Obesity and pelvic organ prolapse: a systematic review and meta-analysis of observational studies

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Condensation: Greater body mass index categories are positively associated with pelvic organ prolapse. The strength of association is largest for objectively-measured prolapse that is relatively advanced.

Short title: Obesity and POP: meta-analysis

Abstract

Background: Studies evaluating the association between obesity and pelvic organ prolapse (POP) report estimates that range from negative to positive associations. Heterogeneous definitions for POP and variable choices for categorizing obesity measures have made it challenging to conduct meta-analysis.

Objective: We systematically evaluated evidence to provide quantitative summaries of association between degrees of obesity and POP, and identify sources of heterogeneity.

Evidence acquisition and method of synthesis: We searched for all indexed publications relevant to POP up until June 18, 2015 in PubMed/Medline to identify analytical observational studies published in English that reported risk ratios (relative risk, odds ratio or hazard ratio) for body mass index (BMI) categories in relation to POP. Random-effects meta-analyses were conducted to report associations with POP for overweight and obese BMI categories compared with women in the normal-weight category (referent: BMI <25 kg/m^2).

Results: Of the seventy studies that reported evidence on obesity and POP, 22 eligible studies provided effect estimates for meta-analysis of the overweight and obese BMI categories. Compared with the referent category, women in the overweight and obese categories had meta-analysis risk ratios of at least 1.36 (95% confidence interval [CI]: 1.20, 1.53) and at least 1.47 (95% CI: 1.35, 1.59), respectively. Subgroup analyses showed effect estimates for objectively-measured clinically-significant POP were higher than for self-reported POP. Other potential sources of heterogeneity included proportion of post-menopausal women in study and reported study design.

Conclusions: Overweight and obese women are more likely to have POP compared with women with BMI in the normal range. The finding that the associations for obesity measures were strongest for objectively-measured, clinically-significant POP further strengthens this evidence. However, prospective investigations evaluating obesity and POP are few.

Key words: meta-analysis, obesity, body mass index, pelvic organ prolapse, modifiable risk factor

Introduction

In pelvic organ prolapse (POP), one or more of the intra-pelvic organs including the uterus, bladder, rectum and the urethra descend into the vaginal space, presumably due to deficiencies in the pelvic support system which normally provides sustained support [1;2]. POP is a highly prevalent condition in women with prevalence rates ranging from 10% in younger women up to 50% in post-menopausal women [3-6]. Nearly one in ten women will undergo surgical correction for POP in their lifetime [7].

Aging and parity have been most consistently associated with POP [8-17]; however, these factors are not modifiable. Obesity is a modifiable risk factor which may be influenced on a population level to reduce the public health and economic burden of POP. However, studies evaluating the relationship between obesity and POP have reported inconsistent conclusions. Effect estimates for POP in obese women (body mass index [BMI] $\geq$30 kg/m^2) range from negative to a 2.5 fold increase in risk, when compared with women of normal weight [3;4;6;8-12;14;15;17-29]. A meta-analysis of measures of obesity and its relationship to POP may not only bring the scientific community closer to a consensus on this association, but also may also help identify reasons for heterogeneous findings in the literature.

Therefore, the goals of this review are twofold. First, we aim to provide overall effect estimates for POP with regard to degree of obesity, as measured by categories of body mass index. We also aimed to evaluate study-level characteristics which may in part help to explain heterogeneous effect estimates reported by studies examining obesity and POP.

Methods

Search Strategy and Manuscript Review

To conduct this review, the PubMed/MEDLINE database was systematically queried using appropriate search terms relating to POP (Supplement Display 1) to identify titles and abstracts of studies indexed since inception of MEDLINE (1971) until the date of search (June 18, 2015). A search-start date was not specified to allow inclusion of reliably indexed articles as early as 1946 by MEDLINE by default. Earliest published article qualifying from the specified search term (Supplement Display 1) dated back to Jan 24, 1975. Title listings were scrutinized by two reviewers to eliminate studies that were clearly not related to the topic of interest. Abstracts of remaining articles were then reviewed by two reviewers to identify original research published in English that evaluated the association between risk-factors for POP. Articles describing or comparing surgical procedures for POP were excluded. At the abstract level, if it was unclear whether a given study evaluated risk factors for POP, then the study was retained for full text review in addition to abstracts that clearly indicated evaluating risk factors for POP. A full-text review of these articles was then conducted to retain articles that evaluated the relationship between BMI and POP for a qualitative summary of the literature and for further eligibility for meta-analysis.

Eligibility criteria for meta-analysis

Population: Studies that reported effect estimates on the relationship between BMI and POP in women of any age were eligible to be included in the meta-analysis. Studies involving women with or without hysterectomy were included. Women with previous hysterectomy are still at risk of developing other forms of prolapse including vaginal vault prolapse, and anterior and posterior vaginal wall prolapse. Studies specifically evaluating prolapse recurrence following surgery for urinary incontinence or POP were not eligible for analysis. The eligibility

criteria for this meta-analysis were kept permissive to extend generalizability of findings to a broad population of women.

Study design: Analytic observational studies of all types including cross-sectional, case-control and cohort designs with at least 40 cases of POP were eligible to be included into the meta-analysis. A minimum of 40 cases was chosen as criteria to only include estimates from studies which provide relatively reliable estimates of the association between categorical BMI and POP. Additionally, studies needed to report a risk ratio (odds ratio (OR), relative risk (RR) or hazard ratio) or must have provided sufficient information to allow calculation of a relevant effect estimate. For the primary analysis, all of these three risk ratios were aggregated together to present a meta-analysis risk ratio, regardless of study design. Case-control studies which specifically matched on BMI status were not considered eligible for analysis.

Outcomes: The primary outcome for this meta-analysis is POP as a dichotomous variable (yes, no). All forms of prolapse reported as POP, uterine prolapse, genital prolapse, enterocele, cystocele/anterior wall prolapse, or rectocele/posterior wall prolapse are counted as an outcome. For our primary aim, we include self-reported symptomatic prolapse, prolapse indicated by ICD codes, surgical procedure codes, as well as prolapse measured through pelvic exams by trained professionals for all severities of prolapse. For ease of data aggregation, reports of Baden-Walker Halfway grading system of grade 2 or more or Pelvic Organ Prolapse Quantification (POP-Q) system Stage II or more were considered comparable.

Assessment of BMI: Studies that presented risk ratios by categories of BMI were considered eligible for meta-analysis. Ideally, studies must have reported risk ratios for the BMI categorized similar to the World Health Organization (WHO) guidelines: BMI <25 kg/m^2 (reference group), BMI 25-30 kg/m^2 (overweight), and BMI ≥30 kg/m^2 (obese). In the event

studies reported risk ratios for categories of BMI that were not conventional, effect estimates were grouped with the nearest conventional BMI category. For example, if studies presented a risk ratio for BMI <25 kg/m^2 (ref) versus BMI ≥25 kg/m^2, then these studies were put into the overweight category. In another example, Parazzini and colleagues used the following BMI categories to report odds ratios: <23.8 (reference), 23.8-27.2 and >27.2 kg/m2, which the meta-analyst grouped as normal-weight, overweight and obese, respectively, with <23.8 kg/m2 still serving as the referent category. Despite these inconsistent, yet, overlapping categories, analysis categories are referred to as normal-weight, overweight and obese for exposition. Studies which combined overweight and/or obese individuals into their lowest category (reference category) were not considered comparable and are therefore only described qualitatively. Studies that only provided mean or median BMI measures by case-control status or only calculated risk ratios using BMI as a continuous measure were not considered eligible for meta-analysis with categorical representation of BMI.

Data duplication: In the event two or more studies used the same or overlapping study populations, the larger of the studies was chosen for the meta-analysis.

Data abstraction: For eligible studies, the following fields were abstracted from each article: study title, first author, year of publication, study design (cross-sectional, case-control, cohort), mean age (SD)/range or median (interquartile range) if provided, percent of post-menopausal women represented in the study if provided (or could be estimated if the study provided adequate information for estimation), racial/ethnic composition of study if provided (or could be estimated based on country of study), method of POP assessment (symptomatic prolapse through self-report, or objectively measured prolapse), categories of BMI utilized by authors, risk ratios provided (OR, RR, or HR) by each category of BMI, raw numbers for risk

ratio calculation by categories of BMI and POP status if adjusted risk ratios or unadjusted risk ratios were not provided, information on whether study adjusted for key covariates (yes, no), and the list of covariates which were adjusted for in regression models. When a given study provided two or more risk ratios for varying definitions of POP for the same population (symptomatic POP, objective POP with any grade of POP, or objective POP with clinically-significant POP), then both reported risk ratios were abstracted as separate entries and marked as duplicate to avoid aggregating correlated data in a given meta-analysis set.

