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ORIGINAL REPORT

METABOLICALLY HEALTHY OBESITY AND SUBCLINICAL ATHEROSCLEROSIS IN PERSONS WITH SPINAL CORD INJURY

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Objective: **Despite preserved metabolic function, metabolically healthy obesity may increase the risk of subclinical atherosclerosis. Given the high prevalence of cardiometabolic diseases in individuals with spinal cord injury, the aim of this study was to investigate the association of insulin resistance, systemic low-grade inflammation, and markers of subclinical atherosclerosis with metabolically healthy obesity in individuals with spinal cord injury.**

Methods: **Insulin resistance index (HOMA-IR), high-sensitivity C-reactive protein, carotid artery intima-media thickness and carotid-femoral pulse wave velocity were measured in individuals with spinal cord injury classified with metabolically healthy obesity ($n = 12$), metabolically unhealthy obesity ($n = 8$), or metabolically healthy normal-weight ($n = 18$). Metabolically healthy obesity was defined as spinal cord injury-specific cut-off of body mass index ≥ 22 kg/m² with < 3 metabolic abnormalities.**

Results: **There were no differences in HOMA-IR or high-sensitivity C-reactive protein in metabolically healthy obesity compared with metabolically healthy normal-weight ($p > 0.05$). Pulse wave velocity was higher in metabolically healthy obesity than in metabolically healthy normal-weight ($p \leq 0.05$), but lower than in metabolically unhealthy obesity ($p \leq 0.05$). Metabolically healthy obesity had similar carotid artery intima-media thickness vs metabolically healthy normal-weight ($p > 0.05$), but lower carotid artery intima-media thickness compared with metabolically unhealthy obesity ($p \leq 0.05$).**

Conclusion: **Despite a somewhat preserved metabolic and inflammatory status, individuals with spinal cord injury with metabolically healthy obesity present with an intermediate subclinical atherosclerotic phenotype, as evidenced by increased aortic stiffness but not carotid thickness.**

Key words: spinal cord injury; metabolically health obesity; subclinical atherosclerosis; insulin resistance.

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LAY ABSTRACT

Metabolically healthy obesity is defined as a cohort of obese individuals with relatively low risks of cardiovascular and metabolic diseases. It remains unclear whether metabolically healthy obesity confers protection from cardiometabolic risks in individuals with spinal cord injury. This study investigated the association of insulin resistance, systemic low-grade inflammation, and markers of subclinical atherosclerosis with metabolically healthy obesity individuals with spinal cord injury. Our novel findings show that metabolically healthy obesity individuals with spinal cord injury were not at an increased risk for insulin resistance or systemic low-grade inflammation, supporting the possibility that metabolically healthy obesity exists in individuals with spinal cord injury.

Although obesity is generally associated with an increased risk of cardiometabolic diseases, there is substantial heterogeneity in cardiovascular disease (CVD) morbidity and mortality across the obesity spectrum. Approximately 10–25% of the obese population do not experience metabolic disturbances, and this obesity phenotype is referred to as metabolically healthy obesity (MHO) (1). Despite increased body mass index (BMI), individuals with MHO have favourable blood lipid and glucose profiles, lower blood pressure, preserved insulin sensitivity and low inflammatory markers compared with metabolically unhealthy obesity (MUO) (2, 3). Whether MHO confers protection from CVD remains controversial. While some studies note similar CVD mortality between those considered MHO and those considered metabolically healthy normal weight (MHNW), others suggest that CVD risk is higher in MHO and that this obesity subtype is not a benign condition (4–7). Indeed, evidence is emerging that MHO is associated with subclinical atherosclerosis (e.g. endothelial dysfunction, increased aortic stiffness, increased carotid intima-media thickness and increased coronary artery calcification) (3, 8, 9).

The prevalence of obesity in individuals with SCI varies from 40% to 66% and remains higher than in the able-bodied population (10–12). The high prevalence of obesity among individuals with SCI is associated

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with an increased risk of CVD and type 2 diabetes (11, 13, 14). To date, no studies have explored MHO in SCI (15). A better understanding of obesity phenotypes, particularly within SCI as it relates to risk of CVD, is needed to better guide risk prediction/management and subsequent clinical care. The purpose of the present study was to examine the association of MHO with cardiometabolic disease risk in SCI. To this end, we assessed insulin resistance, systemic low-grade inflammation and markers of subclinical atherosclerosis in individuals with SCI across varying obesity phenotypes.

