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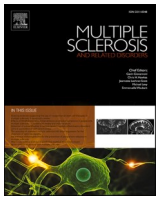

Original article

Increased central obesity correlates with physical activity and food processing in recently diagnosed multiple sclerosis

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ABSTRACT

Background: Environmental and lifestyle factors are associated with an increased risk of Multiple Sclerosis (MS). Metabolic syndrome (MetS) contributes to systemic inflammation, which is associated with poorer MS disease evolution. We compared persons with MS (PwMS) and controls to assess metabolic and lifestyle parameters associated with MS.
Methods: We pooled data from two prospective observational studies with the same eligibility criteria, matching PwMS and controls (1:2 ratio) by sex, age, and body mass index (BMI). We compared anthropometric, biological and lifestyle parameters, including sleep and physical activity.
Results: We included 53 PwMS and 106 controls with a median age of 35 years and 79% of women. PwMS had low Expanded Disability Status Scale (median 1.5). Compared to controls, PwMS had increased waist-to-hip ($p<0.001$) and waist-to-height ($p=0.007$) ratios, and practiced less physical activity ($p=0.03$). In regression models, lifestyle factors with the strongest factor loadings to predict central obesity were processed food consumption, and vigorous physical activity.
Discussion: Although both groups were matched by age, sex, and BMI, we found increased central obesity in PwMS. Even with minimal neurological impairment, PwMS practiced less physical activity. This suggests that improvement of lifestyle and metabolic parameters should be targeted in MS.

1. Introduction

1.1. Multiple sclerosis, an environmental disease

The incidence of multiple sclerosis (MS) has been increasing worldwide (Koch-Henriksen and Sørensen, 2010) emphasizing the role of environmental factors, e.g. the higher prevalence of previous Epstein-Barr virus (EBV) infection observed in persons with MS (PwMS) (Jacobs et al., 2020). Similarly, the incidence of obesity and metabolic diseases is growing (Anon, 2016). The parallel rise in both MS and obesity underlines their potential association and possibly shared lifestyle factors. Indeed obesity before adulthood is associated with an increased MS risk (Munger et al., 2013).

1.2. Central obesity in MS

Obesity is defined by a body mass index (BMI) >30 Kg/m^2, but this definition does not account for the regional distribution of fat. Central obesity, i.e. the accumulation of abdominal adiposity, is defined by elevated waist circumference (WC) and waist-to-hip ratio (WHR, WC divided by the hip circumference), which are associated with cardiovascular disease (Dagenais et al., 2005). A derived measurement of

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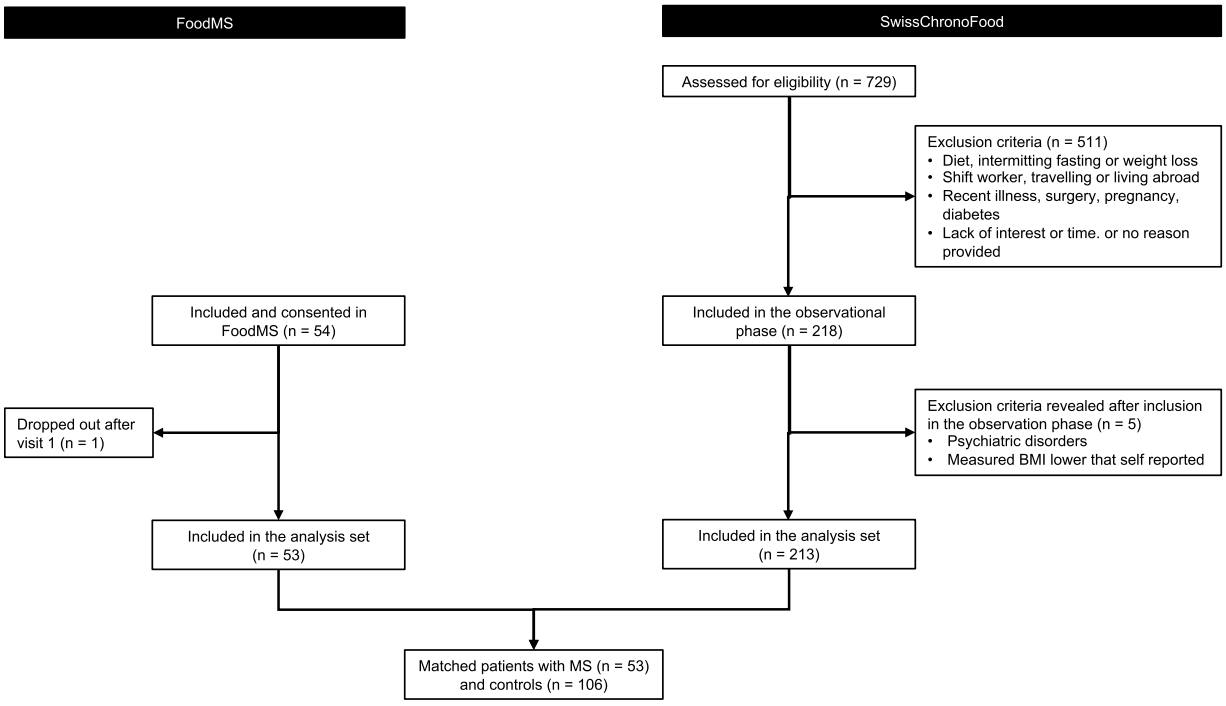

