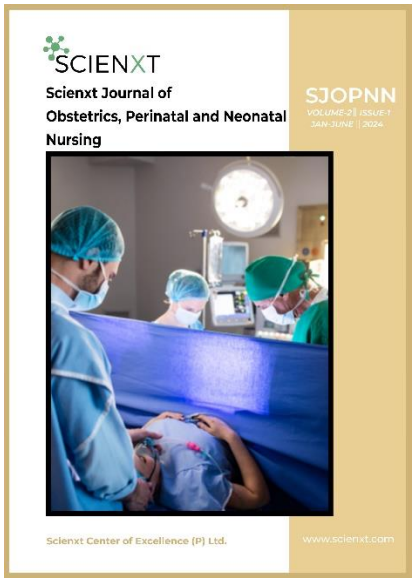

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Review of risk factors for primary pelvic organ prolapse

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Abstract:

To update a previously published systematic review and perform a meta-analysis on the risk factors for primary pelvic organ prolapse and prolapse recurrence.Randomized controlled trials and cross-sectional and cohort studies conducted in the Western developed countries that reported on multivariable analysis of risk factors for primary prolapse or prolapse recurrence were included. The definition of prolapse was based on anatomic references, and prolapse recurrence was defined as anatomic recurrence after native tissue repair. Studies on prolapse recurrence with a median follow-up of ≥1 year after surgery were included. Quality assessment was performed with the Newcastle-Ottawa Scale. Data from the previous review and this review were combined into forest plots, and meta-analyses were performed where possible. If the data could not be pooled, "confirmed risk factors" were identified if ≥2 studies reported a significant association in multivariable analysis. Vaginal delivery, parity, birthweight, age, body mass index, levator defect, and levator hiatal area are risk factors, and cesarean delivery and smoking are protective factors for primary prolapse. Preoperative prolapse stage and younger age are risk factors for prolapse recurrence after native tissue surgery.

Keywords:

Anatomy, forest, plot meta-analysis, native tissue repair, pelvic organ prolapse, Pelvic Organ Prolapse Quantification system, primary prolapse, prolapse recurrence, risk factors, surgery, systematic review

1. Introduction:

Pelvic organ prolapse (POP) is a common medical condition worldwide impairing many women in their daily life. Although POP is not a life-threatening disease, it has a significant impact on the quality of life. Studies show that women have a lifetime risk of 12.6% to undergo surgical correction for POP by the age of 80 years. This number indicates not only the burden of POP on society and healthcare systems but also its financial impact on healthcare. With increasing life-expectancy in general, it is estimated that the number of care- seeking women and surgeries will increase tremendously in the coming 20–40 years. These high rates for POP surgery demand a focus on preventive strategies.

The key to finding the right prevention strategies is knowledge about etiology and risk factors. With an eye on the emerging preventive medicine, several studies investigating the risk factors for POP development and POP recurrence after surgery have been carried out. This knowledge about risk factors not only contributes to developing prevention strategies but also helps in the counseling of patients preoperatively and managing expectations. The systematic review by Vergeldt et alidentified parity, vaginal delivery, age, and body mass index (BMI) as confirmed risk factors for the development of POP and preoperative stage 3 and 4 as confirmed risk factors for POP recurrence after native tissue repair (on the basis of definition in ≥2 studies with significant association in multivariable analysis). In the years after this publication, multiple studies have been published on this subject. Among others, the meta-analysis of Cattani et al identified forceps delivery and first vaginal birth as risk factors for anatomic and symptomatic primary POP. For POP recurrence, the meta-analysis of Friedman et al showed that levator defect, preoperative prolapse stage 3 or 4, family history of prolapse, and levator hiatal area are significant risk factors for POP recurrence. In this paper, we will update the review of Vergeldt et al and perform a meta-analysis not only on the risk factors for primary POP but also on POP recurrence for women in the Western developed countries.

2. Methods:

This systematic review and meta-analysis was conducted in accordance with a prospectively registered protocol (International Prospective Register of Systematic Reviews [PROSPERO]; PROSPERO number CRD42021230813, March 26, 2021), the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines, and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.

2.1. Information sources and search strategy:

A database search was performed by the primary reviewer (S.F.S.) and a librarian in PubMed and Embase using the search terms “pelvic organ prolapse” AND “recurrence” and “pelvic organ prolapse” AND “risk factors.” The search for the previous publication ended on August 4, 2014. Therefore, we searched from July 1, 2014 until July 5, 2021. The same search terms were used. No language restrictions were used. For the complete search, see appendix A.

2.2. Study selection and eligibility criteria:

We used the same evaluation strategy as in the previous review. All the articles were evaluated by title and/or abstract by 2 independent reviewers (S.F.S. and M.C.). In case of disagreement, a third reviewer (K.B.K.) solved conflicts by consensus. Clinical studies reporting on the etiology or risk factors for primary POP or POP recurrence were included. A manual reference check of the included abstracts was performed. The included articles after abstract selection were screened on full text with a standardized in- and exclusion form. The authors were contacted to retrieve the article in case the full text was not available. Randomized controlled trials, cross-sectional and cohort studies conducted in the Western developed countries that reported on multivariable analysis with sufficient data (including odds, risk, or hazard ratio [HR] with 95% confidence intervals) of risk factors for POP or POP recurrence were included.

