



Prevalence of metabolic syndrome and its components in women with and without pelvic organ prolapse and its association with prolapse severity according to the Pelvic Organ Prolapse Quantification system

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Received: 27 September 2018 / Accepted: 26 November 2018 / Published online: 12 December 2018

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Abstract

Introduction and hypothesis Data regarding possible associations between metabolic syndrome (MS) and pelvic organ prolapse (POP) are scarce. The primary hypothesis was that the prevalence of MS and its components was higher in postmenopausal women with POP than in age-matched women without POP staged with the Pelvic Organ Prolapse Quantification system (POP-Q). The secondary aim of the study was to analyze the association between MS and its components with POP severity.

Methods Presence of MS and its components [elevated triglycerides (TG), waist circumference, blood pressure, and fasting glucose (FG) and decreased high-density lipoprotein cholesterol (HDL-C)] were assessed in 122 women with POP (POP-Q stage I–IV) and 77 without (POP-Q 0). Fasting insulin resistance [homeostasis model assessment for fasting insulin resistance (HOMA-IR)] was also assessed.

Results TG levels, FG, and HOMA index were significantly higher in POP-Q stage I–IV compared with POP-Q 0 ($p = 0.04$, $p = 0.0005$ and $p = 0.04$); HDL-C was significantly reduced in POP-Q stage I–IV compared with POP-Q 0 ($p = 0.0003$). TG levels ($p = 0.0315$) were significantly higher in POP-Q stage III and IV vs. POP-Q 0; FG and HOMA-IR ($p = 0.0015$ and $p = 0.0204$) were significantly higher in POP-Q stage IV vs. POP-Q 0; HDL-C ($p = 0.0047$) was significantly lower in all stages vs. POP-Q 0. The prevalence of MS was different between groups ($p = 0.04$) and higher in POP-Q IV. Elevated TG [odds ratio (OR) 4.6, 95% confidence interval (CI) 1.5–9.3, $p = 0.004$] and reduced HDL-C (OR 2.0, 95% CI 1.1–3.7, $p = 0.0241$) significantly increased the risk of POP-Q stage \geq III.

Conclusions MS and its components may be associated with POP. Elevated TG and reduced HDL-C are associated with POP severity.

Keywords Metabolic risk factors · Metabolic syndrome · Pelvic floor · Pelvic floor dysfunctions · Pelvic organ prolapse

Introduction

Pelvic organ prolapse (POP) is a common condition among women, and the reported lifetime risk of POP or incontinence surgery ranges from 11.1 to 19% [1, 2]. Rates of asymptomatic POP are probably higher, with studies reporting that 31–

47.7% of women present some extent of prolapse at gynecological examination [3–5]. POP can impact women's daily activities, sexuality, and body image, requiring intervention from relevant healthcare resources. Furthermore, the diffusion of POP is likely to increase with the growing population of elderly women [6]. Recognized risk factors are parity, genetic factors, advancing age, and obesity [7, 8]. The mainstream theory explaining the association between obesity and POP focuses on the chronically increased abdominal pressure that can lead to damage of ligaments and nerves. In recent years, some authors have suggested an association between metabolic and vascular risk factors and pelvic floor dysfunctions (PFD) [9–13]. Lower urinary tract symptoms (LUTS) were reported to be more frequent in the presence of vascular risk factors. Urinary incontinence (UI) has been reported to be more frequent in women with increased fasting glucose levels

Summary Metabolic syndrome and its components may be associated with pelvic organ prolapse and increasing pelvic organ prolapse severity.

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and type 2 diabetes mellitus (DM) and in particular in those with microvascular complications [9–11]. However, data regarding analysis of the association between metabolic risk factors and metabolic syndrome (MS) and POP are limited: Kim et al. reported the association of MS with the severity of POP symptoms [12], and Rogowski et al. associated MS and hypertriglyceridemia with the severity of POP [13].

This study was aimed at evaluating the prevalence of MS and its components in postmenopausal Italian women with POP in comparison with age-matched women without POP assessed through gynecological examination and staged using the Pelvic Organ Prolapse Quantification (POP-Q) system. The secondary aim of the study was to analyze the association between MS and its components with POP severity.