Fig. 1. Flow diagram and overview of inclusion and exclusion of participants in the FoodMS and SwissChronoFood studies
Flow of patients with multiple sclerosis (MS) in the FoodMS study (left) and their matching by age, sex and body mass index (1:2 ratio) with controls from the observational phase of the SwissChronoFood study.

central obesity, waist-to-height ratio (WHtR, WC divided by the height) has been suggested to be a better predictor of cardiovascular risk in a meta-analysis comparing BMI, WC, WHR, and WHtR (Lee et al., 2008). In PwMS, body composition is associated with disability levels and MS severity, and higher WHR, WC, and WHtR were observed in PwMS with moderate disability as assessed by the Expanded Disability Status Scale (EDSS, 4.5-6.5) (Matusik et al., 2022).

1.3. The influence of lifestyle on MS

In MS, the role of nutrition is debated, but the disease is more prevalent in Western countries where the lifestyle is sedentary and the diet rich in calorie-dense, saturated fat (World Health Organization 2009), ultra-processed food (Monteiro et al., 2018). Furthermore, physical activity might also benefit PwMS by reducing the disease progression and the severity of the symptoms (Kalb et al., 2020).

Lifestyle control is key in the non-medical management of central obesity, and thus of MetS, a cluster of multiple conditions including also hypertension, insulin resistance and dyslipidemia (Bertoli et al., 2015). MetS increases cardiovascular disease risk, but also neurodegeneration and neuroinflammation risk (Więckowska-Gacek et al., 2021). Several factors contribute to central obesity, and thus to MetS, including physical activity and nutrition (Bertoli et al., 2015). In addition, the timing of eating has been shown to influence metabolic conditions (Panda, 2016).

PwMS often report fatigue and sleep disorders such as sleep-related breathing disorders and insomnia (Brass et al., 2014). Several sleep and metabolic conditions coexist, and sleep disorders are more prevalent in MetS (Peppard et al., 2013). How diet affects sleep hygiene is still open to debate, but people with regular sleep habits have healthier lifestyle including their diet (Peuhkuri et al., 2012). By combining two prospective observational studies, we aimed to characterize the differences in metabolic and lifestyle parameters between PwMS and controls. Our second objective was to explore the most important lifestyle factors contributing to metabolic parameters in PwMS.

2. Materials and Methods

2.1. Project population and eligibility criteria

This observational study pooled data from two prospective studies performed in parallel by the same study team using a case-control study design. PwMS (cases) were recruited in the FoodMS cohort after MS was diagnosed according to the McDonald 2017 criteria (Thompson et al., 2018). They were matched with controls from the SwissChronoFood study (Phillips et al., 2021) with a 1:2 ratio by sex, age (within 5 years), and BMI (within 2 Kg/m^2). Both studies have been approved by the local Ethics Committee (CER-VD, Lausanne, Switzerland) and each participant signed a written informed consent.

PwMS were prospectively recruited within the CoolinBrain cohort (CER-VD 2018-01622). Controls were recruited into SwissChronoFood in two different cultural regions of Switzerland (CER-VD 2017-00487, clinicaltrials.gov NCT03241121). For this analysis, we used data from the 4-week observational phase of this trial (Phillips et al., 2021).

In both studies, we included adults older than 18 years, with a BMI $\geq$ 18 Kg/m^2, stable weight ($\pm$ 2 Kg) over the previous 3 months, and owning a smartphone compatible with the research application MyCircadianClock (Gill and Panda, 2015). We excluded pregnant and breastfeeding women, individuals who had a major illness, those on a diet, with an eating disorder, prior bariatric surgery, sleep disorders, those on centrally acting medications (benzodiazepines, zolpidem, zopiclone, antidepressants, neuroleptics, and psychotropic drugs), shift workers, or those traveling to another time zone during the study.

2.2. Study procedures

We recorded clinical data and fasting blood tests using standard biochemistry assays at baseline. BMI was the weight in light clothing in Kg divided by the height in meters squared. WC was measured at midpoint between the 12th ribs and iliac crest, and hip circumference at the greater trochanters level. WHR was defined as WC divided by hip circumference, and WHtR as WC divided by height, all in the same units.

Table 1
Baseline clinical characteristics and central obesity parameters.