The definition of POP or POP recurrence had to be based on anatomic references or POP-Quantification (POP-Q) ≥ stage 2. For POP recurrence, only studies that reported on recurrence after native tissue repair with a median follow-up of at least 1 year were included. In case studies used the same population in multiple publications, only the most recent publication was included.

2.3. Data extraction:

Data extraction was conducted by 2 reviewers (S.F.S. and M.C.) using a predefined data extraction form with data on study design, sample size, study population, definition of outcome, investigated risk factors, and results of the multivariable analysis. The corresponding authors were contacted in case additional information was needed on the study results. To provide a comprehensive overview, the results of the previous review were used again in this paper. The template data collection forms and data extracted from included studies are available on request.

2.4. Assessment of risk of bias:

A quality assessment was performed by 2 independent reviewers (S.F.S. and M.C.) on the final included articles using the Newcastle-Ottawa Scale (NOS) for cross-sectional and cohort studies comprising of the following: participant selection, comparability of study groups, and assessment of outcome or exposure.

2.5. Data synthesis:

In case a risk factor was studied in at least 2 studies using the same type of outcome and adjusted for at least the following confounders: parity, delivery mode, age, and BMI for primary POP and preoperative POP-Q stage for POP recurrence, we pooled the adjusted results with a random-effects meta-analysis using the inverse variance method on the log-transformed ratios and corresponding standard errors and presented the 95% confidence intervals of the back-transformed ratios. If necessary and possible, data conversion was applied (eg, conversion of per 1 year to per 10 years). In the case of a similar outcome but on the basis of different sets of adjustment variables, the results were only pooled in case of sufficiently low between-study heterogeneity (I^2<50%). Variation across studies (heterogeneity) was estimated with a restricted maximum likelihood estimator for τ^2. If studies could be pooled, an extra line in the forest plot below the studies was added to present the pooled result of the meta-analysis in bold. If the effects of a risk factor were presented in different measures, eg, odds ratio (OR) and HR, these were not pooled but were presented graphically in forest plots separated by effect measure. In addition to the risk factors identified by meta-analyses, we identified “confirmed risk factors” also. A confirmed risk factor was defined as a statistically significant association on the basis of multivariable data analysis that was reported in at least 2 studies that could not be pooled because of heterogenic outcome definitions or effect measures, without other studies reporting contradicting results. This definition was based on the definition used in the previous publication. No subgroup or sensitivity analyses were performed because of the small number of studies per potential risk factor and the large heterogeneity in risk factors. Publication bias was not evaluated, as the meta-analyses were based on 5 studies each at the most. All analyses were performed with the statistical software R version 3.6.3, packages Meta version 2.4-0, and forest plot version 1.10.1. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach was used to interpret the certainty in the body of the evidence.

As publication biases were not evaluated because of the small number of available studies per risk factor, the certainty of evidence was not downgraded for this domain.

3. Results:

3.1. Study selection:

A total of 5284 articles were retrieved by our search update. After the removal of duplicates, 3381 articles were screened by title and/or abstract. The full texts of 112 articles were evaluated using the in- and exclusion form. No extra articles were included after cross checking reference lists. After final selection, an additional 14 articles met our inclusion criteria, of which 8 articles were on the risk factors for primary POP and 6 articles were on the risk factors for POP recurrence. One article was excluded in the previous review and now included because of exclusion of an older study with the same population.

Three articles that were included in the previous review were now partly or totally, excluded, because they used the same study population in a more recent publication or the country of investigation was not a Western developed one. Three studies appeared to meet the inclusion criteria but were excluded, because no separate analysis was performed for anatomic POP recurrence. In total (with the included articles of the previous publication), we included 16 articles on primary POP and 11 articles on POP recurrence. Figure 1 shows the flow diagram of the selection process. Because of high heterogeneity or differences in definitions and effect measures, not all studies could be pooled. Forest plots were made to visualize the results and to be able to recognize trends; see Fig. 2, Fig. 3, Fig. 4, Fig. 5, Fig. 6, Fig. 7, and Fig. 8. The results of the studies that could not be included in the forest plots are listed in the tables; see appendix B.