Statistical Analysis

For primary analyses, all studies with non-overlapping study populations reporting risk ratios were meta-analyzed together using inverse-variance weighted random effects models. Meta-analysis summary effect estimates and corresponding 95% confidence intervals for POP are presented for two main analyses: 1) effect estimates and 95% CIs for overweight women, and 2) effect estimates and 95% CIs for obese women; both were compared to women with BMI <25 kg/m^2. To accommodate effect estimates from studies that provided two or more effect estimates (various methods of POP measurement), we performed two sets of analyses (for both the overweight and obese categories): one utilizing the smallest of the two or more effect estimates (referred from here on as minimum scenario) and another utilizing the largest of the two or more effect estimates (referred from here on as maximum scenario). Since all but one study included in the meta-analysis reported odds ratios, or were calculated by meta-analyst when raw numbers were presented, meta-analysis risk ratios may be interpreted as odds ratios. Evidence for publication bias was evaluated by visual inspection of funnel plots, then formally using the Egger's test.

In addition to obtaining overall effect estimates for the relationship between obesity measures and POP, we also evaluated potential sources of heterogeneity across studies. Heterogeneity across studies was formally assessed using the I-squared statistic [30]. Study-level characteristics which were of interest in evaluating sources of heterogeneity included: method of POP assessment (self-reported symptomatic POP, objective POP of any grade, objective POP of severe/moderate grade [defined as Baden-Walker grade ≥2, POP-Q Stage >II, POP at or below the hymen, or POP which warranted surgical correction]), whether the study provided effect estimates adjusted for key covariates (yes, no), percent of post-menopausal women in study (<50%, ≥50%), whether study presented effect estimates by WHO categories of BMI (yes, no), and study design (case-control, cross-sectional, or cohort). These categories were then utilized to perform sub-group analyses by strata of defined study attribute to present sub-group-specific meta-analysis effect estimates, and 95% confidence intervals. This systematic review and meta-analysis was conducted following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria.

Results

We identified 70 original-research articles of which 22 studies with non-overlapping study populations reported risk ratios between categories of BMI and POP or provided numbers which allowed for calculation of a risk ratio. A flow diagram of the selection process and reasons for ineligibility for primary meta-analysis are presented in Figure 1. Of the 22 studies which were considered eligible for meta-analysis, 21 studies provided 22 effect estimates from non-overlapping populations which could be utilized in the overweight vs. normal-weight meta-analysis set, and 12 studies provided 13 effect estimates from non-overlapping populations

which could be utilized in the obese vs. normal-weight meta-analysis set. Of the 22 studies, nine studies were based within a cohort [3;8;10-12;15;17;20;21], nine studies were cross-sectional [6;19;25-27;29;31-33] and 4 studies were case-control [18;28;34;35] (Table 1). However, only one study provided a relative risk [12] based on Poisson regression; all other studies either provided odds ratios from logistic regression or odds ratios were calculated based on raw numbers. A total of 10 out of the 22 studies presented risk ratios based on the WHO BMI categorization criteria. Of the 22 studies, 11 studies reported positive associations with confidence intervals not including unity either for the overweight and/or the obese meta-analysis set. Seven out of the 22 studies did not provide adjusted risk ratios. All other studies appropriately adjusted for at least age and parity as confounding variables, with the exception of studies which evaluated only primi-parous women, where authors adjusted for mode of delivery or presented effect estimates for BMI and POP by strata of mode of delivery. Four studies presented one or more risk ratios for varying methods of POP assessment. The 22 studies included in the meta-analysis contributed more than 96,875 participants and 17,249 POP cases (regardless of measurement method), of which 3,043 cases were considered clinically-significant POP, and 2,359 cases were considered self-reported/symptomatic POP based on self-reported questionnaire (Supplemental Table 1). The total number of participants and POP-cases included in the overweight and obese category could not be determined as not all studies provided stratum specific numbers.

Meta-analysis results

Compared with women in the normal-weight (referent) category, meta-analysis risk ratio for women in the overweight category ranged from 1.36 (95% CI: 1.20, 1.53) for the minimum analysis set, to 1.40 (95% CI: 1.25, 1.58) in the maximum analysis set (Table 2 and Figure 2).

Similarly, compared with women in the referent category, meta-analysis risk ratios for women in the obese category ranged from 1.47 (95% CI: 1.35, 1.59) for the minimum analysis set, to 1.61 (95% CI: 1.45, 1.78) in the maximum analysis set (Table 2 and Figure 3). There was some evidence of heterogeneity for effect estimates in the overweight analyses scenario (I^2 = 50% for minimum set; I^2 = 49% for maximum set) but very little heterogeneity in the obese categories of analyses. Visual examination of the funnel plots (Supplemental Figures 1 and 2) and formal evaluation with the Egger's test showed very little evidence of small-study bias in either the overweight or the obese analysis sets.

We performed several sensitivity analyses by strata of study attribute to identify sources of heterogeneity. Meta-analysis effect estimates from minimum and maximum scenarios for sub-group analyses were comparable in trends, hence only the minimum analysis set results are reported here for brevity. Effect estimates summarizing clinically-significant, objectively measured POP were considerably larger than effect estimates summarizing any grade/stage of objectively measured POP or symptomatic/self-reported POP for both the overweight (Table 3) and obese analysis categories (Table 4). Compared with women in the referent category, women in the overweight category had a meta-analysis risk ratio of 1.34 (95% CI: 1.21, 1.48) if any grade of objectively measured POP was assessed, 1.23 (95% CI: 0.97, 1.55) if self-reported symptomatic POP was assessed and 1.54 (95% CI: 1.29, 1.83) if objectively measured clinically-significant POP was assessed (Table 3). Compared with women in the referent category, women in the obese category had a meta-analysis risk ratio of 1.45 (95% CI: 1.31, 1.60) if any grade of objectively measured POP was assessed, 1.44 (95% CI: 1.18, 1.76) if self-reported symptomatic POP was assessed and 1.71 (95% CI: 1.42, 2.06) if objectively measured clinically-significant

POP was assessed (Table 4). Heterogeneity estimates were low for the objectively measured POP, and highest for symptomatic/self-reported POP in the overweight and obese analyses.

Studies presenting adjusted analyses reported higher effect estimates than studies that presented unadjusted estimates; this was true for both BMI categories. Meta-analysis risk ratios for unadjusted group and adjusted group were 1.05 (95% CI: 0.76, 1.47) and 1.51 (95% CI: 1.36, 1.68), respectively, in the obese category. Studies with patient composition of <50% post-menopausal women tended to report larger effect estimates on average than studies with ≥50% post-menopausal women; difference in effects were more pronounced in analyses evaluating overweight women (Table 3) than obese women (Table 4). Case-control and cross-sectional studies were more likely to report higher effect estimates than studies that were identified as originating from a cohort design. Of the 22 eligible studies, only one study presented a relative risk. Excluding this effect estimate from the meta-analysis sets to only include odds ratios did not change the meta-analysis effect estimates considerably.

Comment

We performed a systematic review of the medical literature published in English to evaluate analytic observational studies that reported the association between obesity measures and POP. Since BMI was the most widely reported obesity trait, we performed the first meta-analysis evaluating the association between categories of BMI in relation to POP. We show that among studies that evaluated a relative measure of risk/odds, women in the overweight and obese categories were more likely to have POP than women in the normal-weight category.

In a recent systematic review of the risk factors for POP and recurrence, Vergeldt and colleagues performed a qualitative review of articles evaluating the association between measures of obesity and POP, among other risk factors [16]. The authors used stringent criteria

to only include studies that reported clinically-significant, objectively measured POP in cross-sectional and cohort studies. They concluded that of the various suspected risk factors for POP, obesity was the only practically modifiable risk factor since genetic predisposition, aging and child birth can hardly be considered modifiable. However, the authors did not perform a meta-analysis of the studies, likely due to the small pool of studies.