Median (IQR)	Persons with Multiple Sclerosis (n = 53)	Controls (n = 106)	P-value
Women, no (%)	42 (79%)	84 (79%)	1.00
Age, years	34 (29 – 43)	35 (29 – 43)	0.72
Systolic BP, mmHg	114.0 (109.5 – 122.0)	115.0 (108.5 – 123.0)	0.77
Diastolic BP, mmHg	73.5 (68.5 – 81.5)	75.5 (68.5 – 80.5)	0.74
Central obesity parameters			
Weight, Kg	69.2 (59.1 – 76.6)	70.9 (64.7 – 80.4)	0.17
Height, cm	168.0 (162.0 – 174.0)	170.2 (165.0 - 176.0)	0.08
Body mass index, Kg/m^2	23.9 (21.6 – 26.6)	24.2 (22.0 – 26.8)	0.54
Waist circumference, cm	85.0 (79.0 – 96.0)	81.5 (74.5 – 89.0)	0.06
Waist-to-hip ratio	0.91 (0.87 – 0.94)	0.83 (0.79 – 0.89)	< 0.001
Waist-to-height ratio	0.50 (0.46 – 0.56)	0.48 (0.44 – 0.52)	0.007
Blood results			
Total cholesterol, mmol/L	4.6 (4.0 – 5.8)	4.7 (4.2 – 5.1)	0.92
HDL cholesterol, mmol/L	1.6 (1.5 – 1.8)	1.6 (1.4 – 1.8)	0.55
LDL cholesterol, mmol/L	2.5 (1.9 – 3.3)	2.6 (2.2 – 3.0)	0.87
Triglycerides, mmol/L	0.8 (0.7 – 1.1)	0.8 (0.6 – 1.1)	0.98
Glucose, mmol/L	4.7 (4.6 – 5.0)	4.8 (4.6 – 5.1)	0.22
HbA1c, %	5.0 (4.9 – 5.3)	5.1 (4.9 – 5.3)	0.24
Creatinine, μmol/L	67.0 (61.0 – 74.0)	69.0 (62.0 – 76.0)	0.21
eGFR, mL/min/1.73 m^2	108 (99 – 118)	102 (95 – 113)	0.08

P-values were determined using Mann-Whitney U rank sum test.
Abbreviations: BP, blood pressure; eGFR; estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low density lipoprotein.

Blood pressure was measured three times with a calibrated monitor (Omron Intellisense® BP monitor, Omron Healthcare) and the last two values were averaged. Sleep quality was evaluated with the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) and the chronotype using the Munich Chronotype Questionnaire (Roenneberg et al., 2003). Physical activity was assessed with the International Physical Activity Questionnaire (IPAQ) short form (Craig et al., 2003) which considers walking, moderate physical activity, and vigorous physical activity in 10 min. bouts and estimates total activity of the past week in METs-min/week.

MS-related disability was measured with the EDSS ranged from 0 (no physical disability) to 10 (death due to MS) (Meyer-Moock et al., 2014), and fatigue with EMIF-SEP from 0 (no fatigue) to 120 (maximum fatigue) into four dimensions of fatigue, i.e. cognitive, physical, social, and psychological (Pittion-Vouyovitch et al., 2006).

Participants were asked to take pictures of all consumed food and drinks with the smartphone application MyCircadianClock over 4 weeks (Gill and Panda, 2015). Eating duration was calculated as the time interval between the 2.5th and the 97.5th percentiles of all timestamped food and drink consumption. To account for social habits and the nadir of ingestion events, we calculated these percentiles from 4am to 4am the following night (Phillips et al., 2021). The level of food processing of food and drink consumption was evaluated using the NOVA classification, ranging from raw and unprocessed food (NOVA1) to ultra-processed food (NOVA4) (Monteiro et al., 2018).

2.3. Primary and secondary outcomes

The primary outcome was the difference in metabolic parameters between PwMS and controls. The secondary outcomes were the differences in lifestyle habits, including physical activity, sleep quantity and quality, and consumption of processed food between cases and controls.

2.4. Statistical analyses

Descriptive analyses of baseline characteristics were presented with median ± interquartile range (IQR) and comparisons were calculated with non-parametric tests, since many variables were not normally distributed. A two-tailed p-value < 0.05 was considered statistically significant. Variables with non-normal distribution were transformed before multivariate regression in Stata software (version 17.0, College Station, TX, USA).

Because central obesity parameters (WC, WHR, and WHtR) differed between cases and controls, we devised two models to predict their values: (1) with linear regression adjusted for age and sex, and (2) using Partial Least Squares (PLS) regression with age, sex, and lifestyle factors. PLS regression with one latent variable was used to find a multivariable lifestyle score from the X matrix (multiple lifestyle factors: measurements of meal timing, food processing, sleep, and physical activity) to explain the Y matrix (central obesity parameters) in Python (version 3.7.7, with SciPy 1.7.3). To summarize how atypical the temporal eating profile is compared to all participants, we calculated for each participant the Kuiper statistic (kuiper_two function in Astropy 4.3.1). This D metric quantifies how distant an individual eating profile is from the average eating profile. The higher the value of D, the more atypical is the eating profile. Consumption of unprocessed or minimally processed foods (NOVA1%) and of ultra-processed foods (NOVA4%) was expressed in percentage of the total individual intake. The sleep variables Δ(Bedtime) and Δ(Sleep dur) were calculated as the absolute difference between bedtime and 22:30, and sleep duration and 7.5 hours, respectively. These values were chosen as they are close to the median in our population, and within the recommended range of bedtime and sleep duration for healthy adults (Hirshkowitz et al., 2015). We compared the model predictions to the data using leave-one-out cross-validation (LOO-CV), and calculated the Pearson correlation coefficient and the 95% confidence intervals using bootstrap resampling with 1000 samples.

Table 2
Clinical presentation of Multiple Sclerosis.