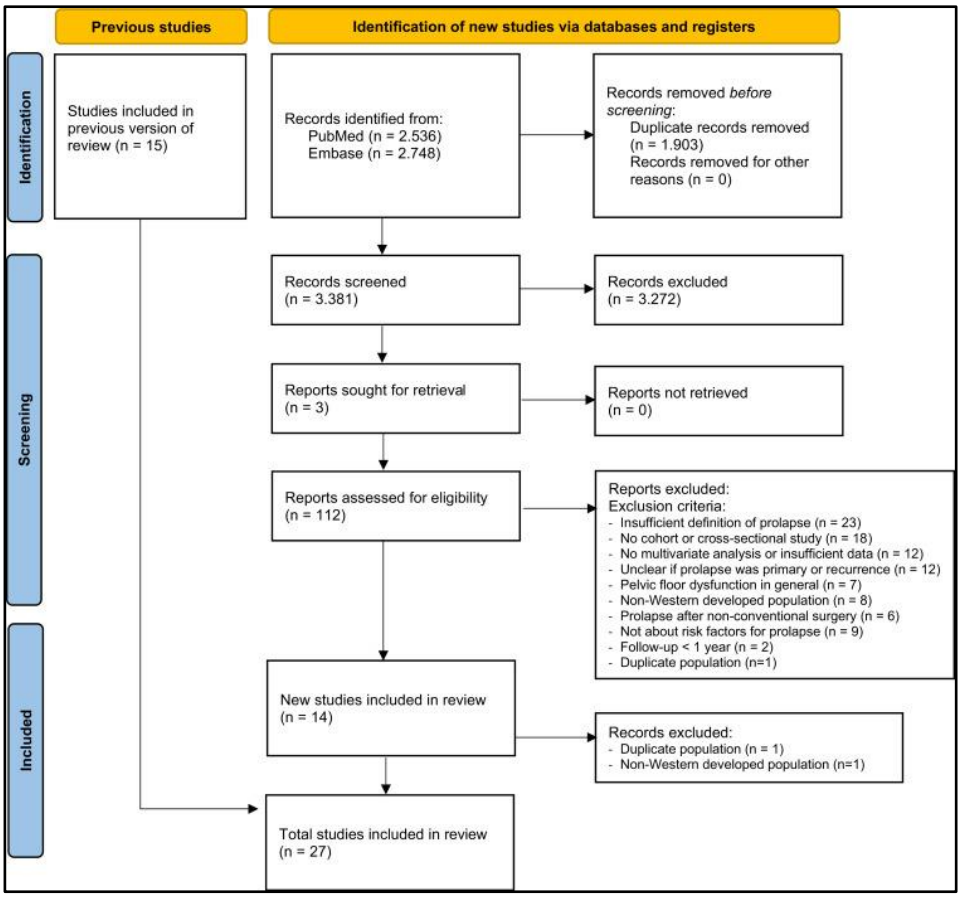

Figure. 1: Flow diagram of study selection process

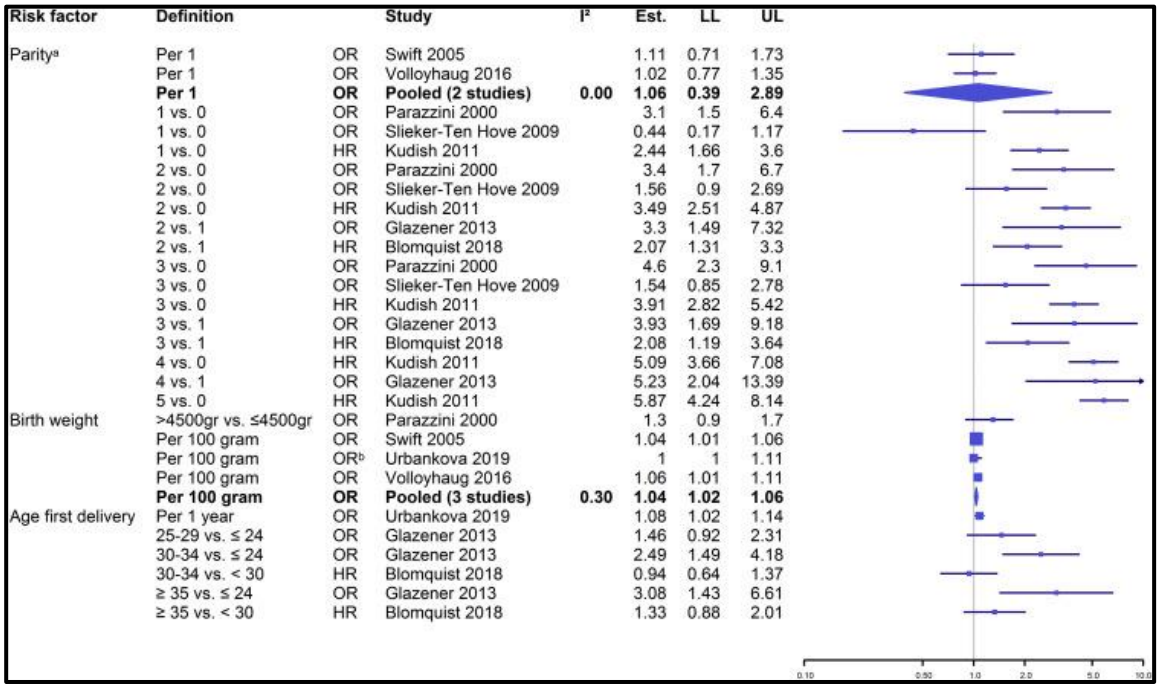

Figure. 2: Forest plot and meta-analyses for primary POP in association with the obstetrical risk factors parity, birthweight, and age at first delivery

