of 90 obesity measurements are associated with DPN. Moreover, we found obesity was not a risk factor for pDPN, indicating that although obesity increases the DPN likelihood, it is unlikely to play a role in whether patients with DPN experience pain. For male participants, adipose tissue distribution did not differentially associate with DPN, whereas for female participants, central obesity measures had the best discriminatory attributes for DPN. Additionally, in male participants, we found that anthropometric assessments of obesity had similar discriminatory characteristics to more advanced obesity assessment techniques, and thus, should be the primary tool used to assess DPN risk. However, in female participants, aMRI obesity measures had better discriminatory capability for DPN, but come with greater costs and inconvenience.

Author Contributions

E.L.R., D.L.B., B.C.C.: conceptualization. E.L.R., D.L.B., B.C.C.: methodology. E.L.R., D.R.: formal analysis. E.L.R.: writing – original draft. D.R., G.B., E.L.F., D.L.B., B.C.C.: writing – review and editing.

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Ethics Statement

Data for this study were obtained from the UK Biobank for project “Risk factors for chronic pain,” Application ID: 49572. UK Biobank has approval from the North West Multicentre Research Ethics Committee (MREC) as a Research Tissue Bank (RTB) approval, REC reference: 21/NW/0157, IRAS project ID: 299116. This approval means that researchers do not require separate ethical clearance and can operate under the RTB approval.

Conflicts of Interest

Dr. Reynolds, Mr. Russman, Dr. Baskozos, and Dr. Feldman reports no disclosures. Dr. Bennett has acted as a consultant for 5am ventures, AditumBio, Astra Zeneca Biogen Biointervene, Combigene, LatigoBio, GSK, Ionis, Lexicon therapeutics, Neuvati, Novo Ventures, Olipass, Orion, Replay, SC Health Managers, Third Rock ventures, Vida Ventures, Vertex on behalf of Oxford University Innovation. Dr. Callaghan consults for DynaMed, receives research support from the American Academy of Neurology and performs medical-legal consultations, including consultations for the Vaccine Injury Compensation Program.

Data Availability Statement

The data that support the findings of this study are available from UK Biobank. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from https://www.ukbiobank.ac.uk/ with the permission of UK Biobank.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** ene70447-sup-0001-DataS1.docx.