Risk factors for primary pelvic organ prolapse and prolapse recurrence: an updated systematic review and meta-analysis

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OBJECTIVE: To update a previously published systematic review and perform a meta-analysis on the risk factors for primary pelvic organ prolapse and prolapse recurrence.

DATA SOURCES: PubMed and Embase were systematically searched. We searched from July 1, 2014 until July 5, 2021. The previous search was from inception until August 4, 2014.

STUDY ELIGIBILITY CRITERIA: 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.

METHODS: 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.

RESULTS: After screening, 14 additional studies were selected—8 on the risk factors for primary prolapse and 6 on prolapse recurrence. Combined with the results from the previous review, 27 studies met the inclusion criteria, representing the data of 47,429 women. Not all studies could be pooled because of heterogeneity. Meta-analyses showed that birthweight (n=3, odds ratio, 1.04; 95% confidence interval, 1.02−1.06), age (n=3, odds ratio, 1.34; 95% confidence interval, 1.23−1.47), body mass index (n=2, odds ratio, 1.75; 95% confidence interval, 1.17−2.62), and levator defect (n=2, odds ratio, 3.99; 95% confidence interval, 2.57−6.18) are statistically significant risk factors, and cesarean delivery (n=2, pooled odds ratio, 0.08; 95% confidence interval, 0.03−0.20) and smoking (n=3, odds ratio, 0.59; 95% confidence interval, 0.46−0.75) are protective factors for primary prolapse. Parity, vaginal delivery, and levator hiatal area are identified as "confirmed risk factors." For prolapse recurrence, preoperative prolapse stage (n=5, odds ratio, 2.68; 95% confidence interval, 1.93−3.73) and age (n=2, odds ratio, 3.48; 95% confidence interval, 1.99−6.08) are statistically significant risk factors.

CONCLUSION: 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.

Key words: 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

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AJOG at a Glance

Why was this study conducted?

This study aimed to perform an update of a systematic review and perform a meta-analysis on the risk factors for primary pelvic organ prolapse (POP) and POP recurrence after native tissue surgery.

Key findings

The risk factors for primary POP are vaginal delivery, parity, birthweight, older age, body mass index, levator defect, and a larger levator hiatal area. Cesarean delivery and smoking are protective factors against primary POP. The risk factors for POP recurrence are younger age and preoperative prolapse stage 3 or 4.

What does this add to what is known?

This systematic review and meta-analysis provides a comprehensive overview on all types of risk factors and illustrates the results in forest plots.

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.[1] Studies show that women have a lifetime risk of 12.6% to undergo surgical correction for POP by the age of 80 years.[2] 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.[3]

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 al[4] identified 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.[5] 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.[6] 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.[7]

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.[8,9]

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.

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[7] 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.

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.

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.[10]

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,[11] packages meta[12] version 2.4-0, and forest plot[13] 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.[14,15] 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.

Results

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.[16] Three articles that were included in the previous review were now partly[17] or totally[18,19] excluded, because they used the same study population in a more recent publication or the country of investigation was not a Western developed one.[7] Three studies appeared to meet the inclusion criteria but were excluded, because no separate analysis was performed for anatomic POP recurrence.[20–22] 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 Figures 2–8. The results of the studies that could not be included in the forest plots are listed in the tables; see appendix B.