Materials and methods

The study was approved by the local Medical Ethics Committee in accordance with the 1975 Declaration of Helsinki, and all patients gave written informed consent. Postmenopausal women with and without prolapse were selected from women who attended the Gynecology and Physiopathology of Human Reproduction Unit at S. Orsola University Hospital of Bologna, Italy. Enrollment was proposed to 212 consecutive patients from the outpatient ambulatory clinic for routine checkups of postmenopausal women. A sample size of 192 was calculated to achieve 80% power with the following assumptions: 34% prevalence of MS among postmenopausal women [14], 5% precision and 95% CI, and probability of type 1 error 5%. The enrollment period lasted 6 months. Menopausal status was defined as spontaneous amenorrhea for at least 1 year. Women receiving menopausal hormone therapy (MHT) at time of enrollment or in the previous 6 months were excluded.

At the time of enrollment, clinical, biochemical, and anthropometric parameters were recorded for each participant. Anthropometric assessment was performed for evaluation of weight, height, body mass index (BMI), and waist and hip circumferences according to standardized procedures [15]. Blood pressure (BP) was calculated from the mean of three measurements taken 5 min apart and after 5 min of rest in the sitting position by medical staff trained in performing BP measurements according to criteria described by the European Society of Cardiology and the European Society of Hypertension [16].

Fasting total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), triglycerides (TG), and plasma glucose concentrations were assessed in our hospital laboratory. We used the National Cholesterol Education Program - Adult Treatment Panel III, 2009 (NCEP-ATP III) criteria for MS diagnosis: waist circumference ≥ 88 cm, BP $\geq 130/85$ mmHg; glycemia ≥ 100 mg/dl, TG ≥ 150 mg/dl and

HDL-C < 50 mg/dl; diagnosis was confirmed when at least three of the five risk factors were present [17]. The homeostasis model assessment for fasting insulin resistance (HOMA-IR) was calculated using the formula $HOMA-IR = [\text{fasting insulin in } \mu\text{U/mL} \times \text{fasting glucose in nmol/l}] / 22.5$ to investigate insulin sensitivity. A pelvic examination was performed with the patient in the dorsal lithotomy position according to the standards recommended by the International Urogynecological Association and the International Continence Society (IUGA/ICS) [18]. To quantify POP severity, the POP-Q system was used [19]. All women were questioned regarding their personal health and smoking status. Gynecologic and obstetric history was obtained, including age at menopause, number of full-term deliveries, type of delivery, and previous use of MHT.

Statistical analysis

All continuous data were expressed as mean and standard deviation (SD), and all categorical data were expressed by frequency rate and percentage. The Kolmogorov–Smirnov test was used to assess normality of distributions. One-way analysis of variance (ANOVA) was performed to assess differences between groups when data were normally distributed and the Levene test for homogeneity of variances was not significant ($p < 0.05$); otherwise, the Mann–Whitney test (two groups) or the Kruskal–Wallis test (more than two groups) were used. The Scheffè test was used as post hoc pairwise comparisons of one-way ANOVA. The Mann–Whitney test with Bonferroni correction for multiple comparisons was used as post hoc pairwise comparisons of Kruskal–Wallis test. Pearson’s nonparametric chi-squared test (more than two groups) or Fisher’s nonparametric chi-squared test (two groups) was performed to investigate relationships between categorical variables. Spearman’s rank correlation was used to assess the correlation between continuous variables. Univariate regression analysis was used to assess the influence of continuous variables on POP severity and as multivariate analysis to find the combined influence of risk factors. $P < 0.05$ was considered significant. Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) software version 23.0 (SPSS Inc., Chicago, IL, USA).

Results

Two hundred and twelve women were potentially eligible and were enrolled. Thirteen women undergoing MHT were excluded. The remaining 199 Caucasian postmenopausal women were included in data analysis. At pelvic examination, 77 did not have POP (control group, POP-Q 0) and 122 women had POP, with POP-Q stage ranging from I–IV. A summary of demographic and clinical characteristics of enrolled women is

presented in Table 1. Mean age was 63.2 ± 6.8 (range 52–80) and 65.1 ± 8.0 (range 54–81) years for POP-Q 0 and POP-Q I–IV, respectively ($p = \text{nonsignificant}$). The two groups were homogeneous for age, BMI, gravidity, parity, smoking status, and previous MHT (Table 1).