In this systematic review, we placed no restriction on the age ranges of women which were evaluated in the study, or on the measurement criteria that studies utilized for assessing POP and additionally allowed studies with sample sizes as small as 40 POP cases to be included in the meta-analysis. This strategy was adopted *a priori* for the following reasons: 1) larger sample size provides higher statistical power for detecting associations, 2) an inclusive strategy allows for greater generalization of the study results, 3) including small and large studies allows for a more meaningful assessment of potential publication bias, and 4) larger number of studies allows for sub-group analyses to evaluate potential sources of heterogeneity by strata of study attribute. There was a considerable amount of heterogeneity in primary effect-estimates (I^2 as high as 50%) attributed to factors other than random error in the overweight analysis category, but not in the obese analysis category. This is likely because the normal-weight (referent) and obese categories were far enough apart for studies to more consistently report larger effect estimates.

To identify potential sources of heterogeneity, especially for the primary overweight category meta-analysis, we conducted several sub-group meta-analyses. Some of the heterogeneity can most likely be attributed to the aggregation of the various methods of POP measurement. Sub-group analyses clearly showed that on average effect estimates from studies reporting clinically-significant, objectively measured POP were higher than effect estimates from

studies that reported symptomatic POP or any grade of objectively measured POP. We also found that studies which had higher proportions of post-menopausal women on average reported smaller effect estimates than studies with a lower proportion of post-menopausal women, suggesting another source of heterogeneity.

Studies that adjusted for key covariates tended to report on average stronger effect estimates than studies that did not adjust for key covariates. This was most apparent in the obese-category analyses; however, within-subgroup sample sizes were small. More so than identifying another potential source of heterogeneity, this difference illuminates on the nature of scientific reporting where studies that had effect estimates with p-values less than 0.05 were more likely to present analyses adjusted for key covariates than studies that did not. The potential for publication bias, although not evident as small-study bias in the meta-analysis sets we assessed, is suggested by the reality that a majority of the analytic studies which were not eligible in our meta-analysis were case-control studies. These studies either reported only mean/median BMI by case-control status [14;36-42] or only reported effect estimate for BMI as a continuous variable [9;22;43-47]. Six out of the seven studies which used BMI as a continuous measure were case-control studies. Similarly, six out of the eight studies which only reported mean/median BMI were case-control studies. A majority of these studies had relatively small sample sizes.

In our sub-group analyses, although we present separate effect estimates for case-control, cross-sectional and cohort status, it should be mentioned that almost all of these studies performed cross-sectional analyses where assessment of BMI did not necessarily precede assessment of POP. Therefore, the results of the meta-analysis are limited in its conclusions and does not shed light on the relationship between BMI and incident POP development. Of the 22 studies included in the meta-analysis, only one study prospectively evaluated BMI and POP to

report a positive association between BMI and POP [12]. Kudish and colleagues additionally performed a time-to-event analysis [23] and a longitudinal investigation of POP progression in the Women's Health Initiative Hormone Therapy study; however these results were not included in the meta-analysis due to overlapping populations [48]. In the longitudinal study, they reported that the risk of rectocele, cystocele and uterine prolapse progression in overweight and obese women ranged from 32-69% (largest increase for uterine prolapse) compared with the referent category at baseline [48]. In their analysis they also reported that weight loss did not significantly reduce POP regression and suggested that damage to the pelvic floor associated with obesity may be irreversible. However, the generalizability of these results are likely limited to post-menopausal women, and it is not clear if weight-loss in younger, middle-aged women can reduce risk of developing POP or reverse descent. We note that there is a dearth of studies that prospectively evaluate the association between obesity measures and POP and the association between weight loss and POP progression. Our meta-analytic investigation of obesity measures and POP was limited to BMI as only two studies reported the association between waist-circumference and POP.

We note several other limitations of this meta-analysis, which are in part reflective of the available evidence in the literature. Over time as assessment methods for POP have evolved, for example from Baden-Walker halfway system to the POP-Q system, the definitions of POP across studies overtime are not fully consistent. Incorporating information regarding grades or stages of descent in defining POP adds yet another layer of complexity that introduces considerable heterogeneity between studies. Yet, despite such heterogeneity, we observe a positive association between higher categories of BMI and POP. The observation that statistical heterogeneity between studies decreases and that the strength of association increases as the definition of POP

is made relatively more stringent and as the difference between the comparator BMI groups get larger suggests that the association between obesity and POP that is clinically actionable is likely greater in magnitude than the associations reported in this meta-analysis. Another important limitation of this study is that the synthesis of evidence can only be generalized to POP as a composite outcome. However, at the same time, it is not clear if and how obesity affects prolapse differently at various anatomical positions in the pelvic region. Research on this topic is even more limited. Intriguingly, only one study, the WHI-HT specifically, reported effect estimates evaluating obesity in relation to cystocele, rectocele and uterine prolapse. The effect estimates for categories of obesity were very similar for all three types of POP that were evaluated. Additionally, the reality that women seeking help for POP often present with prolapse at more than one anatomical location in the pelvic area suggests similar effects of obesity on the various types of POP. Finally, for several studies included in the meta-analysis, the authors of the original study or the meta-analyst were compelled to combine overweight and obese categories into one category. However, when analyses were stratified by whether studies reported conventional or collapsed BMI categories, the conclusions of this study remain unchanged.

There were several other notable studies that were not eligible for meta-analysis. Based on the National Health and Nutrition Examination survey of 1,961 women across the US (with 58 POP cases), Nygaard and colleagues reported weighted prevalence rates for self-reported POP to be 1.7 (95% CI: 0.6, 2.9) in women with BMI <25 kg/m^2, 3.4 (95% CI: 1.2, 2.5) in women with BMI 25.0-29.9 kg/m^2, and 3.6 (95% CI: 2.0, 5.2) in women with BMI ≥30 kg/m^2 [4]. Three studies compared non-obese (BMI <30 kg/m^2) versus obese women (BMI ≥30 kg/m^2) and did not find any meaningful relationships between BMI and POP [49-51]. In a population-based, cross-sectional assessment of middle-aged women in Michigan, Trowbridge and colleagues

evaluated obese vs. non-obese women with POP-Q points as a continuous variable (while adjusting for age, race, parity, hysterectomy, estrogen use and stress urinary incontinence), and did not report any meaningful correlations [51]. It is possible that the authors may have over-adjusted their models, as we know from the literature that BMI is correlated with urinary incontinence, and adjusting for this variable may have over-corrected for the association between BMI and POP. Handa and colleagues [49] (N = 394, mean age = 47.6) and Washington and colleagues [52;53] (N = 1,011, median age = 39.5), did not find meaningful differences in the percent of women with clinically-significant POP in non-obese (BMI <30 kg/m^2) versus obese women (BMI ≥30 kg/m^2). One possible explanation for disagreement with our conclusions could be that the reference group in these studies included overweight women, who we show in this meta-analysis, have higher odds of POP than normal-weight women. Interestingly, Whitcomb and colleagues evaluated 1,155 (mean age = 56.4) obese women and reported that compared with obese women (BMI 30-34.9 kg/m^2), women who were severely obese (BMI 35-39.9 kg/m^2) and morbidly obese (BMI ≥40 kg/m^2) had odds ratios of 1.55 (95% CI: 0.92, 2.60) and 2.09 (95% CI: 1.18, 3.68) for POP, respectively, in analyses adjusted for age, mode of delivery and parity [53].

In conclusion, our analytic review of the literature suggests that obesity as measured by BMI is positively associated with POP. The association between BMI and POP increases in magnitude with increasing categories of BMI and is larger for clinically-significant POP. Obesity is one of the few modifiable risk factors for POP. Given the dearth of studies which prospectively evaluate the association between obesity measures and POP and our lack of understanding of the underlying mechanisms involved in obesity and POP, there is a need for prospective and mechanistic investigations. From a policy perspective, educating parous women about the association between obesity and POP, a common, yet less often talked about condition

with debilitating effects on quality of life, may not only help reduce future burden of POP but may also help reduce obesity and related co-morbidities in the population.

References

(1) Jelovsek JE, Maher C, Barber MD. Pelvic organ prolapse. The Lancet 2007;369(9566):1027-38.

(2) Weber AM, Richter HE. Pelvic organ prolapse. Obstetrics & Gynecology 2005;106(3):615-34.

(3) Hendrix SL, Clark A, Nygaard I, Aragaki A, Barnabei V, McTiernan A. Pelvic organ prolapse in the women's health initiative: Gravity and gravidity. American Journal of Obstetrics and Gynecology 2002 Jun;186(6):1160-6.

(4) Nygaard I. Prevalence of symptomatic pelvic floor disorders in us women. JAMA 2008 Sep 17;300(11):1311-6.

(5) Samuelsson EC, Arne Victor FT, Tibblin G, Svärdsudd KF. Signs of genital prolapse in a Swedish population of women 20 to 59 years of age and possible related factors. American Journal of Obstetrics and Gynecology 1999;180(2):299-305.