Study characteristics

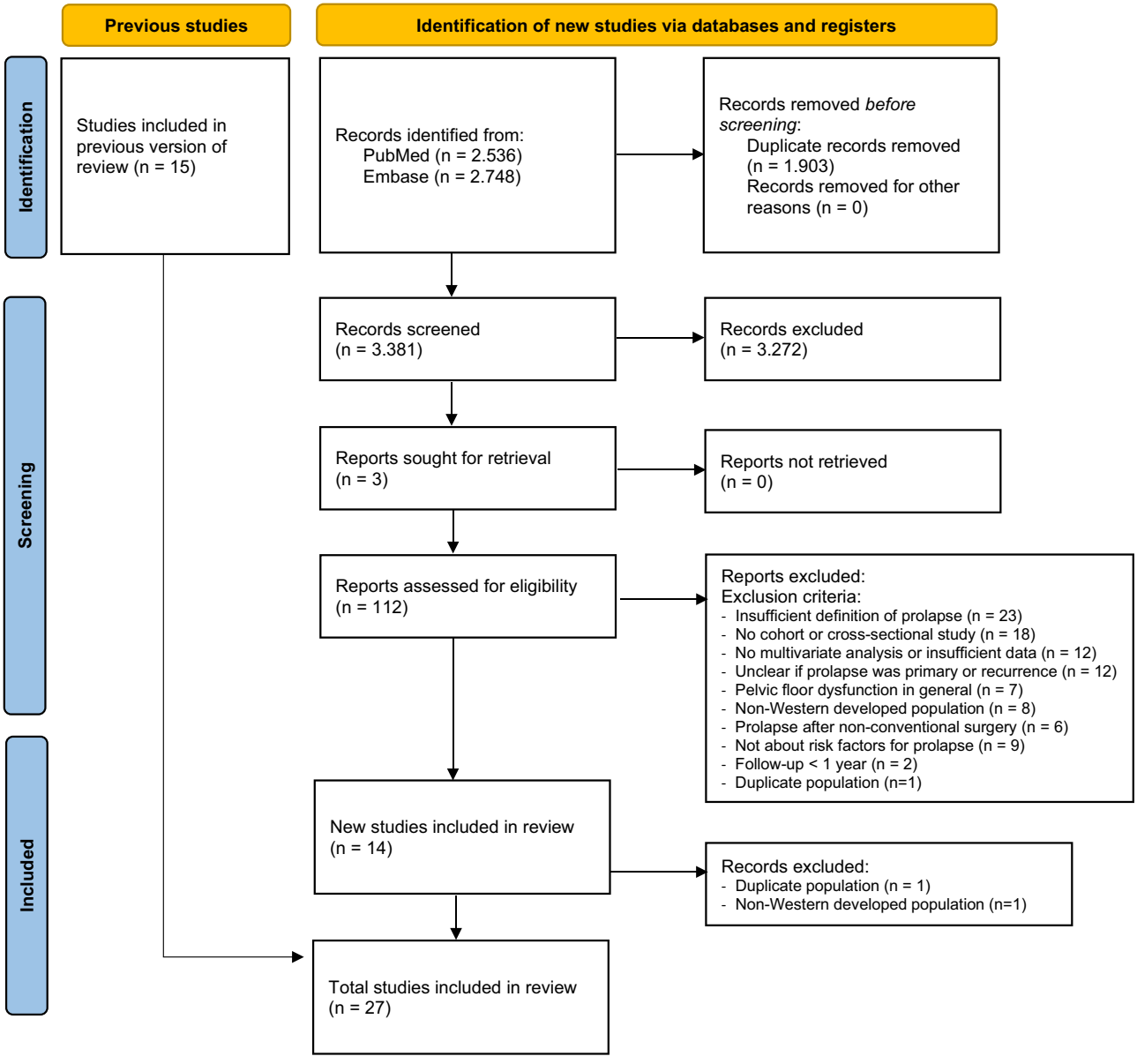
Studies on primary pelvic organ prolapse

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,[23–29] POP beyond the hymen in 5 studies,[30–34] degree 2 or 3 in the Baden-Walker classification in 1 study,[35] 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,[36] the most dependent point of the vaginal wall or the cervix to or beyond the hymen[16] and the most descended point of the vaginal wall −0.5 cm above the hymenal remnants in 1 study.[37] 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.

Studies on pelvic organ prolapse recurrence

The characteristics of the studies concerning POP recurrence are summarized in Table 2. In total, data on 2132 women were analyzed in 4 retrospective and 6 prospective cohort studies and 1 secondary analysis of an RCT. POP recurrence was defined as POP-Q stage 2 or higher in 10 studies[38–46] and as descent of the vaginal apex (point C of the POP-Q system) more than one-third into the vaginal canal or anterior or posterior vaginal wall descent beyond the hymen in 1 study.[47] See appendix table B.3 for the risk factors for POP recurrence.

FIGURE 1
Flow diagram of study selection process



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Risk of bias of included studies