Women with POP were grouped according to their POP-Q stage: stage I ($n = 8$), stage II ($n = 27$), stage III ($n = 58$), and stage IV ($n = 29$). Given the small number of women with stage I, for statistical analysis, stages I and II were pooled in one group ($n = 35$). A summary of demographic and clinical characteristics of these patients is presented in Table 2.

Groups were homogeneous for the assessed variables; BMI was homogeneous among groups and in those in the overweight range for all four groups analyzed (Table 2). TG levels, fasting glucose, and HOMA index were significantly higher in women with POP compared with POP-Q 0 ($p = 0.04$, $p = 0.0005$, and $p = 0.04$, respectively); HDL-C was significantly reduced in POP-Q I–V compared with POP-Q 0 ($p = 0.0003$) (Table 3). The association of elevated BP and hyperglycemia was more frequent in the group of women with POP (3.9% in POP-Q 0 vs. 14.1% in POP-Q I–IV, $p = 0.03$).

Metabolic characteristics were analyzed according to each POP stage. TG levels ($p = 0.0315$) were significantly higher in POP-Q III and IV vs. POP-Q 0; fasting glycemia and HOMA-IR ($p = 0.0015$ and $p = 0.0204$, respectively) were significantly higher in POP-Q IV vs. POP-Q 0; HDL-C ($p = 0.0047$) was significantly lower in all stage groups vs. POP-Q 0 (Table 4).

The distribution of MS and its components in the different POP-Q stages is shown in Table 5. The prevalence of MS, hypertriglyceridemia, and hyperglycemia were significantly different between groups ($p = 0.04$, $p = 0.0114$, and $p = 0.0149$, respectively). MS was higher in POP-Q IV than other

groups, while hypertriglyceridemia was higher in POP-Q III and IV groups vs. POP-Q 0. Hyperglycemia was more frequent in POP-Q IV vs. POP-Q 0. Rate of elevated waist circumference, reduced HDL-C, and elevated BP did not differ between the four groups. The association of elevated BP and hyperglycemia was different among groups: 3.9, 14.3, 10.4, and 24.1%, respectively ($p = 0.03$).

The association between MS risk factors and POP-Q stage \geq III was calculated. Elevated TG (OR 4.6, 95% CI 1.5–9.3, $P = 0.004$) and reduced HDL-C (OR 2.0, 95% CI 1.1–3.7, $P = 0.0241$) significantly increased the risk of POP-Q stage \geq III. Otherwise, MS presented an OR of 1.9 (95% CI 1.0–3.4) but was not statistically significant ($p = 0.0541$).

Discussion

In this study, we evaluated the prevalence of MS and its components in postmenopausal women with and without POP. We also analyzed the association between metabolic risk factors and POP severity as assessed through the POP-Q system. We found that TG levels, fasting glucose, and HOMA index were significantly higher and HDL-C lower in women with POP compared with the control group. In particular, TG levels were significantly higher in POP-Q III and IV vs. POP-Q 0; fasting glycemia and HOMA-IR were higher in POP-Q IV vs. POP-Q 0; and HDL-C showed lower levels in all stage groups vs. POP-Q 0. The prevalence of MS was significantly different between POP stages and higher in POP-Q IV than in other groups. The prevalence of elevated levels of glucose and TG increased with higher POP severity; in particular, hypertriglyceridemia was higher in POP-Q III and IV vs. POP-Q 0, while hyperglycemia was more frequent in POP-Q IV vs. POP-Q 0. Elevated TG and reduced HDL-C were significantly associated with a risk of POP-Q stage \geq III.

These data are in agreement with and expand the limited data available in the literature. To the best of our knowledge, this is the first study to assess metabolic risk factors in women with POP versus a control group using a validated staging system (POP-Q system). Rogowski et al., in a smaller cohort of patients and with no control group, found that the diagnosis of MS and hypertriglyceridemia were associated with POP severity assessed through the POP-Q system [13]. The author did not report any other associations with other components of MS, but the smaller number of enrolled participants may have limited detection of further associations.

Our results are also similar to those reported by Kim et al. [12], who found that diagnosis of MS was associated with severity of POP symptoms assessed via a questionnaire [Pelvic Organ Prolapse Distress Inventory 6 (POPDI-6)] without gynecological examination.