MATERIAL AND METHODS

This study included 40 individuals with SCI (mean age 41 (standard deviation 8) years, male 60%) at the cervical ($n=3$), thoracic ($n=30$) and lumbar ($n=7$) neurological levels. The mean duration of SCI was 15 ± 10 years. According to the American Spinal Injury Association (ASIA) impairment scale, 27 participants with SCI were grade A, 5 were grade B, and 8 were grade C. Of the included participants 62.5% had a complete injury and 37.5% had an incomplete injury. None of the participants had an abnormal electrocardiogram or coronary artery disease (previously diagnosed by a physician). All participants abstained from caffeine and exercise on the testing day and were at least 8-h postprandial upon arrival to the laboratory for testing. Written informed consent was obtained from all participants, and all procedures conducted in the present study were in accordance with ethical standards and the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board (IRB) Committee of the University of Seoul (IRB number 2016-02).

Body weight was obtained by self-report (kg) and height was measured using a tape measure in the supine position (cm). BMI was calculated as weight (kg) divided by height (m) squared. Waist circumference (cm) was measured using a standard tape measure at the level of the umbilicus; the mean of 2 measurements was used. Information on physical activity was obtained by self-report using the Korean version of the Physical Activity Scale for Individuals with Physical Disabilities (16).

Blood pressure (BP) was measured in the seated position following at least 5 min of quiet rest using an automated BP monitor (Dinamap PRO 100, Milwaukee, WI, USA). Hypertension was defined as systolic and/or diastolic blood pressure ≥140/90 mmHg, diagnosed hypertension by a physician, and/or the use of antihypertensive medications. Blood samples were collected in the morning following an overnight fast. Total cholesterol (TC) and high-density lipoprotein cholesterol (HDL) were measured using an enzymatic colorimetric test. Glucose and triglycerides (TG) were analysed using GPO-PAP methods and hexokinase method, respectively. Low-density lipoprotein cholesterol (LDL) was calculated using the Friedewald formula. High-sensitivity C-reactive protein (hsCRP) was measured using a CRP (II) Latex X2 turbidimetric method (Hitachi Corporation, Tokyo, Japan). Fasting insulin levels were determined by an enzyme immunoassay (Boehringer Manheim Immunodiagnostics, Mumbai, India). Inter- and intra-assay coefficients of variation were <6% for all blood variables. Insulin resistance was assessed according to the homeostasis model assessment of insulin resistance index (HOMA-IR). The HOMA-IR was calculated as the product of the fasting blood glucose and the insulin levels: [fasting blood glucose (mg/dl) × insulin (μU/ml)]/405.

Aortic stiffness was measured as carotid-femoral pulse wave velocity (PWV) using applanation tonometry (SphygmoCor; Atcor Medical, Sydney, Australia) according to current recommendations (17). Applanation tonometry measurements of PWV are reliable in individuals with SCI (18, 19). The distance between the super-sternal notch and the carotid pulse-site, as well as the distance between the super-sternal notch and the femoral pulse-site, were measured using a standard tape measure. These distances were subtracted to determine the carotid – femoral PWV path length. The equation used to determine PWV was: Δ distance (m)/Δ time (s), where change in time is the difference between carotid and femoral pressure waves (obtained from simultaneous ECG R-wave gating).

Carotid artery ultrasound imaging was performed using a high-resolution B-mode ultrasound system (ACUSON X 300; Siemens, Mountain View, CA, USA). The intima media thickness (IMT) was defined as the distance from the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface of the far wall of the carotid artery. All measurements were made at end diastole according to ECG gating. The carotid IMT of the common carotid artery was determined from a semi-automated measurement obtained 2-cm proximal to the carotid bifurcation. The value for carotid IMT was defined as the mean of the IMT. A reproducibility (i.e. intraclass correlation coefficient; ICC) of 0.99 was achieved within technicians.

Obesity was defined as BMI ≥22 kg/m² based on SCI-specific BMI cut-off values (20, 21). Being metabolically unhealthy was defined as participants having ≥2 of the following risk factors: waist girth >90 cm, BP >130/85 mmHg, HDL <40 mg/dl, TG >150 mg/dl, and glucose >100 mg/dl. Participants were divided into 4 groups based on cross-classifications of BMI and metabolic health status using the ATP-III criteria (22) as metabolically healthy normal weight (MHNW, <2 metabolic abnormalities with BMI <22 kg/m²), metabolically unhealthy normal weight (MUNW, ≥2 metabolic abnormalities with BMI <22 kg/m²), metabolically healthy obese (MHO, <2 metabolic abnormalities with BMI ≥22 kg/m²), and metabolically unhealthy obese (MUO, ≥2 metabolic abnormalities with BMI ≥22 kg/m²).