Characteristics	Median (IQR)
Time since MS diagnosis, months	22 (12 – 44)
MS type	
Relapsing-Remitting MS	51 (96 %)
Secondary-Progressive MS	1 (2%)
Clinically isolated syndrome	1 (2%)
MS-related disability and fatigue	
EDSS[a]	1.5 (1.0 – 2.0)
EMIF-SEP[b] total score	35.9 (21.4 – 50.0)
MS disease modifying therapies	
First line injectable (IFN, Glatiramer)	10 (18.9%)
Oral treatments (Cytostatic, Fumarate, S1P-Blockade, Nucleoside analogue)	22 (41.6%)
Monoclonal antibodies (Anti-CD20, Anti-CD52, Anti-VLA4)	13 (24.6%)
None	8 (15.1%)

Data are presented as median (IQR) for continuous variables, or as no. individuals (%) for categorical variables.
[a] EDSS is a scale of disability in MS, ranging from 0 (normal neurological function) to 10 (death due to MS), with 0.5 increment.
[b] EMIF-SEP is a MS-related fatigue score ranging from 0 (no fatigue) to 120 (maximum fatigue).
Abbreviations: EDSS, Expanded Disability Status Scale; IFN, interferon; IQR, interquartile range; MS, multiple sclerosis.

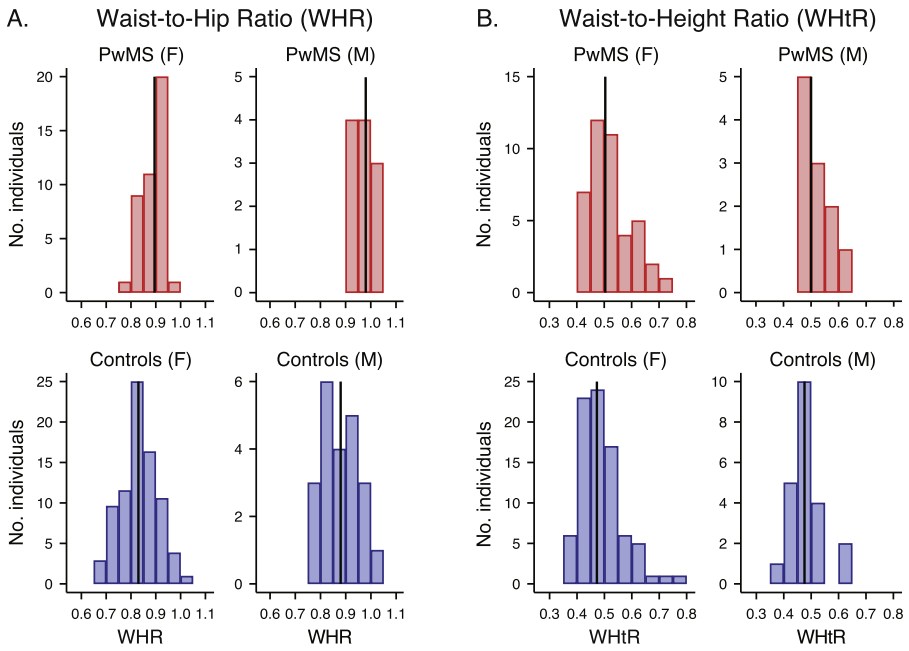

Fig. 2. Multiple Sclerosis (MS) associated with a higher Waist-to-Hip ratio and Waist-to-Height ratio compared to controls
(A) Histograms on the distribution of Waist-to-Hip ratio (WHR) showing a higher WHR in women with MS (F, left panel) and men (M, right panel) compared to respective controls (blue bars, lower panels, $p < 0.001$ for both sex). (B) Histograms on the distribution of Waist-to-Height ratio (WHtR) showing a similar pattern among women with MS (F, left panel) and men (M, right panel) compared to respective controls with significant statistical difference in women (blue bars in the lower panel, $p = 0.007$), but not in men ($p = 0.13$).

Table 3
Eating habits, sleep, and lifestyle parameters.

Median (IQR)	Persons with Multiple Sclerosis (n = 53)	Controls (n = 106)	P-value
Eating habits			
Eating duration, hours:mins	14h12 (12h44 – 14h47)	14h37 (13h50 – 15h33)	0.01
Level of food processing, % of all ingestion events per month			
Raw, unprocessed, or minimally processed foods (NOVA1)	44.1 (33.3 – 50.9)	44.3 (36.7 – 56.3)	0.18
Processed culinary ingredients (NOVA2)	12.5 (9.4 – 17.2)	11.1 (7.7 – 15.6)	0.19
Processed foods (NOVA3)	17.9 (13.2 – 19.9)	17.9 (13.1 – 22.7)	0.41
Ultra-processed foods (NOVA4)	25.1 (18.4 – 33.3)	20.7 (15.9 – 30.0)	0.07
Sleep and lifestyle			
Sleep duration, hours:mins	07h34 (07h00 – 08h09)	07h30 (07h05 – 08h00)	0.50
Sleep quality, PSQI[a] score	5 (3 – 7)	5 (3 – 7)	0.59
Physical activity[b], METs-mins/week	1058 (537 – 1992)	1399 (861 – 2804)	0.03
Regular alcohol consumption[c]	45 (84.9%)	94 (88.7%)	0.50
Current smokers	14 (26.4%)	23 (21.7%)	0.51
Smoking pack-years	4.5 (1 – 11)	3 (1 – 7)	0.29

Data are presented as median (IQR) for continuous variables, or as no. individuals (%) for categorical variables.

[a] PSQI assesses sleep quality, ranging from 0 (excellent sleep quality) to 21 (very poor sleep quality).