The global prevalence of MS in our cohort (28.6%) was consistent with that reported in postmenopausal Italian

Table 1 Demographic and clinical characteristics of women with and without pelvic organ prolapse (POP)

	POP-Q 0 ($n = 77$)	POP-Q I–IV ($n = 122$)	<i>P</i> value
Age (years)	63.2 ± 6.8	65.1 ± 8.0	ns
BMI (kg/m^2)	25.9 ± 5.5	26.4 ± 4.4	ns
Gravidity	1.9 ± 0.7	2.0 ± 0.8	ns
Parity	1.7 ± 0.5	1.7 ± 0.9	ns
Age at menopause (years)	50.6 ± 3.3	50.9 ± 3.1	ns
Previous MHT <i>n</i> (%)	27/77 (35.1)	31/122 (25.4)	ns
Current smoker (%)	13/77 (16.8)	11/122 (9.0)	ns
Stipsis <i>n</i> (%)	14/77 (18.2)	28/122 (22.9)	ns
SUI <i>n</i> (%)	17/77 (22.1)	36/122 (29.5)	ns
OAB <i>n</i> (%)	20/77 (25.9)	37/122 (30.2)	ns

Values are expressed as mean \pm standard deviation unless otherwise noted

POP-Q Pelvic Organ Prolapse Quantification system, BMI body mass index, MHT menopausal hormone therapy, SUI stress urinary incontinence, OAB overactive bladder Syndrome

Table 2 Demographic and clinical characteristics of women according to Pelvic Organ Prolapse Quantification system (POP-Q) stage

	POP-Q 0 (n = 77)	POP-Q I–II (n = 35)	POP-Q III (n = 58)	POP-Q IV (n = 29)	P value
Age (years)	63.2 ± 6.8	64.3 ± 8.3	65.8 ± 8.2	64.4 ± 7.5	ns
BMI (kg/m ²)	25.9 ± 5.5	26.0 ± 6.0	25.8 ± 3.2	27.4 ± 4.6	ns
Gravidity	1.9 ± 0.7	1.8 ± 0.9	2.0 ± 0.8	2.1 ± 0.6	ns
Parity	1.7 ± 0.5	1.6 ± 0.7	1.8 ± 0.8	1.9 ± 0.5	ns
Age at menopause (years)	50.6 ± 3.3	51.0 ± 3.5	50.1 ± 4.0	51.2 ± 4.6	ns
Previous MHT n (%)	27/77 (35.1)	9/35 (25.7)	15/58 (25.9)	7/29 (24.1)	ns
Current smoker (%)	13/77 (16.8)	4/35 (11.4)	5/58 (8.6)	2/29 (6.9)	ns
Stipsis n (%)	14/77 (18.2)	5/35 (14.3)	15/58 (25.9)	8/29 (27.9)	ns
SUI n (%)	17/77 (22.1)	10/35 (28.6)	19/58 (32.7)	7/29 (24.1)	ns
OAB n (%)	20/77 (25.9)	9/35 (25.7)	18/58 (31.0)	10/29 (34.5)	ns

Values are expressed as mean ± standard deviation unless otherwise noted

BMI body mass index, MHT menopausal hormone therapy, SUI stress urinary incontinence, OAB overactive bladder syndrome, ns not significant

women (34%) [14], thus reinforcing the strength of our data. In our cohort, prevalence of MS was significantly higher in POP-Q IV than in other groups. It can be noted that the POP-Q I–II group had an MS prevalence lower than expected and than that of POP-Q 0. We believe this could have been influenced by the small size of the POP-Q I–II group.

BMI was similar between groups and in the overweight range for all POP stages. This result is significant, as it reduces the potentially confounding impact of body weight on POP severity. Neither BMI nor waist circumference were associated with POP severity, suggesting that increased BMI and obesity are risk factors for POP occurrence but not necessarily of POP severity. These results are similar to other studies [20, 21], while recently Young et al. reported a positive association between BMI and posterior-compartment prolapse on clinical

examination and ultrasound imaging [22]. Studies with larger cohorts are needed to further evaluate the exact nature of the association of BMI and POP.