Data are presented as mean with standard deviation (SD) and as proportions for categorical variables. For group comparisons

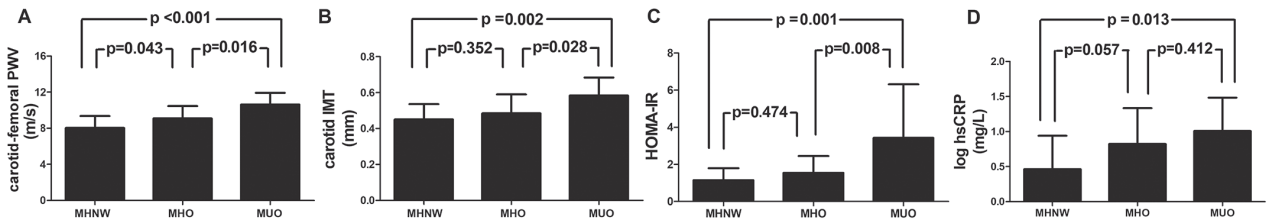

Fig. 1. Comparison of: (a) carotid femoral pulse wave velocity (PWV); (b) carotid intima media thickness (IMT); (c) homeostasis model assessment for insulin resistance (HOMA-IR); and (d) high-sensitivity C-reactive protein (hsCRP) according to metabolically obese phenotypes.

by obesity phenotypes, variables were assessed using an analysis of variance (ANOVA) with LSD (Least Significant Differences) *post hoc* and χ^2 tests for continuous and categorical variables, respectively. There were only 2 participants categorized as MUNW and, as such, were excluded from data analyses. Univariate associations between lesion level and cardiometabolic risk was assessed with Pearson correlation. Statistical significance was set at $p \leq 0.05$, and analyses were conducted using the SPSS 22.0 (SPSS, Armonk, NY, USA).

RESULTS

The characteristics of the participants are shown in Table I. Table II shows the characteristics of participants stratified by metabolic health status and BMI. Thirty percent ($n=12$) of obese individuals with SCI were classified as MHO. In general, MUO had a poorer cardiovascular risk profile than MHNW: higher SBP, DBP, TG, glucose, HOMA-IR, hsCRP, PWV and carotid IMT ($p \leq 0.05$). HOMA-IR was lower in MHO compared with MUO ($p \leq 0.05$) and did not differ between MHO and MHNW ($p > 0.05$). hsCRP was similar between MHO and MHNW ($p > 0.05$) as well as between MHO and MUO ($p > 0.05$). cfPWV was higher in MHO compared with MHNW ($p \leq 0.05$) and lower than MUO ($p \leq 0.05$). CIMT was lower in MHO compared with MUO ($p \leq 0.05$) and similar to MHNW ($p > 0.05$) (Fig. 1). There was a positive correlation between level of injury and HDL ($r = 0.320$, $p = 0.044$). There was a negative correlation between level of injury and waist circumference ($r = -0.390$, $p = 0.017$). Level of injury was not associated with any other cardiometabolic risk factor. There was no difference in level of injury across different MHO groups ($p > 0.05$).

Table I. Characteristics of participants ($n = 40$)