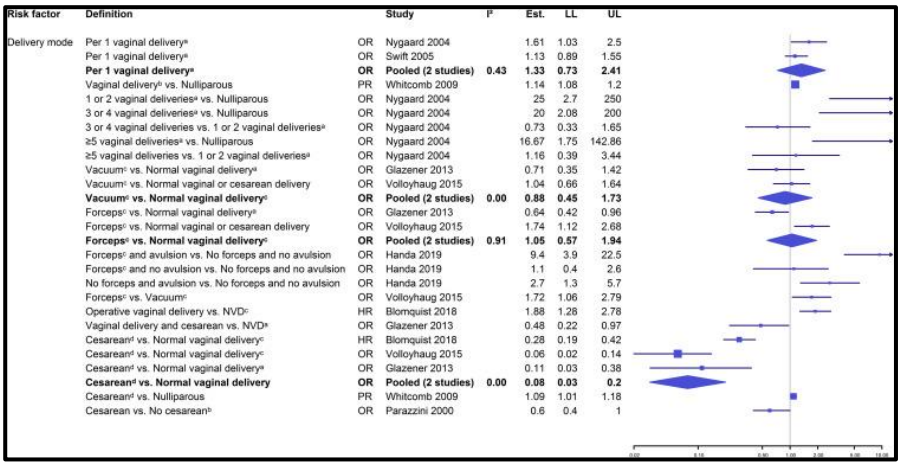

Figure. 3: Forest plot and meta-analyses for primary POP in association with the obstetrical risk factor delivery mode

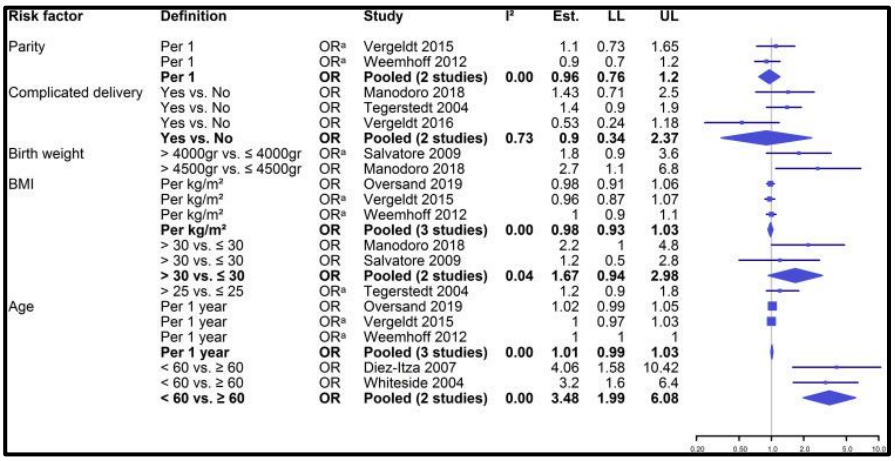

Figure. 4: Forest plot and meta-analyses for POP recurrence in association with the risk factors parity, complicated delivery, birthweight, BMI, and age

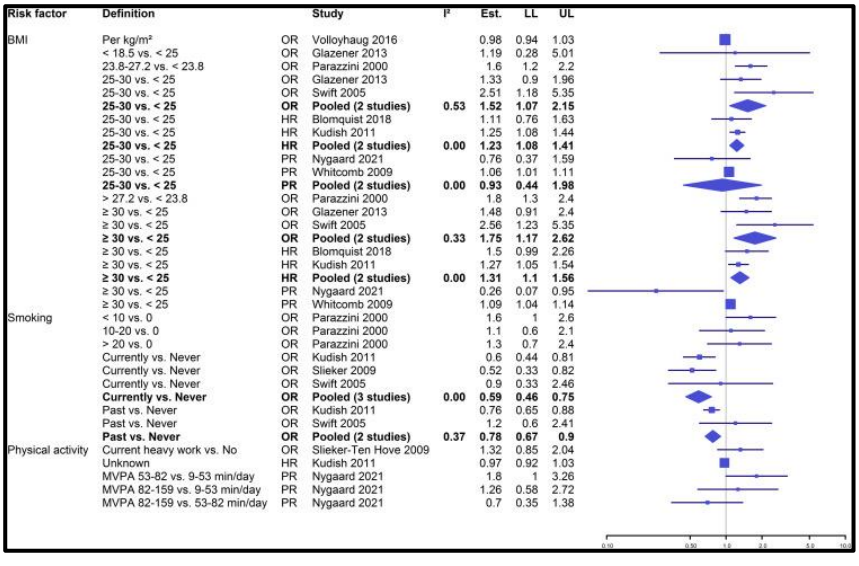

Figure. 5: Forest plot and meta-analyses for primary POP in association with the nonobstetrical risk factors BMI, smoking, and physical activity

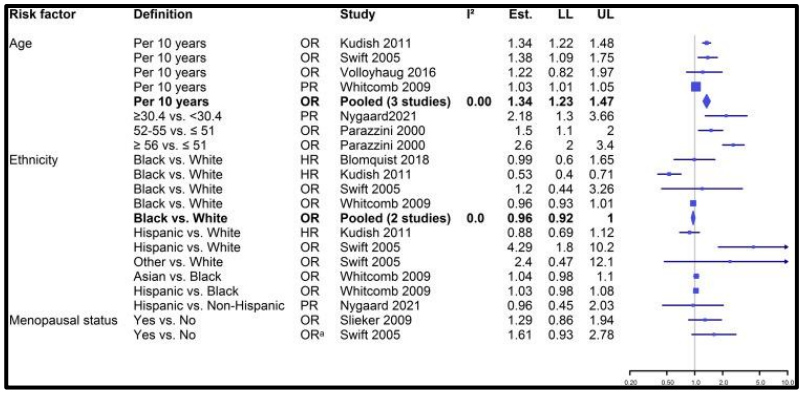

Figure. 6: Forest plot and meta-analyses for primary POP in association with the nonobstetrical risk factors age, ethnicity, and menopausal status