(6) Swift S, Woodman P, O'Boyle A, Kahn M, Valley M, Bland D, et al. Pelvic Organ Support Study (POSST): the distribution, clinical definition, and epidemiologic condition of pelvic organ support defects. American Journal of Obstetrics and Gynecology 2005;192(3):795-806.

(7) Smith FJ, Holman CD, Moorin RE, Tsokos N. Lifetime Risk of Undergoing Surgery for Pelvic Organ Prolapse. Obstetrics & Gynecology 2010;116(5).

(8) Dolan LM, Hilton P. Obstetric risk factors and pelvic floor dysfunction 20 years after first delivery. International Urogynecology Journal 2010;21(5):535-44.

(9) Erata YE, Kilic B, Güçlü S, Saygili U, Uslu T. Risk factors for pelvic surgery. Archives of gynecology and obstetrics 2002;267(1):14-8.

(10) Glazener C, Elders A, MacArthur C, Lancashire RJ, Herbison P, Hagen S, et al. Childbirth and prolapse: long–term associations with the symptoms and objective measurement of pelvic organ prolapse. BJOG: An International Journal of Obstetrics & Gynaecology 2013;120(2):161-8.

(11) Gyhagen M, Bullarbo M, Nielsen TF, Milsom I. Prevalence and risk factors for pelvic organ prolapse 20-years after childbirth: a national cohort study in singleton primiparae after vaginal or caesarean delivery. BJOG: An International Journal of Obstetrics & Gynaecology 2013 Jan 1;120(2):152-60.

(12) Mant J, Painter R, Vessey M. Epidemiology of genital prolapse: observations from the Oxford Family Planning Association Study. BJOG: An International Journal of Obstetrics & Gynaecology 1997;104(5):579-85.

(13) Nygaard I, Bradley C, Brandt D. Pelvic organ prolapse in older women: prevalence and risk factors. Obstetrics & Gynecology 2004;104(3):489-97.

(14) Quiroz LH, Muñoz A, Shippey SH, Gutman RE, Handa VL. Vaginal parity and pelvic organ prolapse. The Journal of reproductive medicine 2010;55(3-4):93.

(15) Rortveit G, Brown JS, Thom DH, Van Den Eeden SK, Creasman JM, Subak LL. Symptomatic Pelvic Organ Prolapse: Prevalence and Risk Factors in a Population-Based, Racially Diverse Cohort. Obstetrics & Gynecology 2007;109(6).

(16) Vergeldt TF, Weemhoff M, IntHout J, Kluivers KB. Risk factors for pelvic organ prolapse and its recurrence: a systematic review. International Urogynecology Journal 2015;1-15.

(17) Whitcomb EL, Rortveit G, Brown JS, Creasman JM, Thom DH, Van Den Eeden SK, et al. Racial Differences in Pelvic Organ Prolapse. Obstetrics & Gynecology 2009;114(6).

(18) Chiaffarino F, Chatenoud L, Dindelli M, Meschia M, Buonaguidi A, Amicarelli F, et al. Reproductive factors, family history, occupation and risk of urogenital prolapse. European Journal of Obstetrics & Gynecology and Reproductive Biology 1999;82(1):63-7.

(19) de Araujo MP, Takano CC, Girao MJBC. Pelvic floor disorders among indigenous women living in Xingu Indian Park, Brazil. International Urogynecology Journal 2009;20(9):1079-84.

(20) Forsman M, Iliadou A, Magnusson P, Falconer C, Altman D. Diabetes and obesity-related risks for pelvic reconstructive surgery in a cohort of Swedish twins. Diabetes care 2008;31(10):1997-9.

(21) Fritel X, Varnoux Nl, Zins M, Breart G+, Ringa V. Symptomatic pelvic organ prolapse at midlife, quality of life, and risk factors. Obstetrics and gynecology 2009;113(3):609.

(22) Ghetti C, Gregory WT, Clark AL. Risk factors for surgically managed pelvic organ prolapse and urinary incontinence. International Journal of Gynecology & Obstetrics 2007;98(1):63-4.

(23) Kudish BI, Iglesia CB, Gutman RE, Sokol AI, Rodgers AK, Gass M, et al. Risk factors for prolapse development in white, black, and Hispanic women. Female Pelvic Medicine & Reconstructive Surgery 2011;17(2):80-90.

(24) Martins KdF, de Jármy-DiBella ZI, da Fonseca AMRM, Castro RA, da Silva G, Cotrim ID, et al. Evaluation of demographic, clinical characteristics, and genetic polymorphism as risk factors for pelvic organ prolapse in Brazilian women. Neurourology and urodynamics 2011;30(7):1325-8.

(25) Miedel A, Tegerstedt G, Maehle-Schmidt M, Nyrén O, Hammarström M. Nonobstetric risk factors for symptomatic pelvic organ prolapse. Obstetrics & Gynecology 2009;113(5):1089-97.

(26) Progetto Menopausa Italia Study Group. Risk factors for genital prolapse in non-hysterectomized women around menopause. Results from a large cross-sectional study in menopausal clinics in Italy. Eur J Obstet Gynecol Reprod Biol 2000;93(2):135-40.

(27) Scherf C, Morison L, Fiander A, Ekpo G, Walraven G. Epidemiology of pelvic organ prolapse in rural Gambia, West Africa. BJOG: An International Journal of Obstetrics & Gynaecology 2002;109(4):431-6.

(28) Tegerstedt G, Miedel A, Maehle-Schmidt M, Nyrén O, Hammarström M. Obstetric risk factors for symptomatic prolapse: a population-based approach. American Journal of Obstetrics and Gynecology 2006;194(1):75-81.

(29) Uustal Fornell E, Wingren G, Kj+ÿlhede P. Factors associated with pelvic floor dysfunction with emphasis on urinary and fecal incontinence and genital prolapse: an epidemiological study. Acta obstetricia et gynecologica Scandinavica 2004;83(4):383-9.

(30) Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. 5 ed. Wiley Online Library; 2008.

(31) Awwad J, Sayegh R, Yeretzian J, Deeb ME. Prevalence, risk factors, and predictors of pelvic organ prolapse: a community-based study. Menopause 2012;19(11):1235-41.

(32) Diez-Itza I, Arrue M, Ibanez L, Paredes J, Murgiondo A, Sarasqueta C. Influence of mode of delivery on pelvic organ support 6 months postpartum. Gynecologic and Obstetric Investigation 2011;72(2):123-9.

(33) Seo JT, Kim JM. Pelvic organ support and prevalence by Pelvic Organ Prolapse-Quantification (POP-Q) in Korean women. The Journal of urology 2006;175(5):1769-72.

(34) Braekken IH, Majida M, Ellström Engh M, Holme IM, Bø K. Pelvic floor function is independently associated with pelvic organ prolapse. BJOG: An International Journal of Obstetrics & Gynaecology 2009;116(13):1706-14.

(35) CHEN HUEY, CHUNG YA, LIN WEI, CHEN WEN, TSAI FUU, TSAI CHAN. Progesterone receptor polymorphism is associated with pelvic organ prolapse risk. Acta obstetricia et gynecologica Scandinavica 2009;88(7):835-8.

(36) DeLancey JO, Morgan DM, Fenner DE, Kearney R, Guire K, Miller JM, et al. Comparison of levator ani muscle defects and function in women with and without pelvic organ prolapse. Obstetrics & Gynecology 2007;109(2, Part 1):295-302.

(37) Ferrari MM, Rossi G, Biondi ML, Viganò P, Dell'Utri C, Meschia M. Type I collagen and matrix metalloproteinase 1, 3 and 9 gene polymorphisms in the predisposition to pelvic organ prolapse. Archives of gynecology and obstetrics 2012;285(6):1581-6.

(38) Kim CM, Jeon MJ, Chung DJ, Kim SK, Kim JW, Bai SW. Risk factors for pelvic organ prolapse. International Journal of Gynecology & Obstetrics 2007;98(3):248-51.

(39) Skorupski P, Jankiewicz K, Miotla P, Marczak M, Kulik-Rechberger B, Rechberger T. The polymorphisms of the MMP-1 and the MMP-3 genes and the risk of pelvic organ prolapse. International Urogynecology Journal 2012;1-6.

(40) Swift SE, Pound T, Dias JK. Case–Control Study of Etiologic Factors in the Development of Severe Pelvic Organ Prolapse. Int Urogynecol J 2001;12(3):187-92.