[b] N = 100 in the control group, because one participant had invalid answers according to the IPAQ short form, and five others did not know how many minutes per week they practiced for some activities.

[c] At least one standard unit of alcohol per week.

Abbreviations: IPAQ, international physical activity questionnaire; IQR, interquartile range; PSQI, Pittsburg sleep quality index.

3. Results

3.1. Baseline characteristics

Out of the 54 included PwMS, 1 participant dropped out after inclusion and is not included in this analysis. Among the 729 adults screened for the SwissChronoFood study, 516 did not meet the eligibility criteria (Fig. 1) (Phillips et al., 2021). From the remaining 213 adults, 106 were matched with the 53 PwMS with a 1:2 ratio according to sex, age, and BMI.

Among the 159 participants (Table 1), 79% were women. Our study consists of PwMS with matched controls with the same proportion of women due to matching for sex. This male-to-female ratio is similar to the ratio found in the general population with MS (Voskuhl, 2020). The median age was 34 years (IQR 29-43) for PwMS and 35 (IQR 29-43) for controls, and the median BMI was 23.9 Kg/m^2 (IQR 21.6-26.6) and 24.2 (IQR 22-26.8), respectively (both $p \geq 0.50$). No significant difference was observed between groups in terms of blood pressure, lipid profile, glycosylated hemoglobin (HbA1c), or renal function (Table 1, all $p \geq 0.08$). MS-specific clinical characteristics among PwMS are summarized in Table 2: 51 had RRMS, 1 SPMS, and 1 clinically isolated syndrome. The median EDSS was 1.5 (IQR 1.0-2.0) and the median duration since diagnosis was 22 months (IQR 12-44). Eight PwMS were not under disease-modifying therapies.

3.2. WHR and WHtR are increased in PwMS compared to controls

Despite both groups were matched for BMI, a marker of *overall* obesity, we observed a significantly higher WHR, an indicator of *central* obesity, in PwMS compared to controls (median 0.91, IQR 0.87-0.94 vs. 0.83, IQR 0.79-0.89, respectively, $p < 0.001$, Table 1). WHR is known to differ between sexes, thus we confirmed this difference in a stratified analysis in women (PwMS: median 0.90, IQR 0.85-0.92 vs. controls: 0.83, IQR 0.78-0.89, $p < 0.001$, Fig. 2A, left panels) and in men (PwMS: median 0.98, IQR 0.94-1.02 vs. controls: 0.88, IQR 0.82-0.95, $p = 0.001$, Fig. 2a, right panels). Similarly, the other central obesity parameter

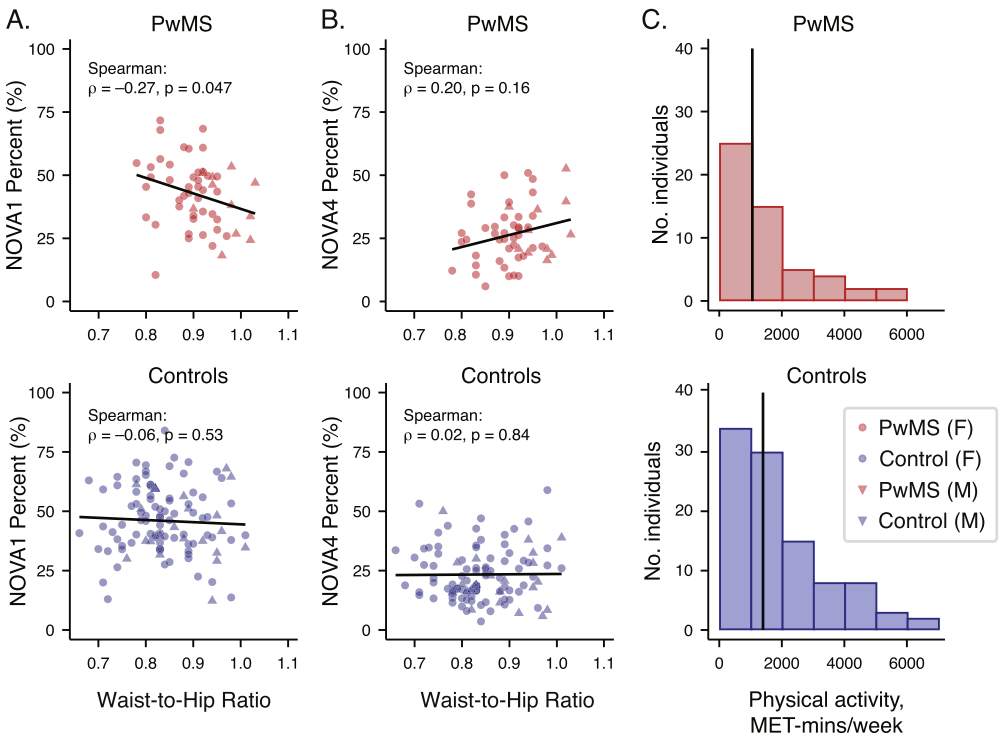

Fig. 3. Food processing and physical activity are associated with central obesity in PwMS compared to controls
(A) Proportion of consumed unprocessed food (NOVA1) and (B) ultra-processed food (NOVA4) according to WHR in persons with multiple sclerosis (PwMS, upper panels) versus controls (lower panels). The consumption of NOVA1 food negatively correlated with WHR ($p = 0.047$, Spearman's correlations in the plots) and inversely for NOVA4 (despite no significance, $p = 0.16$) in PwMS, but not in controls ($p = 0.53$ and 0.84, respectively).
(C) PwMS (top) practiced less physical activity than controls (bottom), as assessed by the international physical activity questionnaire in METs-min/week ($p = 0.03$).