Studies on primary prolapse

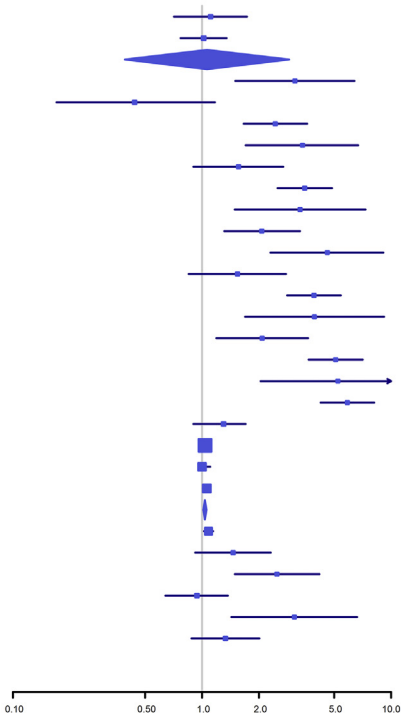
The overall quality of the articles was adequate; all the included articles had a sufficient description of in- and exclusion criteria and outcomes. In 15 articles, the number of risk factors for analysis was limited to 10% of the number of events; in 1 article, the 10% was exceeded.[33] Blinding was applied in 9 articles. Quality assessment showed NOS scores of 5 studies being 9,[24,25,27,28,34] that of another 5 studies being 8,[26,30,31,35,37] of 3 studies being 7,[29,33,36] of 1 study being 6,[16] and of 2 studies being 5.[23,32] A score of 7 or higher is considered high quality.

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.[45,46] Three studies did not apply the limitation of the number of risk factors to be 10% of the number of events.[38,41,42]

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

Risk factor	Definition		Study	I²	Est.	LL	UL
Parity[a]	Per 1	OR	Swift 2005		1.11	0.71	1.73
	Per 1	OR	Volloyhaug 2016		1.02	0.77	1.35
	Per 1	**OR**	**Pooled (2 studies)**	**0.00**	**1.06**	**0.39**	**2.89**
	1 vs. 0	OR	Parazzini 2000		3.1	1.5	6.4
	1 vs. 0	OR	Slieker-Ten Hove 2009		0.44	0.17	1.17
	1 vs. 0	HR	Kudish 2011		2.44	1.66	3.6
	2 vs. 0	OR	Parazzini 2000		3.4	1.7	6.7
	2 vs. 0	OR	Slieker-Ten Hove 2009		1.56	0.9	2.69
	2 vs. 0	HR	Kudish 2011		3.49	2.51	4.87
	2 vs. 1	OR	Glazener 2013		3.3	1.49	7.32
	2 vs. 1	HR	Blomquist 2018		2.07	1.31	3.3
	3 vs. 0	OR	Parazzini 2000		4.6	2.3	9.1
	3 vs. 0	OR	Slieker-Ten Hove 2009		1.54	0.85	2.78
	3 vs. 0	HR	Kudish 2011		3.91	2.82	5.42
	3 vs. 1	OR	Glazener 2013		3.93	1.69	9.18
	3 vs. 1	HR	Blomquist 2018		2.08	1.19	3.64
	4 vs. 0	HR	Kudish 2011		5.09	3.66	7.08
	4 vs. 1	OR	Glazener 2013		5.23	2.04	13.39
	5 vs. 0	HR	Kudish 2011		5.87	4.24	8.14
Birth weight	>4500gr vs. ≤4500gr	OR	Parazzini 2000		1.3	0.9	1.7
	Per 100 gram	OR	Swift 2005		1.04	1.01	1.06
	Per 100 gram	OR[b]	Urbankova 2019		1	1	1.11
	Per 100 gram	OR	Volloyhaug 2016		1.06	1.01	1.11
	Per 100 gram	**OR**	**Pooled (3 studies)**	**0.30**	**1.04**	**1.02**	**1.06**
Age first delivery	Per 1 year	OR	Urbankova 2019		1.08	1.02	1.14
	25-29 vs. ≤ 24	OR	Glazener 2013		1.46	0.92	2.31
	30-34 vs. ≤ 24	OR	Glazener 2013		2.49	1.49	4.18
	30-34 vs. < 30	HR	Blomquist 2018		0.94	0.64	1.37
	≥ 35 vs. ≤ 24	OR	Glazener 2013		3.08	1.43	6.61
	≥ 35 vs. < 30	HR	Blomquist 2018		1.33	0.88	2.01



For each study, the estimate, that is, odds ratio or hazard ratio with the corresponding 95% confidence interval, and if appropriate, the pooled results of random-effects meta-analysis, are shown. The *superscript letter a* denotes total number of births, *superscript letter b* denotes data of univariable analysis.

I2, the estimated between-study heterogeneity; *LL*, lower limit of 95% confidence interval; *POP*, pelvic organ prolapse; *UL*, upper limit of 95% confidence interval.

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Blinded assessment was applied in 6 studies. The quality assessment showed NOS scores of 3 studies being 9,[39,40,43] of 4 studies being 8[17,38,41,44] and of 4 studies being 7.[42,45–47]

Synthesis of results

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.[30,34–36] 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);[27,37] see Figure 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);[26,27,37] Figure 2.