(41) Lince SL, van Kempen LC, Dijkstra JR, IntHout J, Vierhout ME, Kluivers KB. Collagen type III alpha 1 polymorphism (rs1800255, COL3A1 2209 G> A) assessed with high-resolution melting analysis is not associated with pelvic organ prolapse in the Dutch population. International Urogynecology Journal 2014;25(9):1237-42.

(42) Kim JY, Kim EJ, Jeon MJ, Kim R, Lee MW, Kim SW. Association between susceptibility to advanced pelvic organ prolapse and glutathione S-transferase P1 Ile105Val polymorphism. European Journal of Obstetrics & Gynecology and Reproductive Biology 2014;175:205-8.

(43) Chen HY, Chung YW, Lin WY, Chen WC, Tsai FJ, Tsai CH. Estrogen receptor alpha polymorphism is associated with pelvic organ prolapse risk. International Urogynecology Journal 2008;19(8):1159-63.

(44) Rodrigues AM, Giaro MJBC, da Silva IDCG, Sartori MGF, de Falco Martins K, de Aquino Castro R. COL1A1 Sp1-binding site polymorphism as a risk factor for genital prolapse. International Urogynecology Journal 2008;19(11):1471-5.

(45) Slieker-ten Hove MCP, Pool-Goudzwaard AL, Eijkemans MJC, Steegers-Theunissen RPM, Burger CW, Vierhout ME. Symptomatic pelvic organ prolapse and possible risk factors in a general population. American Journal of Obstetrics and Gynecology 2009 Feb;200(2):184.

(46) Yeniel AÖ, Ergenoglu AM, Askar N, Itil IM, Meseri R. How do delivery mode and parity affect pelvic organ prolapse? Acta obstetricia et gynecologica Scandinavica 2013;92(7):847-51.

(47) Levin PJ, Visco AG, Shah SH, Fulton RG, Wu JM. Characterizing the phenotype of advanced pelvic organ prolapse. Female Pelvic Medicine & Reconstructive Surgery 2012;18(5):299.

(48) Kudish BI, Iglesia CB, Sokol RJ, Cochrane B, Richter HE, Larson J, et al. Effect of weight change on natural history of pelvic organ prolapse. Obstetrics and gynecology 2009;113(1):81.

(49) Handa VL, Blomquist JL, Knoepp LR, Hoskey KA, McDermott KC, Muñoz A. Pelvic floor disorders 5-10 years after vaginal or cesarean childbirth. Obstetrics and gynecology 2011;118(4):777.

(50) Shalom DF, Lin SN, St Louis S, Winkler HA. Effect of age, body mass index, and parity on Pelvic Organ Prolapse Quantification system measurements in women with symptomatic pelvic organ prolapse. Journal of Obstetrics and Gynaecology Research 2012.

(51) Trowbridge ER, Fultz NH, Patel DA, DeLancey JO, Fenner DE. Distribution of pelvic organ support measures in a population-based sample of middle-aged, community-dwelling African American and white women in southeastern Michigan. American Journal of Obstetrics and Gynecology 2008;198(5):548-e1.

(52) Washington BB, Erekson EA, Kassis NC, Myers DL. The association between obesity and stage II or greater prolapse. American Journal of Obstetrics and Gynecology 2010;202(5):503-e1.

(53) Whitcomb EL, Lukacz ES, Lawrence JM, Nager CW, Luber KM. Prevalence and degree of bother from pelvic floor disorders in obese women. International Urogynecology Journal 2009;20(3):289-94.

Table 1. Description of study characteristics of the 22 studies eligible for meta-analysis

Author (Publication Year) [Ref]	Study Design, sample size	Mean Age (yrs) (SD)/Age Category(%); %post-menopausal	Country of Study or %Race/Ethnicity	Obesity Measure	POP Measurement	Covariates adjusted for	Results RR/OR/HR (95% CI)	Comments
Mant et al. (1997) [12]	Population-based longitudinal study; 17,032	Age: >25; % post-menopausal not provided and could not be inferred	English and Scottish; 100% European	BMI: <20 (Ref); 20-21.9; 22-23.9; 24-25.9; 26-27.9; ≥28	ICD9 codes for POP; no degree staging information provided	Age, parity, and calendar period	RR Ref BMI: <20: 1.0; RR BMI > 28: 1.31 (0.9-1.81)	Used RR calculated from Poisson regression model as presented by authors to be used in the normal-weight vs. obese analysis
Chiaffarino et al. (1999) [18]	Hospital based case-control; 208	Cases: 58.5; 81% post-menopausal. Controls: 59.8; 88% post-menopausal	Italians; Possibly 100% European	BMI: ≤ 23 (Ref); 24-26; >26	Baden-Walker classification for both cases and controls (Cases Grade II or III uterine or cystocele)	Age	OR Ref BMI <23: 1.0; OR BMI 24-26: 1.1 (0.5-2.1); OR BMI >26: 0.9 (0.5-1.7)	Meta-analyst recalculated OR to make between-study comparisons similar: BMI Ref: <26 vs. BMI ≥26
Parazzini et al. (2000) [26]	Multi-center cross-sectional study of women with intact uterus; 21,449	Age category (%): ≤51: 39.8; 52-55: 28.5; ≥56: 30.9; % post-menopausal not specified; Inferred: 59% ≥52 years of age	Italian women; Ethnicity not specified; most likely mostly European	BMI: <23.8 (Ref); 23.8-27.2; >27.2	POP measured using Baden Walker classification system, uterine prolapse; Grade 0 - ≥ II; Analysis classification Grade 0 vs. Grades ≥I; Grade 0 vs. Grade I; Grade 0 vs. Grade ≥ II	Age, education, and parity	Grade 0 vs. ≥I; OR BMI <23.8 (Ref); OR BMI 23.8-27.2: 1.4 (1.2-1.7); OR BMI >27.2: 1.6 (1.3-1.8); Grade 0 vs. I: OR BMI <23.8 (Ref); OR BMI 23.8-27.2: 1.3 (1.1-1.6); OR BMI >27.2: 1.5 (1.2-1.8); Grade 0 vs. ≥II: OR BMI <23.8 (Ref); OR BMI 23.8-27.2: 1.6 (1.2-1.8); OR BMI >27.2: 1.8 (1.3-2.4)	Meta-analyst used Grade 0 vs. Grade I->II and Grade 0 vs. Grade >II analyses odds ratios as presented by authors for normal vs. overweight and normal vs. obese analysis categories;

Author (Publication Year) [Ref]	Study Design, sample size	Mean Age (SD)/Age Category(%); %post-menopausal	Country of Study or %Race/Ethnicity	Obesity Measure	POP Measurement	Covariates adjusted for	Results	Comments
Scherf et al. (2002) [27]	Population-based cross-sectional study of 40 villages; 1067	Mean age: 32.6; range 25-44; 0% post-menopausal	Gambian; 100% West African	BMI: < 18; 18-25 (Ref); >25	Objectively measured prolapse using mild, moderate and severe	Unadjusted	OR Ref BMI: 18-25: 1.0; OR BMI > 25: 1.33 (0.86-2.04)	Used OR as presented by authors to be used in the normal-weight vs. overweight analysis
Hendrix et al. (2002) [3]	Clinical trial participants, cross-sectional analysis; 27,187	Age range: 50-79; 100% post-menopausal	US; 88.4% white; 6.3% black, and 5.3% Hispanic	BMI: <25 (Ref); 25-<30; ≥30	POP measured using WHI POP-Grading System (Grades 1-3 as POP); Analysis provided for Grade 0 vs. Grade 1-3 for uterine prolapse, cystocele and rectocele separately	Age, ethnicity, parity, smoking, constipation, asthma, emphysema, HRT use history, hormone treatment vs placebo, Incontinence, waist circumference and physical activity	Grade 0 vs. Grade 1-3 POP: Smallest OR BMI Uterine POP< 25 (Ref): 1.0; OR BMI 25-<30: 1.31 (1.15-1.40); : Largest OR BMI cystocele OR BMI25-<30: 1.39 (1.28-1.51); Smallest OR BMI Uterine POP OR BMI ≥30: 1.40 (1.24-1.59); Largest OR BMI rectocele OR BMI ≥30: 1.75 (1.54-1.99)	Largest investigation of POP conducted to date. Meta-analyst used smallest and largest effect estimate from multiple types of prolapse for normal-weight vs. overweight and normal-weight vs. obese analysis.
Fornell et al. (2004) [29]	Population-based cross-sectional study if 40 year olds and 60 year olds; 1336	Age: 40-year olds (48.6%); 60 year-olds; 51.4% post-menopausal (inferred)	Swedish; possibly 100% European	BMI: <25 (Ref); 25-30; >30	Symptomatic POP measured through standardized questionnaire	Univariate OR	OR BMI < 25 (Ref): 1.0; OR BMI 25-30: 1.6 (0.9-3.0); OR BMI >30: 1.2 (0.5-3.2)	Authors measured three tyupes of genital prolapse symptoms: pelvic heaviness, genital bulge and digitation by defecation; Meta-analyst used OR for genital bulge