WHtR was significantly higher in PwMS (median 0.50, IQR 0.46-0.56 vs. 0.48, IQR 0.44-0.52, $p = 0.007$, Table 1). This difference was mostly driven by women (median 0.50, IQR 0.46-0.56 vs. 0.47, IQR 0.44-0.52, $p = 0.02$, Fig. 2b, left panels), while no difference was observed in men (median 0.50, IQR 0.46-0.56 vs 0.48, IQR 0.45-0.50, $p = 0.13$, Fig. 2b, right panels), probably due to the lower number of men. The exploration of other MetS components showed no significant difference in terms of lipid profile, glycemia, or HbA1c between groups (all $p > 0.20$, Table 1).

3.3. *Lifestyle parameters are associated with central obesity in PwMS compared to controls*

PwMS had a significantly shorter eating duration than controls (median 14h12, IQR 12h44-14h47 vs. 14h37, IQR 13h50-15h33, respectively, $p = 0.01$, Table 3). The consumption of processed food expressed as the proportion of each NOVA class was not different between PwMS and controls (all $p \geq 0.07$, Table 3). However, the proportion of processed food according to WHR was different between study groups. Higher consumption of unprocessed or minimally processed food (NOVA1) was associated with a lower WHR in PwMS (Spearman's $\rho = -0.27$, $p = 0.047$), but not in controls ($p = 0.53$, Fig. 3a). At the other end of the spectrum of food processing, consumption of ultra-processed food (NOVA4) was not associated with WHR either in PwMS or in controls (both $p \geq 0.10$, Fig. 3b).

No difference was found between groups in sleep duration, sleep quality, alcohol consumption, and tobacco smoking (Table 3, all $p \geq 0.29$). However, PwMS performed less physical activity than controls (median 1058 METs-min/week, IQR 537-1992, vs. median 1399, IQR 861-2804, respectively, $p = 0.03$, Fig. 3c). This difference was driven by women (PwMS: median 985.5 METs-min/week, IQR 495-1638, vs. controls: median 1399 METs-min/week, IQR 815-2827, $p = 0.02$), while no difference was observed among men (PwMS: median 1386 METs-min/week, IQR 678-2835, vs. controls: median 1606 METs-min/week, IQR 918-2804, $p = 0.82$), probably due to the lower number of men in this study. Furthermore, more physical activity was associated with a lower WHR in controls ($p = 0.043$), however, this association was not observed in PwMS ($p > 0.80$). Similarly, for WHtR, more physical activity was associated with a lower WHtR among controls ($p = 0.029$), while no association was observed among PwMS ($p = 0.26$). Finally, WHR and WHtR were not associated with the eating duration (both $p > 0.08$).

3.4. *Lifestyle parameters play a significant role in predicting central obesity*

After identifying the differences in WHR and WHtR between groups, despite being matched for age, sex, and BMI, we sought out to determine a 'lifestyle score' predicting central obesity parameters (WHR, WC, and WHtR). The 24-hour eating profiles of PwMS and controls were similar at the average level (Table 3), yet PwMS seemed to be eating more erratically upon visual inspection. Individual temporal eating patterns were compared with the D metric, which was lower in controls (median 0.16, IQR 0.14-0.20) than in PwMS (median 0.19, IQR 0.14-0.25, $p = 0.049$). Visual inspection of bedtime and sleep duration in relation to the central obesity variables indicated funnel-shaped relationships, motivating the transformed variables Δ(Bedtime) and Δ(Sleep dur).

In prediction models of central obesity parameters using age and sex, the correlation between the predictions and measured values using LOO-CV was highest for WHR ($R = 0.30$, $p < 0.001$), intermediate for WC ($R = 0.16$, $p = 0.05$), and lowest and non-significant for WHtR ($R = 0.02$, $p = 0.80$, Fig. 4a). The addition of lifestyle factors to the models showed better predictive accuracy (Fig. 4b) than the model with only age and sex (Fig. 4a). This difference was smallest for WHR ($R = 0.38$ vs. 0.30), intermediate for WC ($R = 0.36$ vs. 0.16), and largest for WHtR ($R = 0.33$ vs. 0.02).