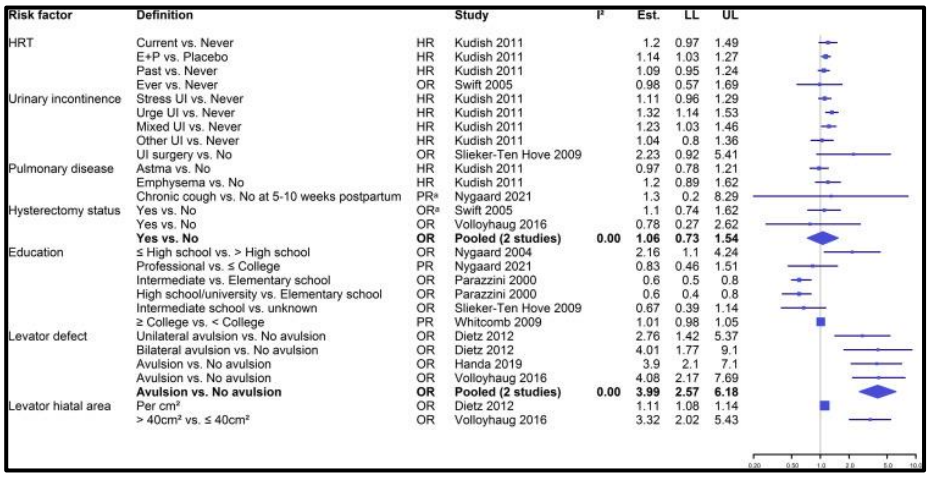

Figure. 7: Forest plot and meta-analyses for primary POP in association with the risk factors HRT, urinary incontinence, pulmonary disease, hysterectomy status, education, levator defect, and levator hiatal area

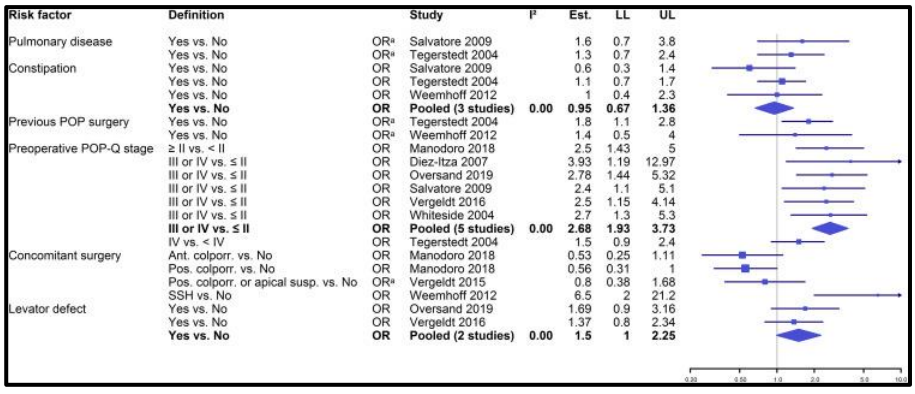

Figure. 8: Forest plot and meta-analyses for POP recurrence in association with the risk factors pulmonary disease, constipation, previous POP surgery, preoperative POP-Q stage, concomitant surgery, and levator defect

3.2. Study characteristics:

The characteristics of the studies concerning the risk factors for primary POP are summarized in Table 1. In total, data on 43,333 women were analyzed in 8 prospective cohort studies and

8 cross-sectional studies. POP was defined as POP-Q stage 2 or higher in 7 studies, POP beyond the hymen in 5 studies, degree 2 or 3 in the Baden-Walker classification in 1 study, the most descended point of the vaginal wall to the introitus or outside of the vagina (according to the Women's Health Initiative classification system) in 1 study, the most dependent point of the vaginal wall or the cervix to or beyond the hymen and the most descended point of the vaginal wall −0.5 cm above the hymenal remnants in 1 study. See appendix table B.1 for the obstetrical risk factors for primary POP and appendix table B.2 for the nonobstetrical risk factors for primary POP.