Age at first delivery was reported by 3 studies, of which 1 study[34] reported ages above 30 as a risk factor compared with age ≤24; see Figure 2.

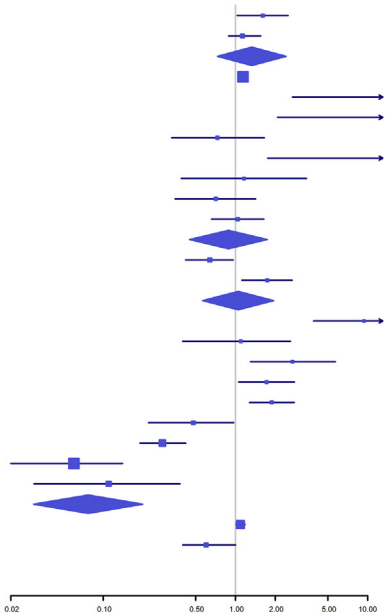
Vaginal delivery was reported by 4 studies, of which 2 reported vaginal delivery as a continuous variable and 2 as a categorical variable. Compared with nulliparity, vaginal delivery was a significant risk factor in 2 studies[24,29] and could therefore be identified as a confirmed risk factor. The pooled OR for vaginal delivery (per 1) was not statistically significant (n=2, OR, 1.33; 95% CI, 0.73−2.41);[24,37] Figure 3.

Forceps delivery was reported as a significant risk factor and as a significant protective factor for primary POP compared with normal vaginal delivery.[28,34] The results were pooled, because both studies corrected for the same confounders. The pooled OR was not statistically significant (n=2, pooled OR, 1.05; 95% CI, 0.57−1.94).[28,34] In combination with levator defect, forceps delivery was a strong significant risk factor in 1 study.[31] One study reported on "operative vaginal delivery" (ie, forceps and vacuum delivery), which was a risk factor when compared with normal vaginal delivery.[30] No significant association was found between vacuum delivery and primary POP (n=2, pooled OR, 0.88; 95% CI, 0.45−1.73);[28,34] Figure 3.

Cesarean delivery was reported by 5 studies, of which 3 compared it with normal vaginal delivery and reported a

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

Risk factor	Definition		Study	I^2	Est.	LL	UL
Delivery mode	Per 1 vaginal delivery[a]	OR	Nygaard 2004		1.61	1.03	2.5
	Per 1 vaginal delivery[a]	OR	Swift 2005		1.13	0.89	1.55
	Per 1 vaginal delivery[a]	**OR**	**Pooled (2 studies)**	**0.43**	**1.33**	**0.73**	**2.41**
	Vaginal delivery[b] vs. Nulliparous	PR	Whitcomb 2009		1.14	1.08	1.2
	1 or 2 vaginal deliveries[a] vs. Nulliparous	OR	Nygaard 2004		25	2.7	250
	3 or 4 vaginal deliveries[a] vs. Nulliparous	OR	Nygaard 2004		20	2.08	200
	3 or 4 vaginal deliveries vs. 1 or 2 vaginal deliveries[a]	OR	Nygaard 2004		0.73	0.33	1.65
	≥5 vaginal deliveries[a] vs. Nulliparous	OR	Nygaard 2004		16.67	1.75	142.86
	≥5 vaginal deliveries vs. 1 or 2 vaginal deliveries[a]	OR	Nygaard 2004		1.16	0.39	3.44
	Vacuum[c] vs. Normal vaginal delivery[a]	OR	Glazener 2013		0.71	0.35	1.42
	Vacuum[c] vs. Normal vaginal or cesarean delivery	OR	Volloyhaug 2015		1.04	0.66	1.64
	Vacuum[c] vs. Normal vaginal delivery[c]	**OR**	**Pooled (2 studies)**	**0.00**	**0.88**	**0.45**	**1.73**
	Forceps[c] vs. Normal vaginal delivery[a]	OR	Glazener 2013		0.64	0.42	0.96
	Forceps[c] vs. Normal vaginal or cesarean delivery	OR	Volloyhaug 2015		1.74	1.12	2.68
	Forceps[c] vs. Normal vaginal delivery[c]	**OR**	**Pooled (2 studies)**	**0.91**	**1.05**	**0.57**	**1.94**
	Forceps[c] and avulsion vs. No forceps and no avulsion	OR	Handa 2019		9.4	3.9	22.5
	Forceps[c] and no avulsion vs. No forceps and no avulsion	OR	Handa 2019		1.1	0.4	2.6
	No forceps and avulsion vs. No forceps and no avulsion	OR	Handa 2019		2.7	1.3	5.7
	Forceps[c] vs. Vacuum[c]	OR	Volloyhaug 2015		1.72	1.06	2.79
	Operative vaginal delivery vs. NVD[c]	HR	Blomquist 2018		1.88	1.28	2.78
	Vaginal delivery and cesarean vs. NVD[a]	OR	Glazener 2013		0.48	0.22	0.97
	Cesarean[d] vs. Normal vaginal delivery[c]	HR	Blomquist 2018		0.28	0.19	0.42
	Cesarean[d] vs. Normal vaginal delivery[c]	OR	Volloyhaug 2015		0.06	0.02	0.14
	Cesarean[d] vs. Normal vaginal delivery[a]	OR	Glazener 2013		0.11	0.03	0.38
	Cesarean[d] vs. Normal vaginal delivery	**OR**	**Pooled (2 studies)**	**0.00**	**0.08**	**0.03**	**0.2**
	Cesarean[d] vs. Nulliparous	PR	Whitcomb 2009		1.09	1.01	1.18
	Cesarean vs. No cesarean[b]	OR	Parazzini 2000		0.6	0.4	1