For decades, researchers have justified the increased risk of POP in obese women with the increase in abdominal pressure and consequent increased stress on the pelvic floor. Meanwhile, the vascular and metabolic complications of obesity received little importance in the study of POP etiology. Even if obese patients can be divided in metabolically unhealthy and metabolically healthy (in the absence of metabolic disturbances) with different risks of cardiovascular diseases and diabetes, it seems that both types of obesity present some similarities in terms of pro-inflammatory and nitro-oxidative stress profile [23]. MS may increase the risk and severity of POP through different mechanisms. It is well known that patients with MS may present microvascular alterations as a consequence of endothelial dysfunction and atherosclerosis [24, 25]. Furthermore, MS and an obesity-inducing diets are associated with chronic inflammation that can result in unregulated tissue repair and in an imbalance toward negative modeling of muscular fibers, resulting in tissue damage [26]. In fact, it should also be considered that many common metabolic and inflammatory pathways have been implicated in the pathogenesis of damaged musculoskeletal tissues (e.g., tendinopathy, osteoporosis, and osteoarthritis) [26].

Similar to the report by Rogowski et al., in our cohort, the presence of hypertriglyceridemia was associated with POP and POP severity and, in the paper by Kim et al., with the severity of POP symptoms [12, 13]. These results suggest that triglycerides may be specifically involved in POP pathology. Hypertriglyceridemia is a common form of dyslipidemia, often of genetic origin, and seems to be independently associated with cardiovascular risk and, in particular, risk of coronary heart disease [27]. The mechanism of TG involvement in POP genesis is still unclear, and little clinical data are available in

Table 3 Metabolic characteristics of study women

	POP-Q 0 (n = 77)	POP-Q I–IV (n = 122)	P value
Waist (cm)	87.1 ± 12.3	93.3 ± 11.9	ns
WHR	0.8 ± 0.1	0.9 ± 0.1	ns
TG (mg/dl)	89.2 ± 35.8	110.5 ± 50.5	0.0414
TC (mg/dl)	220.2 ± 34.5	217.8 ± 43.7	ns
HDL-C (mg/dl)	69.4 ± 15.9	60.7 ± 13.2	0.0003
Fasting glycemia (mg/dl)	87.7 ± 11.0	96.9 ± 18.1	0.0005
HOMA-IR	1.5 ± 0.9	2.3 ± 1.4	0.0392
SBP (mmHg)	131.7 ± 15.8	127.7 ± 16.8	ns
DBP (mmHg)	72.6 ± 9.3	75.6 ± 9.0	ns

Values are expressed as mean ± standard deviation

POP-Q Pelvic Organ Quantification System, WHR waist–hip ratio, HDL high-density lipoprotein-cholesterol, TG triglycerides, TC total cholesterol, HOMA-IR homeostasis model assessment for fasting insulin resistance, SBP systolic blood pressure, DBP diastolic blood pressure, ns not significant

Table 4 Metabolic characteristics of women according to Pelvic Organ Quantification system (POP-Q) stage

	POP-Q 0 (n = 77)	POP-Q I–II (n = 35)	POP-Q III (n = 58)	POP-Q IV (n = 29)	P value
Waist (cm)	87.1 ± 12.3	91.3 ± 14.1	95.1 ± 10.1	93.8 ± 11.6	ns
WHR	0.8 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.01	ns
TG (mg/dl)	89.2 ± 35.8	97.9 ± 40.5	108.9 ± 42.1 ^a	127.0 ± 45.2 ^a	0.0315
TC (mg/dl)	220.2 ± 34.5	210.4 ± 26.5	218.9 ± 47.9	224.4 ± 52.1	ns
HDL-C (mg/dl)	69.4 ± 15.9	60.8 ± 10.6 ^a	60.5 ± 14.3 ^a	61.0 ± 14.3 ^a	0.0047
Fasting glycemia (mg/dl)	87.7 ± 11.0	94.4 ± 12.3	93.9 ± 15.2	104.9 ± 24.9 ^a	0.0015
HOMA-IR	1.5 ± 0.9	2.1 ± 1.4	2.1 ± 1.3	3.1 ± 1.6 ^a	0.0204
SBP (mmHg)	131.7 ± 15.8	132.0 ± 16.4	126.4 ± 16.1	129.8 ± 18.3	ns
DBP (mmHg)	72.6 ± 9.3	75.0 ± 10.1	74.5 ± 8.7	79.0 ± 8.5	ns