Author (Publication Year) [Ref]	Study Design, sample size	Mean Age (SD)/Age Category(%); %post-menopausal	Country of Study or %Race/Ethnicity	Obesity Measure	POP Measurement	Covariates adjusted for	Results	Comments
Swift et al. (2005) [6]	Population-based multicenter cross-sectional study; 1004	Mean age (SD): 42.7 (13.9); 40% post-menopausal	US; 42% white, 24% black, 29% Hispanic, 2% Asian, and 2% other	BMI: <25 (Ref); 25-30; >30	POP-Q system; Used leading edge of prolapse at -0.5 or greater for defining POP	Age, race, parity, gravidity, number of vaginal delivery, weight of vaginally delivered infant, hormone therapy, labor related employment, income categories, and smoking	OR BMI < 25 (Ref): 1.0; OR BMI 25-30: 2.51 (1.18-5.35); OR BMI >30: 2.56 (1.23-5.35)	Used OR as presented by authors to be used in the normal-weight vs. overweight analysis and normal-weight vs. obese analysis categories;
Jun Tae Seo et al. (2006) [33]	Hospital-based cross-sectional, annual gynecologic examinations; 713	41.6 (10.2); 29% post-menopausal	Koreans; Possibly 100% Asian	BMI: ≤18.5; 18.6-22.9; 23-24.9; ≥25	POP-Q system; Stages 0-3; POP-Q stage 0-1 vs. stage ≥ 2	Authors provided raw numbers only	BMI and waist circumference showed positive trend with increasing POPQ stage; P < 0.001; Calculated univariate OR BMI < 25 (Ref): 1.0; OR BMI ≥25: 2.85 (1.72-4.71)	Meta-analyst calculated OR from raw numbers for BMI < 25 vs. BMI ≥25
Tegerstedt et al. (2006) [28]	Population-based case-control study; 554	Age range: 30-79; Mean age not provided; 67.5% ≥50 years of age (inferred)	Swedish; Possibly 100% European	BMI: <20; 20-24.9 (Ref); ≥25;	Self-reported symptomatic POP was used for OR calculation; measured POP-Q on a smaller subset of women	Age and parity	OR Ref BMI: 20-24.9: 1.0: OR BMI ≥25: 1.3 (0.5-5.7)	Used OR as presented by authors to be used in the normal-weight vs. overweight analysis

Author (Publication Year) [Ref]	Study Design, sample size	Mean Age (SD)/Age Category(%); %post-menopausal	Country of Study or %Race/Ethnicity	Obesity Measure	POP Measurement	Covariates adjusted for	Results	Comments
Rortveit et al. (2007) [15]	RRISK; population-based cohort study; Independent group of women than RRISK2; 2,001	Mean age for RRISK (SD): 55.6 (8.6); 66% post-menopausal	US; 47% white; 19% African American; 17% Asian; 17% Latina; 1% Native American/other	BMI: < 25(Ref); 25-<30; 30-<35; 35-<40; ≥ 40	Symptomatic POP measured through standardized questionnaire	Authors present raw numbers only	OR BMI < 25 (Ref): 1.0; OR BMI 25-<30: 0.53 (0.33-0.84); OR BMI ≥30: 0.92 (0.59-1.43)	Meta-analyst calculated OR from raw numbers for BMI < 25 vs. BMI 25-<30 and BMI <25 vs. BMI ≥30
Forsman et al. (2008) [20]	Twin-Cohort Study; 16,886	Mean age (SD): 64.1 (9.2); 66% post-menopausal at least; not specified; although majority most likely post-menopausal; (inferred)	Swedish twins, both monozygotic and di-zygotic; most likely mostly European	BMI: <25 (Ref); 25-30; >30	POP assessed through Swedish inpatient register data, using Swedish Classification of Operations and Major Procedures	Age, and childbirth (ever/never)	OR BMI < 25 (Ref): 1.0; OR BMI 25-30: 1.1 (0.8-1.5); OR BMI >30: 1.4 (0.7-2.8)	Used OR as presented by authors to be used in the normal-weight vs. overweight analysis and normal-weight vs. obese analysis categories;

Author (Publication Year) [Ref]	Study Design, sample size	Mean Age (SD)/Age Category(%); %post-menopausal	Country of Study or %Race/Ethnicity	Obesity Measure	POP Measurement	Covariates adjusted for	Results	Comments
Whitcomb et al. (2009) [17]	Reproductive Risks for Incontinence Study at Kaiser 2 (RRISK2); population-based cohort study; 2,270	Mean age for RRISK2 (SD): 55.0 (9); 72% post-menopausal	US; 44% white; 20% African American; 18% Asian; 18% Latina/Hispanic/Native American/other	BMI: <25 (Ref); 25-<30; ≥30	POP measured in two ways; Symptomatic POP in 2270 women and through POP-Q examination in 1137 women	Age, race/ethnicity, education, parity and diabetes	Analysis in women with symptomatic prolapse: OR BMI < 25 (Ref): 1.0; OR BMI 25-<30: 1.03 (0.53-2.00); OR BMI ≥30: 1.43 (0.76-2.68); Analysis in women with prolapse at or below hymen (POP-Q): OR BMI < 25 (Ref): 1.0; OR BMI 25-<30: 1.46 (1.05-2.02); OR BMI ≥30: 1.67 (1.22-2.39); Analysis in women with prolapse ≥ Stage II (POP-Q): OR BMI < 25 (Ref): 1.0; OR BMI 25-<30: 1.06(1.01-1.11); OR BMI ≥30: 1.09 (1.04-1.14)	The authors presented three types of adjusted odds ratios for both overweight and obese analyses; Meta-analyst used Symptomatic Prolapse and Prolapse at or below the hymen as it is more advanced prolapse than just POP-Q Stage II
Chen Huey-Yi et al. (2009) [35]	Hospital-based case-control; 237	Cases: ≥54 yrs 72%; 71% post-menopausal. Controls: ≥54 yrs 31.3%; 44% post-menopausal	Taiwanese; possibly 100% Asian	BMI: < 23.6 (Ref); ≥ 23.6	POP-Q system; Stages 0-3; POP-Q stage 0-1 vs. stage ≥ 2	Age, parity, BMI, menopause	OR Ref BMI <23.6: 1.0; OR BMI ≥23.6: 1.99 (1.08-3.70)	Used OR as presented by authors to be used in the normal-weight vs. overweight analysis
Braekken et al. (2009) [34]	Hospital-based case-control; 98	Mean age: 47.1 (10.57); 36.7% post-menopausal	Norwegian; possibly 100% European	BMI: ≤25 (Ref); > 25	POP-Q system; Stages 0-4; POP-Q stage 0-1 vs. stage ≥ 2	socioeconomic status and heavy work	OR Ref BMI ≤25: 1.0; OR BMI >24: 5.0 (1.1-23.0)	Matched for age and parity; Used OR as presented by authors