For each study, the estimate, that is, odds ratio, hazard ratio, or prevalence ratio with the corresponding 95% confidence interval, and if appropriate, the pooled results of random-effects meta-analysis, are shown. The *superscript letter a* denotes exclusive vaginal delivery, *superscript letter b* denotes delivery mode not further specified, *superscript letter c* denotes mixed delivery modes, *superscript letter d* denotes exclusive cesarean delivery.

I2, the estimated between-study heterogeneity; *LL*, lower limit of 95% confidence interval; *POP*, pelvic organ prolapse; *UL*, upper limit of 95% confidence interval.

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significant protective effect.[28,30,34] Only 2 of 3 studies could be pooled because of different effect measures. Cesarean delivery was statistically significantly protective against primary POP when compared with normal vaginal delivery (n=2, pooled OR, 0.08; 95% CI, 0.03−0.20);[28,34] Figure 3.

For prolapse recurrence, parity per 1 was not statistically significant (n=2, pooled OR, 0.96; 95% CI, 0.76−1.2).[17,43] Birthweight >4500 g was a significant risk factor for prolapse recurrence in 1 of the 2 studies.[39] Birthweight could not be pooled because of different definitions, but there seems to be a trend. For complicated delivery (ie, instrumental delivery with vacuum or forceps and/or a large vaginal laceration), only 2 of 3 studies could be pooled because of not correcting for preoperative POP-Q stage in 1 study.[42] The pooled OR for complicated delivery was not statistically significant (n=2, pooled OR, 0.90; 95% CI, 0.34−2.37);[39,44] Figure 4.

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[29,35−37], and 2 studies showed no statistically significant association.[30,34] 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[34,37] and OR, 1.75; 95% CI, 1.17−2.62,[34,37] 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[24] (Figure 5).

Smoking was found to be significantly protective against primary POP in 2 studies[25,36], and no association was found in 3 studies.[24,35,36] Two studies could not be pooled because of different definitions[35] or insufficient data.[24] The results of the meta-analysis showed a statistically significantly protective effect of smoking. (n=3, pooled OR currently smoking vs never, 0.59; 95% CI, 0.46−0.75[25,36,37]; n=2, pooled OR past vs never, 0.78; 95% CI, 0.67−0.90[36,37]), Figure 5.

Physical activity was reported by 3 studies, of which 1 reported a borderline significant effect of more activity to be a risk factor for primary POP.[33] The results of the studies could not be pooled because of differences in definitions (Figure 5).

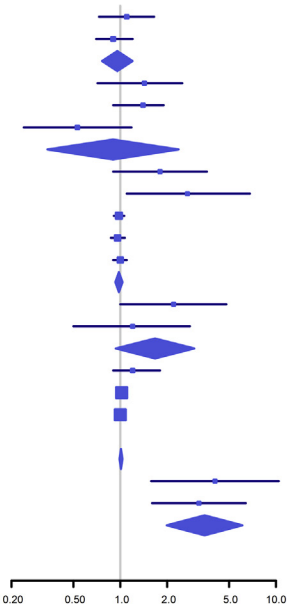
For POP recurrence, BMI was neither statistically significant as a categorical variable (n=2, BMI >30 vs ≤30, 1.67; 95% CI, 0.94−2.98)[39,41] nor as a continuous variable (n=3, pooled OR, 0.98; 95% CI, 0.93−1.03).[17,40,43] However, a slight trend can be observed in the forest plot for BMI >30 vs ≤30 kg/m^2 (Figure 4).