Table. 1: Included articles on primary pelvic organ prolapse

Reference	**Study type**	**N/n**	**Inclusion criteria**	**Investigated risk factors**	**Adjustment variables**
Progetto Menopausa Italia Study Group,	Cross-sectional study	21,449 /410	Nonhysterectomized women around menopause attending an outpatient menopause clinic for general counseling about menopause	Age, BMI, smoking, education, delivery mode, parity, birthweight, age at menarche, age at menopause	Age, BMI, education, parity
Nygaard et al,	Cross-sectional study	270/173	Nonhysterectomized women enrolled in the WHI Hormone Replacement Therapy clinical randomized trial	Age, BMI, delivery mode, waist circumference, smoking, physical activity, education, occupation, birthweight, age at first and last delivery, hormone replacement therapy, family history, pulmonary disease, previous hernia surgery	BMI, waist circumference, education, parity, delivery mode, birthweight, at first and last delivery
Swift et al,	Cross-sectional study	1004/218	Women older than 18 y of age presenting for routine gynecologic healthcare	Age, BMI, smoking, ethnicity, occupation, income, parity, delivery mode, birthweight, gravidity, menopausal status, hormone replacement therapy, hysterectomy status, chronic illness, and constipation	Age, BMI, smoking, ethnicity, occupation, income, parity, delivery mode, birthweight, gravidity, hormone replacement therapy, hysterectomy status, and constipation
Slieker-Ten Hove et al, The Netherlands	Cross-sectional study	649/227	A general population of women aged 45–85 y	Age, BMI, smoking, physical activity, education, parity, menopausal status, family history, UI,	Smoking, physical activity, education, parity, menopausal status, family history, UI,

Reference	Study type	N/n	Inclusion criteria	Investigated risk factors	Adjustment variables
				prolapse during pregnancy	prolapse during pregnancy
Whitcomb et al,	Cross-sectional study	1137/762	Women between 40 and 69 y of age who since age 18 y had been members of the Kaiser Permanente Medical Care Program of Northern California	Age, BMI, ethnicity, education, parity, and diabetes	Age, BMI, ethnicity, education, parity, and diabetes
Kudish et al,	Prospective cohort study	12,650 /2266	Nonhysterectomized, postmenopausal women enrolled in the WHI Estrogen plus Progestin Clinical Trial	Age, BMI, waist circumference, smoking, physical activity, ethnicity, parity, hormone replacement therapy, UI, pulmonary disease, and constipation	Age, BMI, waist circumference, smoking, physical activity, ethnicity, parity, hormone replacement therapy, UI, pulmonary disease, and constipation
Dietz et al,	Cross-sectional study	605/NA [a]	Women without previous incontinence or prolapse surgery with symptoms of pelvic floor dysfunction with data of 4-dimensional ultrasound	Levator defect, hiatal area on Valsalva	Levator defect, hiatal area on Valsalva
Handa et al, es	Prospective cohort study	449/64	Women 5–10 years after first vaginal or cesarean delivery	Forceps delivery, vacuum delivery, episiotomy, spontaneous laceration	Maternal age>35 y at first delivery, multiparity, operative delivery
Glazener et al,	Prospective cohort study	762 / 182	Women who delivered over a 12-mo period in 3 maternity units	Age at first delivery, BMI, parity, delivery mode	Age at first delivery, BMI, parity, delivery mode
VollØyhaug et al,	Cross-sectional study	608/280	Women 16–24 y after first delivery who delivered between 1990 and 1997 through forceps, vacuum, cesarean delivery, or normal vaginal delivery	Delivery mode	Age, BMI, parity, delivery mode, and birthweight
VollØyhaug et al,	Cross-sectional study	608/275	Women 16–24 y after first delivery who delivered between 1990 and 1997.	Age, BMI, parity, birthweight, hysterectomy status, levator defect, and levator hiatal area	Age, BMI, parity, birthweight, hysterectomy status, levator defect, and levator hiatal area
Blomquist et al,	Prospective cohort study	1492/153	Women 5–10 years after first vaginal or cesarean delivery	Age at first delivery, BMI, ethnicity, parity, delivery mode, genital hiatus	Age at first delivery, BMI, ethnicity, parity, delivery mode, genital hiatus

Reference	Study type	N/n	Inclusion criteria	Investigated risk factors	Adjustment variables
Handa et al,	Prospective cohort study	453/116	Women 5–10 years after first delivery with at least 1 vaginal delivery	Levator defect	Age, ethnicity, birthweight, forceps, prolonged second stage of labor
Lovejoy et al,	Prospective cohort study	705/ 143	Women 5–10 y after first delivery	Breastfeeding	BMI, ethnicity, education, parity, and imbalances between exposure groups
Urbankova et al,	Prospective cohort study	987/562	Healthy women in their first pregnancy, singleton, and delivered vaginally at or beyond 37 wk	Age, fetal weight, length of first and second stage of labor, analgesia type	Age and duration first stage of labor
Nygaard et al,	Prospective cohort study	562/53	Women who were 18 y, English- or Spanish-speaking, nulliparous with a singleton gestation, 28 weeks' gestation, planning vaginal delivery, not planning to move to a location precluding follow-up, and living within 60 miles of the research facility	Age, BMI, education, MVPA postpartum, high-risk delivery factor, breastfeeding, pelvic support in third trimester, Chronic cough at 5–10 wk postpartum	Age, BMI, ethnicity, education, high risk delivery factor, pelvic support in third trimester, breastfeeding

BMI, body mass index in kg/m^2; *MVPA*, moderate to vigorous physical activity; *N/n*, number of women included in the study who underwent physical examination/number of women with pelvic organ prolapse; *NA*, not available; *POP*, pelvic organ prolapse; *UI*, urinary incontinence; *WHI*, Women's Health Initiative. A Number of women categorized by type of prolapse: 222 women with cystocele, 159 women with rectocele, and 40 women with apical prolapse.