Variable	
Male, *n* (%)	24 (60)
Age, years, mean (SD)	41 (8)
Smoking, *n* (%)	
No	22 (55)
Yes	18 (45)
Drinking, *n* (%)	
No	30 (75.0)
Yes (≥ 2/week)	8 (20.0)
Diabetes, *n* (%)	2 (5.0)
Hypertension, *n* (%)	4 (10.0)
Dyslipidaemia, *n* (%)	1 (2.5)
Medications, *n* (%)	
Anti-hypertensive	4 (10.0)
Hypoglycaemic	2 (5.0)
Lipid-lowering	1 (2.5)
Pain	4 (10.0)
Bladder	11 (27.5)
Skeletal muscle relaxants	4 (10.0)
SCI duration, years, mean (SD)	14.59 (10.23)
Neurological level, *n* (%)	
Cervical	3 (7.5)
Thoracic	30 (75.0)
Lumbar	7 (17.5)
Completeness of injury, *n* (%)	
Complete	25 (62.5)
Incomplete	15 (37.5)
ASI, *n* (%)	
A	27 (67.5)
B	5 (12.5)
C	8 (20.0)
Sleep time, h/day, mean (SD)	6.89 (1.11)
BMI, kg/m^2, mean (SD)	22.56 (3.59)
Waist circumference, cm, mean (SD)	92.66 (12.58)
Systolic blood pressure, mmHg, mean (SD)	115.78 (11.62)
Diastolic blood pressure, mmHg, mean (SD)	75.78 (10.83)
Heart rate, bpm, mean (SD)	68.73 (8.78)
Carotid femoral pulse wave velocity, m/s, mean (SD)	8.90 (1.66)
Carotid intima media thickness, mm, mean (SD)	0.49 (0.11)
Triglyceride, mg/l, mean (SD)	125.48 (56.42)
High-density lipoprotein-cholesterol, mg/l, mean (SD)	51.05 (13.86)
Low-density lipoprotein-cholesterol, mg/l, mean (SD)	121.20 (33.12)
Total cholesterol, mg/l, mean (SD)	187.28 (32.04)
Glucose, mg/l, mean (SD)	91.05 (15.26)
Insulin, μIU/ml, mean (SD)	7.86 (6.13)
Homeostasis model assessment for insulin resistance, mean (SD)	1.85 (1.70)
High-sensitivity C-reactive protein, mg/l, mean (SD)	3.19 (5.27)
Handgrip strength, kg/BMI, mean (SD)	1.7 (0.5)
Physical activity, MET-h/day, mean (SD)	17.82 (12.08)

SCI: spinal cord injury; SD: standard deviation; BMI: body mass index.

DISCUSSION

MHO individuals with SCI were not found to be at increased risk of insulin resistance or systemic low-grade inflammation, supporting the possibility that metabolically healthy obesity exists in individuals with SCI. To our knowledge, this is the first study to examine subclinical atherosclerotic risk within different obesity phenotypes in SCI. Our findings are in agreement with those previously reported in the able-bodied population and note that, when compared with MHNW, MHO have increased aortic stiffness, but comparable carotid intima-media thickening. When compared with MUO, MHO subjects have lower aortic stiffness and lower carotid intima-media thickening. These findings suggest that, although MHO SCI may not be at risk for metabolic disturbances, they present with an intermediate subclinical atherosclerotic risk profile.

The current study found that approximately 30% of obese individuals with SCI were classified as MHO, defined using a SCI-specific BMI cut-off value ≥22 kg/m^2 and having ≥2 cardiometabolic risk factors. The prevalence rate of MHO in our cohort of individuals with SCI is similar to that reported in previous studies in an able-bodied population (1). Individuals with MHO SCI presented with lower traditional CVD risk factor burden compared with MUO SCI and similar CVD risk factor burden as MHNW SCI and this is similar to previous reports in the able-bodied population. Compared with MHNW SCI, MHO SCI had similar triglycerides, fasting glucose, and blood pressure. Interestingly, MHO SCI also had similar HOMA-IR and hsCRP compared with MHNW SCI, suggesting preserved metabolic function and lower systemic

Table II. Characteristics of participants stratified by metabolic health status and body mass index (BMI) ($n = 38$)