Unmodifiable factors

Age per 10 years was a statistically significant risk factor for primary POP in 3

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

Risk factor	Definition		Study	I²	Est.	LL	UL
Parity	Per 1	OR[a]	Vergeldt 2015		1.1	0.73	1.65
	Per 1	OR[a]	Weemhoff 2012		0.9	0.7	1.2
	Per 1	**OR**	**Pooled (2 studies)**	**0.00**	**0.96**	**0.76**	**1.2**
Complicated delivery	Yes vs. No	OR	Manodoro 2018		1.43	0.71	2.5
	Yes vs. No	OR	Tegerstedt 2004		1.4	0.9	1.9
	Yes vs. No	OR	Vergeldt 2016		0.53	0.24	1.18
	Yes vs. No	**OR**	**Pooled (2 studies)**	**0.73**	**0.9**	**0.34**	**2.37**
Birth weight	> 4000gr vs. ≤ 4000gr	OR[a]	Salvatore 2009		1.8	0.9	3.6
	> 4500gr vs. ≤ 4500gr	OR	Manodoro 2018		2.7	1.1	6.8
BMI	Per kg/m²	OR	Oversand 2019		0.98	0.91	1.06
	Per kg/m²	OR[a]	Vergeldt 2015		0.96	0.87	1.07
	Per kg/m²	OR[a]	Weemhoff 2012		1	0.9	1.1
	Per kg/m²	**OR**	**Pooled (3 studies)**	**0.00**	**0.98**	**0.93**	**1.03**
	> 30 vs. ≤ 30	OR	Manodoro 2018		2.2	1	4.8
	> 30 vs. ≤ 30	OR	Salvatore 2009		1.2	0.5	2.8
	> 30 vs. ≤ 30	**OR**	**Pooled (2 studies)**	**0.04**	**1.67**	**0.94**	**2.98**
	> 25 vs. ≤ 25	OR[a]	Tegerstedt 2004		1.2	0.9	1.8
Age	Per 1 year	OR	Oversand 2019		1.02	0.99	1.05
	Per 1 year	OR[a]	Vergeldt 2015		1	0.97	1.03
	Per 1 year	OR[a]	Weemhoff 2012		1	1	1
	Per 1 year	**OR**	**Pooled (3 studies)**	**0.00**	**1.01**	**0.99**	**1.03**
	< 60 vs. ≥ 60	OR	Diez-Itza 2007		4.06	1.58	10.42
	< 60 vs. ≥ 60	OR	Whiteside 2004		3.2	1.6	6.4
	< 60 vs. ≥ 60	**OR**	**Pooled (2 studies)**	**0.00**	**3.48**	**1.99**	**6.08**



For each study, the estimate, that is, odds ratio with the corresponding 95% confidence interval, and if appropriate, the pooled results of random-effects meta-analysis, are shown. The *superscript letter a* denotes data of univariable analysis.

BMI, body mass index; *I2*, the estimated between-study heterogeneity; *LL*, lower limit of 95% confidence interval; *POP*, pelvic organ prolapse; *UL*, upper limit of 95% confidence interval.

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out of 4 studies (n=3, pooled OR, 1.34; 95% CI, 1.23−1.47).[29,36,37] Age as a categorical variable could not be pooled, but 2 studies showed older age to be a risk factor[24,35] (Figure 6).

For ethnicity, 1 study showed Black ethnicity to be protective against POP,[36] and 3 studies showed no association.[29,30,37] 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),[29,37] Figure 6.

Menopausal status was reported by 2 studies.[25,37] It was not statistically associated with primary POP, and the results could not be pooled because of high heterogeneity, though a slight trend can be observed (Figure 6).

For POP recurrence, age per 1 year was not statistically significant (n=3, pooled OR, 1.01; 95% CI, 0.99−1.03).[17,40,43] Age <60 years was a risk factor for POP recurrence compared with age ≥60 years (n=2, pooled OR, 3.48; 95% CI, 1.99−6.08),[38,45] Figure 4.