Author (Publication Year) [Ref]	Study Design, sample size	Mean Age (SD)/Age Category(%); %post-menopausal	Country of Study or %Race/Ethnicity	Obesity Measure	POP Measurement	Covariates adjusted for	Results	Comments
Fritel et al. (2009) [21]	Cross-sectional analysis of Cohort study; 2,640	Median Age: 54 (range: 50-61); 100% post-menopausal	French; ethnicity mostly European	BMI: <25 (Ref); ≥25	Symptomatic POP measured through standardized questionnaire	Mode of delivery	OR: Ref BMI <25: 1.0; OR BMI ≥25: 1.41 (1.01-1.97)	Authors only included variables in model which were statistically significant; Only mode of delivery was statistically significant
de Araujo et al. (2009) [19]	Population-based cross-sectional, sexually active women; 377	Mean age (SD): 31 (15); %post-menopausal not provided; 14.32% ≥50 (inferred)	Brazilian; Ethnicity stated as indigenous Xingu women; most likely native	BMI: ≤25 (Ref); >25	POP-Q exam; Stage 0-3; Stage 0-1 vs. ≥2; Also Ba point ≥ 0 as cases	Does not explicitly report adjusted variables; most likely age, vaginal delivery, resting pressure and maximum pressure	Analysis Stage 0-1 vs. Stage ≥ II; OR: Ref BMI ≤25 1.0; OR BMI >25: 1.05 (0.60-1.82); Analysis leading edge Ba < 0 vs. ≥0; OR Ref BMI ≤25: 1.0; OR BMI >25: 1.33 (0.79-2.24)	Authors presented adjusted odds ratios for two methods of POP classification as noted in the POP-measurement column; Both were considered
Miedel et al. (2009) [25]	Population-based cross-sectional study; 442	Mean age cases (SD): 53.3 (12.3) Mean age controls (SD): 49.1 (13.5); % post-menopausal status not explicitly stated; inferred based on hormone therapy use: 28% in cases and 29% in controls	Swedish; ethnicity not provided; most likely 100% European	BMI: <19; 19-25 (Ref); 26-30); >30	Self-reported symptomatic POP was used for OR calculation; measured POP-Q on a smaller subset of women	Age, parity, hernia, family history of POP, heavy lifting, and constipation	OR BMI 19-25 (Ref): 1.0; OR BMI 26-30: 1.88 (1.15-3.08); OR BMI >30: 2.07 (0.95-4.5)	Used OR as presented by authors to be used in the normal-weight vs. overweight analysis and normal-weight vs. obese analysis categories;

Author (Publication Year) [Ref]	Study Design, sample size	Mean Age (SD)/Age Category(%); %post-menopausal	Country of Study or %Race/Ethnicity	Obesity Measure	POP Measurement	Covariates adjusted for	Results	Comments
Dolan et al. (2010) [8]	Cross-sectional analysis of registry-based records; 1,787	Mean age: 45.7 (4.8); % post-menopausal not provided; Inferred: at most <33%	English; ethnicity not provided, but most likely mostly European	BMI: <25 (Ref); 25-30; >30	Symptomatic POP measured through standardized questionnaire	Age, social class, parity, birth weight, mode of 1st delivery length of 1st labor, length of 2nd stage labor, epidural/caudal, and perineum status upon delivery	OR BMI < 25 (Ref): 1.0; OR BMI 25-30: 0.98 (0.72-1.34); OR BMI >30: 1.30 (0.89-1.88)	Used OR as presented by authors to be used in the normal-weight vs. overweight analysis and normal-weight vs. obese analysis categories;
Diez-Itza et al. (2011) [32]	Hospital-based cross-sectional study, primi-gravida women; 382	Mean age (range): 31.2 (18-46) % post-menopausal 0%;	Spain; Ethnicity not described; presumably white	BMI: ≤25 (Ref); >25	POP-Q exam; Stage 0-3; Stage 0-1 vs. ≥2	Univariate odds ratio	OR: Ref BMI ≤25 1.0; OR BMI >25: 1.57 (0.90-2.73)	Meta-analyst used univariate odds ratio provided by authors
Glazener et al. (2012) [10]	Cross-sectional analysis of 13 year longitudinal study; 3,763	Mean age at birth index (SD): 29.2 (4.9); Mean age at follow-up (range): 42 (26-58); % post-menopausal not provided, mostly pre-menopausal	English; 95.7% non-Asian	BMI: <18.5; 18.5-24.9 (Ref); 25-29.9); ≥ 30	POP-Q system; used leading edge of prolapse at or beyond hymen for defining POP	Age at first birth, and total number of births	OR BMI 18.5-<24.9 (Ref): 1.0; OR BMI 25-29.9: 1.33 (0.90-1.96); OR BMI ≥30: 1.48 (0.91-2.40)	Used OR as presented by authors to be used in the normal-weight vs. overweight analysis and normal-weight vs. obese analysis categories;

Author (Publication Year) [Ref]	Study Design, sample size	Mean Age (SD)/Age Category(%); %post-menopausal	Country of Study or %Race/Ethnicity	Obesity Measure	POP Measurement	Covariates adjusted for	Results	Comments
Gyhagen et al. (2012) [11]	Registry-based national cohort study of primi-parous women; 5,236	Maternal age range at birth: <23 - ≥ 35; Evaluation of POP 20 years later; Maternal age range during self-reported POP evaluation <43 - ≥55; % post-menopausal at POP evaluation not provided; mostly, pre-menopausal	Swedish; possibly 100% European	BMI: <25 (Ref); 25-29.9; ≥30	Symptomatic POP measured through standardized questionnaire	Age at delivery and infant birth weight	Analysis in women with Caesarean section: OR BMI < 25 (Ref): 1.0; OR BMI 25-29.9: 1.70 (0.99-2.94); OR BMI ≥30: 1.60 (0.86-2.96); Analysis in women with vaginal delivery: OR BMI < 25 (Ref): 1.0; OR BMI 25-29.9: 1.33 (1.08-1.63); OR BMI ≥30: 1.74 (1.38-2.18)	Authors presented adjusted odds ratios for women with C-section and women with vaginal delivery separately. Therefore, two independent odds ratios are provided for normal vs. overweight and normal vs. obese, each
Awwad et al. (2012) [31]	Population-based cross-sectional study; 557	Cases Mean age: 40.42 (9.34); 21.1% post-menopausal; Controls Mean age: 31.78 (9.56); 7.5% post-menopausal	Rural Lebanese women; Ethnicity unknown	BMI: ≤24 (Ref); >24	POP-Q system: Stages 0-4; POP-Q stage 0-1 vs. stage ≥ 2	Age, miscarriage, vaginal parity , age by parity interaction	OR Ref BMI ≤24: 1.0; OR BMI > 24: 1.6242 (1.00-2.63)	Used OR as presented by authors to be used in the normal-weight vs. overweight analysis

BMI measured in kg/m^2

Table 2. Main meta-analysis results evaluating obesity categories in relation to POP

Scenario	BMI Category	N	Risk Ratio (95% CI)	p-value	I^2	Small-Study Bias-p-value
Minimum						
	Overweight	22	1.36 (1.20, 1.53)	$5.73x10^{-7}$	50%	0.34
	Obese	13	1.47 (1.35, 1.59)	$5.18x10^{-20}$	0%	0.86
Maximum						
	Overweight	22	1.40 (1.25, 1.58)	$1.91x10^{-8}$	49%	0.35
	Obese	13	1.61 (1.45, 1.78)	$1.88x10^{-19}$	12%	0.24

p-value = tests the null hypothesis that risk ratio = 1; I^2 = % heterogeneity attributed to factors other than chance; Minimum = represents the meta-analysis risk ratio when comparing the smallest effect estimates provided by each study in the scenario when studies reported two or more effect estimates; Maximum = represents the meta-analysis risk ratio when comparing the largest effect estimates provided by each study in the scenario when studies reported two or more effect estimates

Table 3. Sensitivity analyses for normal-weight vs. overweight categories in relation to POP by study characteristic

		Minimum Scenario			Maximum Scenario		
Study Characteristic	**N**	**Risk Ratio (95% CI)**	**p-value**	**I^2**	**Risk Ratio (95% CI)**	**p-value**	**I^2**
POP Measurement							
Objective (Any grade POP)	3	1.34 (1.21, 1.48)	$7.93x10^{-9}$	0%	1.38 (1.27, 1.51)	$1.23x10^{-13}$	0%
Self-reported POP	9	1.23 (0.97, 1.55)	$8.51x10^{-2}$	61%	-	-	-
Objective (Clinically-significant)	12	1.54 (1.29, 1.83)	$1.84x10^{-6}$	39%	1.55 (1.31, 1.84)	$2.90x10^{-7}$	34%
Analysis Adjusted							
No	7	1.33 (0.87, 2.03)	$8.67x10^{-1}$	76%	-	-	-
Yes	15	1.34 (1.22, 1.48)	$5.64x10^{-10}$	18%	1.39 (1.28, 1.52)	$6.02x10^{-13}$	15%
% Post-menopausal							
<50%	13	1.53 (1.29, 1.83)	$1.75x10^{-6}$	45%	1.55 (1.31, 1.84)	$4.19x10^{-7}$	42%
≥50%	9	1.20 (1.01, 1.42)	$3.40x10^{-2}$	53%	1.26 (1.05, 1.51)	$1.17x10^{-2}$	58%
Reported WHO BMI Categories							
No	11	1.51 (1.28, 1.77)	$4.66x10^{-7}$	23%	1.58 (1.36, 1.84)	$5.88x10^{-9}$	8%
Yes	11	1.25 (1.05, 1.48)	$1.02x10^{-2}$	59%	1.29 (1.10, 1.51)	$1.75x10^{-3}$	62%
Reported Study Design							
Case-control	4	1.61 (1.01, 2.58)	$4.44x10^{-2}$	27%	-	-	-
Cohort	9	1.18 (1.01, 1.38)	$4.04x10^{-2}$	56%	1.23 (1.05, 1.43)	$8.09x10^{-98}$	61%
Cross-sectional	9	1.60 (1.33, 1.91)	$3.40x10^{-7}$	30%	1.68 (1.44, 1.97)	$3.46x10^{-14}$	0%

p-value = tests the null hypothesis that risk ratio = 1; I^2 = % heterogeneity attributed to factors other than chance; Minimum = represents the meta-analysis risk ratio when comparing the smallest effect estimates provided by a study in the scenario when a study reported two or more effect estimates; Maximum = represents the meta-analysis risk ratio when comparing the largest effect estimates provided by a study in the scenario when a study reported two or more effect estimates; - = if no studies report two or more estimates then, minimum = maximum