We examined the contribution of each lifestyle factor in the PLS

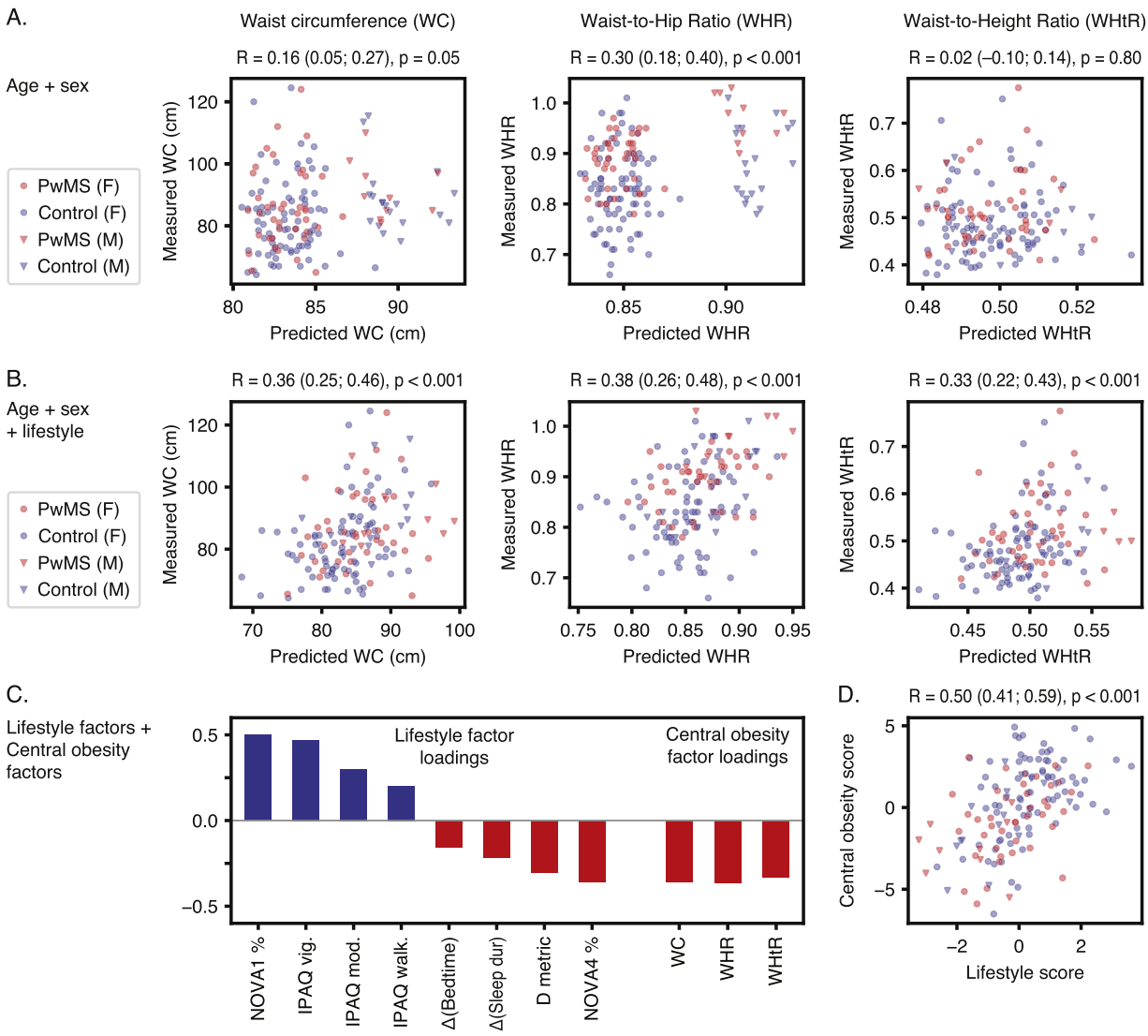

Fig. 4. Prediction of central obesity parameters in multivariate linear regression models
(A) Predicting central obesity parameters waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) using linear regression with age and sex, with leave-one-out cross-validation. (B) Predicting central obesity parameters WC, WHR, and WHtR using Partial Least Squares (PLS) regression with age, sex, and lifestyle factors, with leave-one-out cross-validation. (C) Lifestyle factor loadings (blue bars) and central obesity loadings (red bars) based on the second model using PLS regression with age, sex, and lifestyle factors. (D) Each participant transformed using the PLS regression model to the lifestyle score and the central obesity score. R is the Pearson correlation coefficient and its 95% confidence interval is estimated by bootstrap resampling with 1000 samples. Blue circles: control women; blue triangles: control men; red circles: women with MS; red triangles: men with MS. Abbreviations: IPAQ, international physical activity questionnaire; PLS, Partial Least Squares Regression; PwMS, patients with multiple sclerosis; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

regression. The positive factors associated with less central obesity (ordered by magnitude, Fig. 4c) were the proportion of unprocessed or minimally processed foods (NOVA1, factor loading 0.50), vigorous activity (0.47), moderate activity (0.30), and walking (0.21). The negative contributors to central obesity were the proportion of ultra-processed foods (NOVA4, –0.36), how atypical the eating pattern was (D metric, –0.31), a sleep duration that differed from 7.5 hours (in either direction, –0.22), and a bedtime that differs from 22:30 (in either direction, –0.16) in that order. WC, WHR, and WHtR had similar negative factor loadings for the central obesity score (Fig. 4c), and the lifestyle score was correlated with the central obesity score across the population (Fig. 4d). Neurological disability, reflected by an EDSS score >= 2 could impact ability to perform physical activities. We thus further assessed the repartition of EDSS scores across PwMS in our study and observed nearly 70% had a EDSS score < 2. When additionally adjusted for EDSS score, only the order of variables influencing central obesity are observed (with vigorous activity becoming the most positive factor and atypical eating pattern becoming the most negative) without changing the overall trend.