3.3. Risk of bias of included studies:

The overall quality of the articles was adequate; all the included articles had a sufficient description of in- and exclusion criteria and outcomes. In 15 articles, the number of risk factors for analysis was limited to 10% of the number of events; in 1 article, the 10% was exceeded. Blinding was applied in 9 articles. Quality assessment showed NOS scores of 5 studies being 9, that of another 5 studies being 8, of 3 studies being 7, of 1 study being 6, and of 2 studies being 5. A score of 7 or higher is considered high quality.

3.4. Studies on prolapse recurrence:

The overall quality of the articles was adequate; all the included articles had a sufficient description of the in- and exclusion criteria and outcomes, and the median follow-ups of the studies varied between 1 and 12 years. In 2 studies, selection bias because of selective loss to follow-up could not be ruled out, because both studies reported >50% loss to follow-up without further reporting a comparison between the groups. Three studies did not apply the limitation of the number of risk factors to be 10% of the number of events. Blinded assessment was applied in 6 studies. The quality assessment showed NOS scores of 3 studies being 9, of 4 studies being 8 and of 4 studies being 7.

4. Synthesis of results:

4.1. Obstetrical factors:

Parity was reported by 7 studies, of which 2 reported parity as a continuous variable (per 1) and 5 as categorical. For parity as a categorical variable, a parity of 2 or higher compared with 0 or 1 was a significant risk factor in 4 studies. The categorical variables for parity could not be pooled because of differences in effect measures. Therefore, it is identified as a confirmed risk factor. The pooled OR for parity per 1 was not statistically significant (n=2, OR, 1.06; 95% CI, 0.39–2.89); see Fig. 2. Birthweight per 100 grams was a significant risk factor for primary POP (n=3, pooled OR, 1.04; 95% CI, 1.02–1.06); Fig. 2. Age at first delivery was reported by 3 studies, of which 1 study reported ages above 30 as a risk factor compared with age ≤24; see Fig. 2. Vaginal delivery was reported by 4 studies, of which 2 reported vaginal delivery as a continuous variable and 2 as a categorical variable. Compared with nulliparity, vaginal delivery was a significant risk factor in 2 studies and could therefore be identified as a confirmed risk factor. The pooled OR for vaginal delivery (per 1) was not statistically significant (n=2, OR, 1.33; 95% CI, 0.73–2.41); Fig. 3. Forceps delivery was reported as a significant risk factor and as a significant protective factor for primary POP compared with normal vaginal delivery.

4.2. Lifestyle factors:

BMI as a risk factor for primary POP was reported in 8 studies. Higher BMI as a categorical variable was a significant risk factor for primary POP in 4 studies, and 2 studies showed no statistically significant association. The pooled ORs for BMI 25–30 vs <25 kg/m^2 and ≥30 vs <25 kg/m^2 were statistically significant (OR, 1.52; 95% CI, 1.07–2.15 and OR, 1.75; 95% CI, 1.17–2.62, respectively). One study showed BMI ≥30 kg/m^2 to be a statistically significant protective factor compared with that <25 kg/m^2, but an index of 25–30 kg/m^2 was not

significant when compared with <25 kg/m^2 (Fig. 5). Smoking was found to be significantly protective against primary POP in 2 studies, and no association was found in 3 studies. Two studies could not be pooled because of different definitions or insufficient data.

4.3. Unmodifiable factors:

Age per 10 years was a statistically significant risk factor for primary POP in 3 out of 4 studies (n=3, pooled OR, 1.34; 95% CI, 1.23–1.47). Age as a categorical variable could not be pooled, but 2 studies showed older age to be a risk factor (Fig. 6). For ethnicity, 1 study showed Black ethnicity to be protective against POP, and 3 studies showed no association. of the 2 studies that could be pooled, the OR showed a borderline significant but small effect for Black ethnicity to be protective against primary POP (n=2, pooled OR, 0.96; 95% CI, 0.92–1.00).

4.4. Comorbidity:

Hormone replacement therapy was reported in 2 studies and was only once positively associated with primary POP (Fig. 7). Urinary incontinence (UI) was reported by 2 studies, of which 1 reported mixed and urge UI as significant risk factors for primary POP (Fig. 7). Pulmonary disease was reported by 2 studies and was not associated with primary POP (Fig. 7). Hysterectomy status was reported by 2 studies and was not associated with primary POP (n=2, pooled OR, 1.06; 95% CI, 0.73–1.54), Fig. 7. Regarding POP recurrence, pulmonary disease was reported by 2 studies that showed no statistical association, but only the data of univariable analyses were available (Fig. 8). Constipation was reported by 3 studies and was not statistically significant (n=3, OR, 0.95; 95% CI, 0.67–1.36), Fig. 8. Previous POP surgery was a significant risk factor for POP recurrence in 1 study, but only the data of univariable analyses were available (Fig. 8).

4.5. Social factors:

Education was reported by 5 studies, of which 2 studies reported that a higher form of education is protective against primary POP, but different definitions were used (Fig. 7).