Variable	MHNW (n=18)	MHO (n=12)	MUO (n=8)	p-value
Male, *n* (%)	7 (38.9)	9 (75.0)	6 (75.0)	0.079
Age, years, mean (SD)	38.8 (7.2)	39.5 (5.0)	49.4 (7.7)[a,b]	0.002
Current smoker, *n* (%)	7 (38.9)	7 (58.3)	2 (25.0)	0.311
Drinking, ≥ 2 times/week, *n* (%)	1 (5.9)	5 (45.5)	2 (25.0)	0.047
Diabetes, *n* (%)	0 (0.0)	0 (0.0)	2 (25.0)	0.019
Hypertension, *n* (%)	0 (0.0)	0 (0.0)	4 (50.0)	< 0.001
SCI duration, years, mean (SD)	15.3 (9.4)	12.1 (6.7)	19.6 (16.2)	0.316
Neurological level, *n* (%)				0.582
Cervical	2 (11.1)	0 (0.0)	0 (0.0)	
Thoracic	13 (72.2)	9 (75.0)	7 (87.5)	
Lumbar	3 (16.7)	3 (25.0)	1 (12.5)	
Completeness of injury				0.387
Incomplete, *n* (%)	9 (50.0)	3 (25.0)	3 (37.5)	
Complete, *n* (%)	9 (50.0)	9 (75.0)	5 (62.5)	
Sleep time, h/day, mean (SD)	6.9 (1.3)	6.7 (0.9)	6.9 (1.1)	0.891
BMI, kg/m^2, mean (SD)	19.6 (1.3)	25.0 (3.2)[a]	25.9 (2.4)[a]	< 0.001
Waist circumference, cm, mean (SD)	83.1 (8.8)	99.6 (11.9)[a]	100.4 (8.0)[a]	< 0.001
Systolic blood pressure, mmHg, mean (SD)	109.9 (10.0)	115.3 (6.4)	128.6 (12.7)[a,b]	< 0.001
Diastolic blood pressure, mmHg, mean (SD)	71.6 (10.0)	75.3 (8.6)	84.9 (12.2)[a,b]	0.014
Heart rate, bpm, mean (SD)	65.6 (7.2)	71.4 (9.9)	69.6 (9.1)	0.185
Carotid femoral pulse wave velocity, m/s, mean (SD)	8.0 (1.3)	9.1 (1.4)[a]	10.6 (1.3)[a,b]	< 0.001
Carotid intima media thickness, mm, mean (SD)	0.5 (1.0)	0.5 (0.1)	0.6 (0.1)[a,b]	0.009
Triglyceride, mg/l, mean (SD)	181.6 (26.8)	185.8 (26.2)	204.1 (49.6)	0.269
High-density lipoprotein-cholesterol, mg/l, mean (SD)	56.7 (11.6)	51.0 (12.5)	43.2 (15.5)[a]	0.056
Low-density lipoprotein-cholesterol, mg/l, mean (SD)	112.9 (27.6)	121.6 (30.5)	138.8 (47.5)	0.205
Triglyceride, mg/l, mean (SD)	99.5 (36.4)	117.5 (34.7)	171.1 (73.6)[a,b]	0.003
Glucose, mg/l, mean (SD)	83.7 (8.1)	91.4 (9.6)	108.3 (22.5)[a,b]	< 0.001
Insulin, uU/ml, mean (SD)	5.5 (2.7)	6.8 (3.8)	12.4 (9.8)[a,b]	0.013
HOMA-IR, mean (SD)	1.2 (0.7)	1.5 (0.91)	3.4 (2.9)[a,b]	0.003
log_hsCRP (mg/l)	0.5 (0.5)	0.8 (0.5)	1.0 (0.5)[a]	0.026
Handgrip strength (kg/BMI)	1.7 (0.5)	1.7 (0.4)	1.8 (0.5)	0.814
PAS (MET-h/day)	15.8 (8.4)	16.8 (16.0)	24.8 (12.0)	0.205

[a] < 0.05 vs metabolically healthy normal weight (MHNW), [b] < 0.05 vs metabolically healthy obesity (MHO).
BMI: body mass index; HOMA-IR: homeostasis model assessment for insulin resistance; PAS: physical activity score; SD: standard deviation; SCI: spinal cord injury; PAS: physical activity score; MET-h: metabolic equivalent-hour; MHNW: metabolically healthy normal weight; MHO: metabolically healthy obesity; MUO, metabolically unhealthy obesity.

inflammatory status. This finding is particularly poignant, given that these factors are related in individuals with SCI (23, 24) and have been linked to increased risk for type 2 diabetes and CVD in SCI (13). Additional studies are needed to explore the prevalence of MHO SCI in larger cohorts and potential mechanisms contributing to preserved metabolic status.

It has been suggested that assessment of subclinical atherosclerosis may offer novel insight into risk for CVD above and beyond traditional CVD risk factors, as these measures capture actual disease progression and vascular target organ damage. Carotid intima-media thickness and indices of arterial stiffness, surrogate markers of subclinical atherosclerosis, are associated with increased risk of cardiovascular disease mortality in able-bodied populations even after considering traditional CVD risk factors (17). Individuals with SCI have greater subclinical atherosclerotic burden than their able-bodied peers (25, 26) and SCI itself may accelerate vascular aging (27). Although it is uncertain whether this increased subclinical atherosclerosis is associated with an increased risk of CVD and mortality in person with SCI, these biomarkers have nonetheless been suggested to be important for risk prediction in SCI (28).