4. Discussion

4.1. Central obesity is linked to systemic inflammation and could influence MS course

In our observational study of metabolic health and nutrition, PwMS who were recently diagnosed with MS showed increased central obesity, namely a higher WHR and WHtR, compared to controls despite being matched by age, sex, and BMI. We found no significant differences in other metabolic parameters. We observed that PwMS consuming a higher proportion of unprocessed food (NOVA1) had a lower WHR. Finally, lifestyle factors associated with less central obesity were primarily a high proportion of unprocessed food and the practice of vigorous physical activity.

Central obesity can be assessed clinically with WHR and WHtR, and is linked with the metabolically active visceral adipose tissue (VAT), which releases pro-inflammatory cytokines (Tchernof and Després, 2013). Furthermore, an increased WC is associated with metabolic disorders, e.g. diabetes and hypertension, but also with a higher mortality (Cerhan et al., 2014). The discrepancy between BMI and central obesity in MS has been suggested in previous studies suggesting that WC could be a better predictor of metabolic health than BMI both in MS and controls (Lee et al., 2008, Cerhan et al., 2014).

A lower BMI in PwMS compared to controls was reported in a meta-analysis of 25 studies (Dardiotis et al., 2019). However, most of those studies included PwMS with advanced disease and higher EDSS, which in turn could impact body composition suggesting that higher disability is linked with a lower BMI. Contradictorily, Matusik et al. highlighted the correlation between central obesity (WHtR, WHR, FM%, FFM%) and disability status (EDSS) in PwMS (Matusik et al., 2019). Importantly, PwMS with higher disabilities are more likely to be sedentary due to neurological impairment, leading to increased central obesity and loss of muscle mass. However, body composition was not measured in our study (Delikanlı Akbay et al., 2019). Further studies are needed to evaluate the possible non-linear relationship between central obesity, body composition and the disability status of PwMS.

4.2. Physical activity in the therapeutical management of MS

We found that PwMS performed less physical activity than controls (Motl et al., 2015), although most previous studies compared PwMS with advanced disease. While MS may lead to less activity, PwMS in our study were recently diagnosed (median disease duration 22 months), had low disability (median EDSS 1.5) and low fatigue suggesting that their ability for exercise would not be impacted at this stage (Kalb et al., 2020). Nevertheless, physical activity and exercise are key in MS management, and PwMS should be evaluated by a physical therapist to improve quality of life (Kalb et al., 2020).

4.3. Lifestyle management in MS could reduce the metabolic burden on the disease

Finally, we tested whether lifestyle factors could better predict central obesity assessed by WC, WHR and WHtR than age and sex alone. Ordered by magnitude, the following lifestyle factors were associated with less central obesity: high percentage of unprocessed or minimally processed food, physical activity of various intensity, regular eating timing, sleep duration close to 7.5 hours, and bedtime close to 22:30. Given that the identified lifestyle factors are consistent with guidelines for general and brain health (Bassetti et al., 2023), our data suggests that lifestyle modifications, when possible, could be a useful tool for controlling central obesity in PwMS.

4.4. Conclusions

We found increased central obesity among PwMS compared to controls independently of BMI, in overall analyses and stratified by sex, suggesting an unmeasured metabolic impact of MS, which requires further investigation. In our study, lifestyle factors that were associated the most with lower central obesity were a high proportion of unprocessed food and the practice of vigorous physical activity. Based on our findings in an observational cross-sectional study, it seems reasonable to better address diet quality and physical activity to target central obesity and its metabolic burden among PwMS. The limitation of our study is the small sample size of the study with 159 participants among which 53 PwMS recruited from one center. Additional prospective studies with careful metabolic phenotyping and larger cohort of PwMS are needed to provide stronger evidence of the metabolic risk in MS and the involvement of central obesity.

CRediT authorship contribution statement

Guillaume Thévoz: Writing – original draft, Investigation, Data curation. **Nicholas Edward Phillips:** Writing – review & editing, Investigation, Formal analysis. **Jessica Rebeaud:** Writing – review & editing, Investigation, Data curation. **Pansy Lim-Dubois-Ferriere:** Writing – review & editing, Data curation. **Albane Revaz:** Writing – review & editing, Data curation. **Aude Gauthier-Jaques:** Writing – review & editing, Data curation. **Marie Théaudin:** Writing – review & editing. **Renaud Du Pasquier:** Writing – review & editing. **Satchidananda Panda:** Writing – review & editing. **Caroline Pot:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Tinh-Hai Collet:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

G.T., N.E.P., J.R., P.L.D.F., A.R., A.G.J., S.P., T.H.C. have nothing to disclose. J.K. received speaker fees, research support, travel support, and/or served on advisory boards by the Progressive MS Alliance, Swiss MS Society, Swiss National Research Foundation (320030-189140), University of Basel, Biogen, Celgene, Merck, Novartis, Octave Bioscience, Roche, Sanofi. M.T. received travel grants, advisory board/lecture and consultancy fees from Biogen, Sanofi, Novartis, Merck and Roche. R. D.P. reports that the Lausanne University Hospital received speaker honoraria and travel grants for his activities with Biogen, Genzyme, Merck, Novartis, Roche, and Sanofi. None of them were related to this work. C.P. reports that the Lausanne University Hospital received speaker honoraria, travel grants and consulting services for her activities with Novartis, Roche, Biogen, Merck, Sanofi-Aventis none related to this work.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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