Comorbidity

Hormone replacement therapy was reported in 2 studies and was only once positively associated with primary POP (Figure 7).[36]

Urinary incontinence (UI) was reported by 2 studies, of which 1 reported mixed and urge UI as significant risk factors for primary POP (Figure 7).[36]

Pulmonary disease was reported by 2 studies and was not associated with primary POP (Figure 7).[33,36]

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),[27,37] Figure 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 (Figure 8).[41,42]

Constipation was reported by 3 studies and was not statistically significant (n=3, OR, 0.95; 95% CI, 0.67−1.36),[17,41,42] Figure 8.

Previous POP surgery was a significant risk factor for POP recurrence in 1 study,[42] but only the data of univariable analyses were available (Figure 8).

Social factors

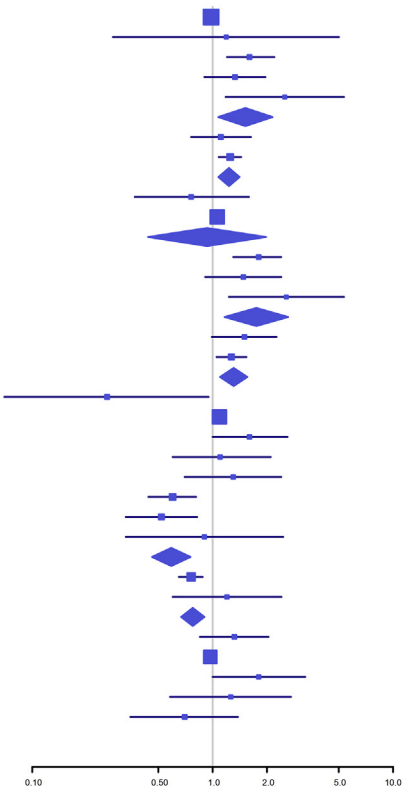
Education was reported by 5 studies, of which 2 studies reported that a higher form of education is protective against primary POP,[24,35] but different definitions were used (Figure 7).

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).[38,40,41,44,45] One study reported that preoperative stage ≥

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

Risk factor	Definition		Study	I²	Est.	LL	UL
BMI	Per kg/m²	OR	Volloyhaug 2016		0.98	0.94	1.03
	< 18.5 vs. < 25	OR	Glazener 2013		1.19	0.28	5.01
	23.8-27.2 vs. < 23.8	OR	Parazzini 2000		1.6	1.2	2.2
	25-30 vs. < 25	OR	Glazener 2013		1.33	0.9	1.96
	25-30 vs. < 25	OR	Swift 2005		2.51	1.18	5.35
	25-30 vs. < 25	**OR**	**Pooled (2 studies)**	**0.53**	**1.52**	**1.07**	**2.15**
	25-30 vs. < 25	HR	Blomquist 2018		1.11	0.76	1.63
	25-30 vs. < 25	HR	Kudish 2011		1.25	1.08	1.44
	25-30 vs. < 25	**HR**	**Pooled (2 studies)**	**0.00**	**1.23**	**1.08**	**1.41**
	25-30 vs. < 25	PR	Nygaard 2021		0.76	0.37	1.59
	25-30 vs. < 25	PR	Whitcomb 2009		1.06	1.01	1.11
	25-30 vs. < 25	**PR**	**Pooled (2 studies)**	**0.00**	**0.93**	**0.44**	**1.98**
	> 27.2 vs. < 23.8	OR	Parazzini 2000		1.8	1.3	2.4
	≥ 30 vs. < 25	OR	Glazener 2013		1.48	0.91	2.4
	≥ 30 vs. < 25	OR	Swift 2005		2.56	1.23	5.35
	≥ 30 vs. < 25	**OR**	**Pooled (2 studies)**	**0.33**	**1.75**	**1.17**	**2.62**
	≥ 30 vs. < 25	HR	Blomquist 2018		1.5	0.99	2.26
	≥ 30 vs. < 25	HR	Kudish 2011		1.27	1.05	1.54
	≥ 30 vs. < 25	**HR**	**Pooled (2 studies)**	**0.00**	**1.31**	**1.1**	**1.56**
	≥ 30 vs. < 25	PR	Nygaard 2021		0.26	0.07	0.95
	≥ 30 vs. < 25	PR	Whitcomb 2009		1.09	1.04	1.14
Smoking	< 10 vs. 0	OR	Parazzini 2000		1.6	1	2.6
	10-20 vs. 0	OR	Parazzini 2000		1.1	0.6	2.1
	> 20 vs. 0	OR	Parazzini 2000		1.3	0.7	2.4
	Currently vs. Never	OR	Kudish 2011		0.6	0.44	0.81
	Currently vs. Never	OR	Slieker 2009		0.52	0.33	0.82
	Currently vs. Never	OR	Swift 2005		0.9	0.33	2.46
	Currently vs. Never	**OR**	**Pooled (3 studies)**	**0.00**	**0.59**	**0.46**	**0.75**
	Past vs. Never	OR	Kudish 2011		0.76	0.65	0.88
	Past vs. Never	OR	Swift 2005		1.2	0.6	2.41
	Past vs. Never	**OR**	**Pooled (2 studies)**	**0.37**	**0.78**	**0.67**	**0.9**
Physical activity	Current heavy work vs. No	OR	Slieker-Ten Hove 2009		1.32	0.85	2.04
	Unknown	HR	Kudish 2011		0.97	0.92	1.03
	MVPA 53-82 vs. 9-53 min/day	PR	Nygaard 2021		1.8	1	3.26
	MVPA 82-159 vs. 9-53 min/day	PR	Nygaard 2021		1.26	0.58	2.72
	MVPA 82-159 vs. 53-82 min/day	PR	Nygaard 2021		0.7	0.35	1.38