Table 4. Sensitivity analyses for normal-weight vs. obese in relation to POP by study characteristic

		Minimum Scenario			Maximum Scenario		
Study Characteristic	**N**	**Risk Ratio (95% CI)**	**p-value**	**I^2**	**Risk Ratio (95% CI)**	**p-value**	**I^2**
POP Measurement							
Objective (Any grade POP)	3	1.45 (1.31, 1.60)	$4.49x10^{-13}$	0%	1.64 (1.45, 1.86)	$4.51x10^{-15}$	21.8%
Self-reported POP	7	1.44 (1.18, 1.76)	$3.43x10^{-4}$	22%	-	-	-
Objective (Clinically-significant)	5	1.71 (1.42, 2.06)	$1.51x10^{-8}$	0%	-	-	-
Analysis Adjusted:							
No	2	0.97 (0.65, 1.44)	$8.70x10^{-1}$	0%	-	-	-
Yes	11	1.50 (1.37, 1.63)	$6.00x10^{-21}$	0%	1.68 (1.54, 1.84)	$7.38x10^{-31}$	0%
% Post-menopausal							
<50%	6	1.65 (1.40, 1.94)	$2.37x10^{-9}$	0%	-	-	-
≥50%	6	1.42 (1.27, 1.59)	$1.64x10^{-9}$	7%	1.56 (1.30, 1.88)	$2.25x10^{-6}$	41%
Reported WHO BMI Categories							
No	2	1.53 (1.29, 1.81)	$6.04x10^{-7}$	0%	1.55 (1.14, 2.12)	$5.00x10^{-3}$	44%
Yes	11	1.45 (1.31, 1.61)	$2.56x10^{-12}$	4%	1.61 (1.43, 1.81)	$2.79x10^{-15}$	15%
Reported Study Design							
Case-control	0	NA	NA	NA	NA	NA	NA
Cohort	9	1.42 (1.29, 1.56)	$1.26x10^{-14}$	0%	1.54 (1.36, 1.75)	$2.39x10^{-11}$	27%
Cross-sectional	4	1.65 (1.38, 1.96)	$2.41x10^{-8}$	0%	1.85 (1.43, 2.39)	$2.48x10^{-6}$	0%

p-value = tests the null hypothesis that risk ratio = 1; I^2 = % heterogeneity attributed to factors other than chance; Minimum = represents the meta-analysis risk ratio when comparing the smallest effect estimates provided by a study in the scenario when a study reported two or more effect estimates; Maximum = represents the meta-analysis risk ratio when comparing the largest effect estimates provided by a study in the scenario when a study reported two or more effect estimates; - = if no studies report two or more estimates then, minimum = maximum; NA = no studies available

Figure legends and foot notes

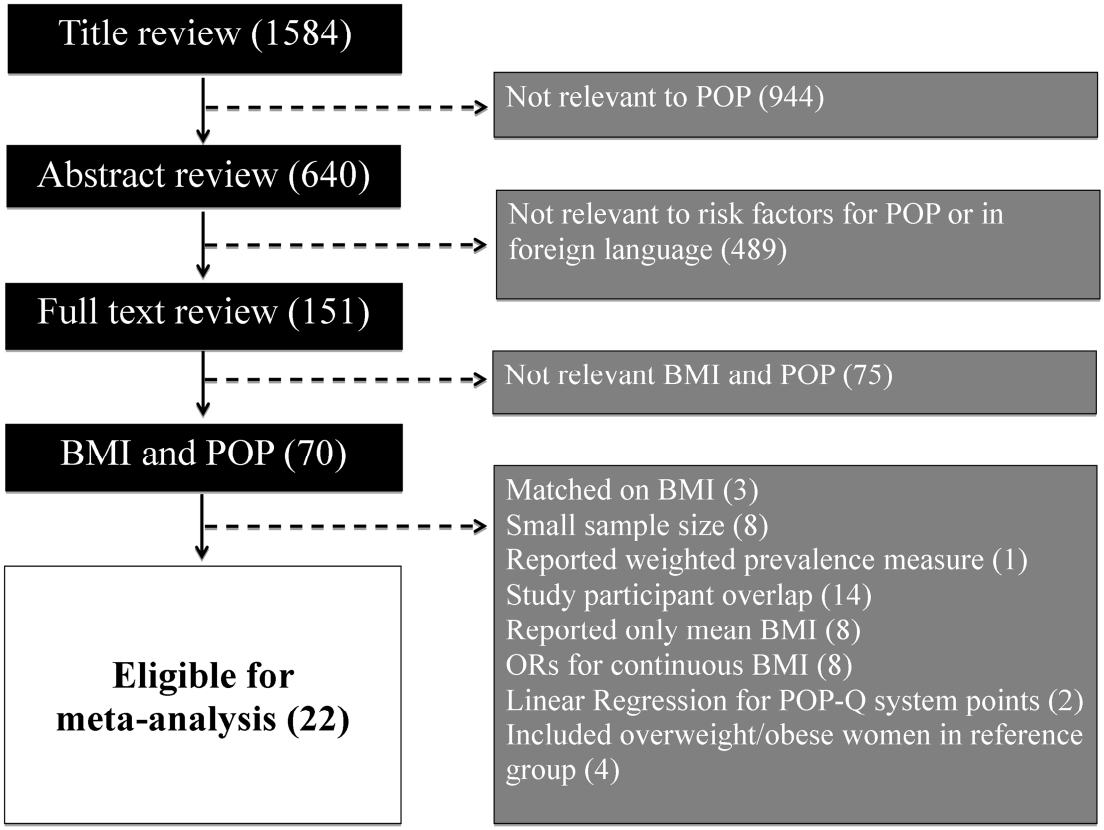
Figure 1. Flow chart of inclusion/exclusion of studies for meta-analysis

Figure 2. Main-analyses: Forest plots for studies evaluating normal-weight vs. overweight categories in relation to POP

A: Minimum Scenario= represents the meta-analysis risk ratio when comparing the smallest effect estimates provided by a study in the scenario when a study reported two or more effect estimates; B: Maximum Scenario= represents the meta-analysis risk ratio when comparing the largest effect estimates provided by a study in the scenario when a study reported two or more effect estimates; * represents the minimum estimate from studies that reported 2 or more estimates; # represents the maximum estimate from studies that reported 2 or more estimates; cs = estimates based on women who had caesarean section; vd= estimates based on women who had vaginal delivery

Figure 3. Main-analyses: Forest plots for studies evaluating normal-weight vs. obese categories in relation to POP

A: Minimum Scenario= represents the meta-analysis risk ratio when comparing the smallest effect estimates provided by a study in the scenario when a study reported two or more effect estimates; B: Maximum Scenario= represents the meta-analysis risk ratio when comparing the largest effect estimates provided by a study in the scenario when a study reported two or more effect estimates; * represents the minimum estimate from studies that reported 2 or more estimates; # represents the maximum estimate from studies that reported 2 or more estimates; cs = estimates based on women who had caesarean section; vd= estimates based on women who had vaginal delivery


Title review (1584)
Not relevant to POP (944)
Abstract review (640)
Not relevant to risk factors for POP or in foreign language (489)
Full text review (151)
Not relevant BMI and POP (75)
BMI and POP (70)
Matched on BMI (3)
Small sample size (8)
Reported weighted prevalence measure (1)
Study participant overlap (14)
Reported only mean BMI (8)
ORs for continuous BMI (8)
Linear Regression for POP-Q system points (2)
Included overweight/obese women in reference group (4)
Eligible for meta-analysis (22)