4.6. Surgical factors:

The preoperative POP-Q stage was reported in 7 studies, of which 5 studies showed that preoperative stage III or IV was a statistically significant risk factor for POP recurrence when compared with stage ≤ II (n=5, pooled OR, 2.68; 95% CI, 1.93–3.73). One study reported that preoperative stage ≥ II was a significant risk factor when compared with stage < II

5. Result:

5.1. Principal findings:

By updating the systematic review and performing meta-analyses, we were able to present a comprehensive overview of the currently available literature on the risk factors for primary POP and POP recurrence. The results of our meta-analyses show that age, BMI, birthweight, and levator defect are identified as statistically significant risk factors for primary POP and vaginal delivery, and parity and levator hiatal area are identified as confirmed risk factors for primary POP. Cesarean delivery and smoking are significant protective factors for primary POP. For POP recurrence, younger age and preoperative POP-Q stage 3 or 4 are statistically significant risk factors.

5.2. Comparison with existing literature:

In the previous publication, risk factors were labeled as “confirmed risk factors” if the factors were significantly associated with POP or POP recurrence in a multivariable analysis in at least 2 studies.

In this current article, we supplemented the results by providing forest plots and meta-analyses. These forest plots gave more insight into several risk factors. For example, the forest plots showed a clear trend for a larger levator hiatal area to be a risk factor for primary POP, which was also labeled as a “confirmed risk factor.” In addition, if a risk factor could not be identified as a confirmed risk factor, eg, levator defect for POP recurrence, the forest plot still illustrates a borderline significant effect of the pooled result. By providing comprehensive forest plots, we give more insight into the results, and the effect of potential risk factors that could not be pooled because of differences in definitions and effect measures (ie, odds ratios, prevalence ratios, and hazard ratios) can still be easily interpreted.

They performed multivariable analysis for the effect of birthweight on levator defect, which was statistically significant and could eventually cause POP. Although the effect of birthweight in our meta-analysis seemed small (OR, 1.04), this was only the effect of an increase of 100 g. If we consider the effect of birthweight of 500 g instead of 100 g, the OR increases to 1.22, which indicates a clear effect with clinical significance. Levator defect has been a widely investigated subject, both as a risk factor and as an outcome measure. Our review is the first review confirming that levator defect is a risk factor for primary POP and POP recurrence by pooling the results into a meta-analysis. Not all studies concerning levator defect were included in this review because of insufficient data.

Concerning unmodifiable risk factors, in contradiction to the meta-analysis of Friedman et al, we pooled the results of age as a potential risk factor for prolapse recurrence.

In our forest plots, younger age was a clear risk factor for POP recurrence, and older age was a risk factor for developing primary POP. Women who are older simply have had more time to develop POP. As mentioned in the previous publication, hereditary tissue weakness could cause POP at a younger age and therefore cause recurrences at a younger age as well. Two recent meta-analyses reported family history as a risk factor for primary POP and POP recurrence.

In contrast to our review, these meta-analyses also included case–control studies, data of univariable analyses, and studies about POP recurrence after mesh surgery. On the basis of our inclusion criteria, we could not include other studies that reported this potential risk factor.

Despite the fact that the pooled OR for smoking was statistically significant, the protective effect of smoking should be interpreted with care. The results of the studies that reported smoking as nonsignificant could not be pooled because of differences in definitions or lacking data.

6. Strengths and limitations:

A strength of this review is the comprehensiveness of the review and meta-analyses with illustrating forest plots to summarize the best available evidence in this field. To the best of our knowledge, this is the first review to provide forest plots to give insight into the possible trends if the risk factors could not be pooled. Where most systematic reviews focus solely on one risk factor category, this systematic review included studies with all types of risk factors. We applied strict in- and exclusion criteria and only included studies with clear populations and outcome measures, multivariable analysis, and adequate follow-up to assure the best quality of the evidence.

7. Conclusions:

In this review, we summarize the evidence on the selection of publications with the strongest evidence on the risk factors for POP. Age, BMI, birthweight, and levator defect are statistically significant risk factors for primary POP, and delivery mode, parity, and levator hiatal area are confirmed risk factors for primary POP. Cesarean delivery and smoking are significant

protective factors against primary POP. For POP recurrence, younger age and higher preoperative POP-Q stage 3 and 4 are statistically significant risk factors.

Future research should focus on the identification of risk factors for POP recurrence. Although several studies have been performed identifying the risk factors for recurrence after mesh surgery, profound knowledge on risk factors after native tissue surgery is lacking. Future studies should also focus on the comparability of risk factors for anatomic outcome measures vs subjective or composite outcome measures. Furthermore, heterogeneity should be avoided by using definitions and outcome measures as used in previous studies. Thereby, future meta-analyses can be performed more accurately, and conclusions could be drawn with more certainty.

This meta-analysis may give clinicians and patients better insight into the individual risk of developing POP and POP recurrence after primary native tissue surgery. This knowledge can be helpful in the identification of high-risk patients and the development of preventive strategies. High-risk patients may need adjustment of counseling or treatment options and management of expectations.

8. References:

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