In able-bodied individuals, MHO is associated with various measures of subclinical atherosclerotic risk including: reduced endothelial function as measured by digital reactive hyperaemia index (29), increased arterial stiffness as assessed via brachial-ankle PWV (3), higher carotid IMT assessed from ultrasonography (8), and increased coronary artery calcium as measured by computed tomography (30). Previous studies have suggested that MHO may attenuate risk for CVD mortality, although a recent meta-analysis disputes earlier findings (5, 7, 31). With a longer duration of follow-up (10 years) it appears that longer exposure to obesity, even in the presence of preserved metabolic function, increases risk of CVD mortality (5, 7, 31). It is possible that the elevated risk of CVD mortality in the absence of metabolic dysfunction may be related to the presence of subclinical atherosclerosis and underlying vascular dysfunction. That is, metabolic health may not be synonymous with vascular health in the setting of obesity.

In the present study, it was noted that MHO had increased aortic stiffness compared with MHNW and lower aortic stiffness compared with MUO, suggesting an intermediate CVD risk phenotype. Interestingly,

MHO had similar carotid IMT as MHNW and lower carotid IMT than MUO. Aortic stiffness and carotid IMT provide unique insight into subclinical atherosclerotic risk (32). Increased carotid IMT is a reflection of change in vascular structure marked by vascular smooth muscle hypertrophy/hyperplasia, lipid deposition and plaque formation. In contrast, the stiffening of arteries is caused by both changes in vascular structure (i.e. calcification, elastin fatigue and fracture, and collagen deposition) and changes in vascular function (i.e. autonomic tone, nitric oxide bioavailability). Although vascular stiffening and thickening often co-exist, vascular stiffening can occur in the absence of thickening (33). Thus, it is possible that MHO in SCI may lead to vascular functional changes prior to vascular structural changes, manifesting as increased aortic stiffness without changes in carotid thickness.

Mechanisms driving vascular stiffening appear to be independent of and/or weakly associated with traditional CVD risk factors, such as: lipids, presence of type 2 diabetes, glucose, smoking and BMI (34). In the SCI population Miyatani et al. (35) has noted that metabolic status (lipids, glucose, glycated haemoglobin) and inflammation (CRP) do not predict aortic stiffness. Thus, it is possible that changes in arterial stiffness in MHO SCI may not be related to traditional CVD risk factor burden, metabolic status and/or inflammatory status. Although MHO SCI are metabolically "healthy" with an overall lower traditional CVD risk factor burden, they may still have underlying vascular dysfunction. An increase in aortic PWV of 1 m/s may confer a 15% increased risk for CVD events (36), thus the differences in PWV noted herein between MHO and MHNW are still clinically relevant.

Limitations

This study has additional methodological limitations. Given the cross-sectional design, causality cannot be determined. Sample size for this examination is relatively small. In addition, it is possible that residual factors not assessed in this study (e.g. socioeconomic status and dietary practices) may influence findings. The operational definition of and criteria used to characterize MHO are debated (37). Moreover, there is no current definition of MHO for SCI. We defined MHO using previous criteria in able-bodied individuals with the exception of using SCI-adjusted BMI cut-points. Additional studies are needed to test the validity and reliability of the present definition of MHO within SCI. In addition, additional studies are needed to clarify whether MHO SCI, as operationally defined herein, is associated with incident type 2 diabetes and CVD in individuals with SCI. Finally, we used the BMI cut-off from body height measured in the supine position and self-reported body weight, which may lead to a suboptimal BMI assessment in individuals with SCI.

It should be noted that MHNW was associated with substantially lower CVD risk in SCI, assessed via traditional (lipids, glucose) and novel risk factors (HOMA-IR, hsCRP, PWV and carotid IMT). Thus, maintaining a healthy weight/body habitus should remain a main therapeutic strategy for mitigating CVD risk in SCI.

Conclusion

These results demonstrate that MHO SCI individuals have similar insulin sensitivity and systemic low-grade inflammation as MHNW SCI. Despite seemingly preserved metabolic function, MHO SCI present with increased aortic stiffness, a measure of subclinical atherosclerosis and CVD risk. Additional studies are needed to further explore the prevalence of MHO in SCI and further characterize the MHO phenotype as it relates to future cardiometabolic risk.

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The authors have no conflicts of interest to declare.

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