Values are expressed as mean ± standard deviation

POP-Q Pelvic Organ Prolapse Quantification System, WHR waist–hip ratio, HDL high-density lipoprotein-cholesterol, TG triglycerides, TC total cholesterol, HOMA-IR homeostasis model assessment for fasting insulin resistance, SBP systolic blood pressure, DBP diastolic blood pressure, ns not significant

^a $p < .05$ vs. POP-Q 0 (posthoc comparison)

the literature. Recently, peroxisome proliferator-activated receptor (PPAR γ -2) and beta-3-adrenergic receptor (ADRB3) polymorphisms have been associated with the co-presence of elevated TG and connective tissue diseases [28]. Further, preclinical and clinical studies are needed to better explain the involvement of TG in POP pathogenesis.

In our cohort, the presence of an impaired glucose profile was associated with the presence and severity of POP. Hypertension did not present a similar association when analyzed alone, while the association of elevated glucose and hypertension was associated with POP and its severity. Similarly, Isik et al. analyzed a cohort of 186 patients with POP and 400 without and reported that the association of hypertension and type 2 DM may be considered risk factors for POP [29]. Apparently in contrast with our results, Isik et al. reported that hypertension only and diabetes only did not increase the risk of POP [29]. The dissimilarities in results seem to be due to the different FG cutoff: 126 mg/dl in Isik's study

(for the diagnosis of diabetes) and 100 mg/dl in ours (according to the NCEP-ATP III criteria for the diagnosis of MS).

Diabetes could contribute to POP occurrence and evolution through a vascular damage mechanism. Anyway, the exact pathway from diabetes to POP is still unknown and histological studies are needed to fill this gap. To the best of our knowledge, there are no data regarding histologic characteristic of pelvic floor structures in women with POP with or without metabolic impairment, but it has been demonstrated in vaginal samples from women with diabetes that there is an increased density of morphologically disrupted microvessels in the lamina propria [30], leading to an unfavorable remodeling of structures.

Some limitations of this study should be acknowledged. Participants in both groups were recruited in hospital clinics and may not necessarily represent the general population. The study was cross-sectional and was not able to recognize a cause–effect relationship between metabolic risk factors and

Table 5 Metabolic syndrome (MS) and its components in enrolled women according to Pelvic Organ Prolapse Quantification system (POP-Q) stages

	POP-Q 0 (n = 77)	POP-Q I–II (n = 35)	POP-Q III (n = 58)	POP-Q IV (n = 29)	P value
Elevated waist circumference	25/77 (32.5)	13/35 (35.1)	21/58 (36.2)	13/29 (44.8)	ns
Elevated TG	4/77 (5.2)	3/35 (8.6)	9/58 (15.5) ^a	8/29 (27.6) ^a	0.0114
Reduced HDL-C	15/77 (19.5)	11/35 (31.4) ^a	21/58 (36.2) ^a	11/29 (37.9) ^a	ns (0.053)
Elevated fasting glycemia	12/77 (15.6)	8/35 (22.9)	12/58 (20.7)	13/29 (44.8) ^a	0.0149
Elevated blood pressure	50/77 (64.9)	24/35 (68.6)	36/58 (62.1)	17/29 (58.6)	ns
MS	20/77 (25.9) ^b	6/35 (17.1) ^b	17/58 (29.3) ^b	14/29 (48.3)	0.04

Values are expressed as n (%)

HDL high-density lipoprotein-cholesterol, TG triglycerides, ns not significant

^a $p < .05$ vs. POP-Q 0

^b $p < .05$ vs. POP-Q IV (post hoc comparison)

the occurrence and progression of POP severity. Larger multicenter studies are required to obtain stronger results and evaluate whether the correction of metabolic impairment through lifestyle modification or specific therapies could modify POP progression.

In conclusion, our cross-sectional study suggests that metabolic risk factors are more common in women with POP compared with a control group. Our data confirms and expands previous limited data suggesting that MS and its components may be associated with increased POP severity. Our results confirm that physicians should pay more attention to pelvic floor dysfunction in women with MS. Given the enormous impact of POP on women's health, future research should longitudinally evaluate the impact of metabolic risk factors and their therapies on the evolution of pelvic floor dysfunctions.

Acknowledgements The authors thank Julie Norbury for English copy editing.

Compliance with ethical standards

Conflicts of interest None.

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