For each study, the estimate, that is, odds ratio or hazard ratio with the corresponding 95% confidence interval, and if appropriate, the pooled results of random-effects meta-analysis, are shown.

BMI, body mass index; *I2*, the estimated between-study heterogeneity; *LL*, lower limit of 95% confidence interval; *MVPA*, moderate to vigorous physical activity; *POP*, pelvic organ prolapse; *UL*, upper limit of 95% confidence interval.

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II was a significant risk factor when compared with stage < II (Figure 4).[39]

Concomitant surgery was reported by 3 studies, of which 1 showed a borderline significant protective effect of posterior colporrhaphy[39] on developing POP recurrence and 1 showed sacrospinous hysteropexy to be a significant risk factor.[17]

Pelvic floor factors

For primary POP, 3 studies reported that levator defect was a statistically significant risk factor (n=2, pooled OR, 3.99; 95% CI, 2.57−6.18),[27,31] Figure 7.

An increased levator hiatal area on Valsalva was a statistically significant risk factor for primary POP in 2 out of 2 studies.[23,27] The results could not be pooled because of differences in definitions, but it can be identified as a confirmed risk factor (Figure 7).

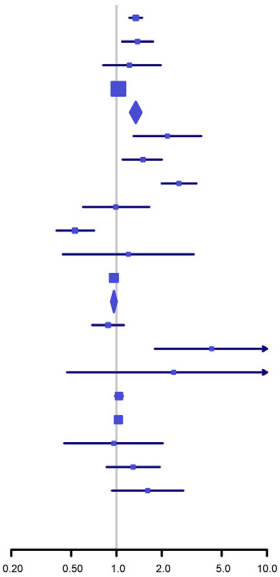
Regarding POP recurrence, levator defect was a statistically significant risk factor in the study by Weemhoff et al,[17] but in the combined study with the results of another database,[44] the OR was no longer statistically significant. Levator defect was not statistically associated with POP recurrence in the 2 studies in our meta-analysis, but the results of our meta-analysis did show a borderline significant effect (n=2, pooled OR, 1.5; 95% CI 1.00−2.25),[40,44] Figure 8. Other pelvic floor factors were only investigated once; see appendix B.

GRADE certainty of the evidence

The GRADE approach was applied on the statistically significant pooled results.[14,15] The certainty of the evidence for primary POP was judged to be "very low" for BMI (OR, 25−30 vs <25 kg/m^2) and smoking (currently vs never). It was judged to be "low" for age, BMI (HR, 25−30 vs <25 kg/m^2 and OR/HR, ≥30 vs <25 kg/m^2), smoking (past vs never), and birthweight. The certainty of evidence was judged as "moderate" for cesarean delivery and levator defect. Regarding POP recurrence, the certainty of evidence for age and preoperative POP-Q stage was judged as "low." The evidence was downgraded for serious imprecision (small sample size) and

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

Risk factor	Definition		Study	I^2	Est.	LL	UL
Age	Per 10 years	OR	Kudish 2011		1.34	1.22	1.48
	Per 10 years	OR	Swift 2005		1.38	1.09	1.75
	Per 10 years	OR	Volloyhaug 2016		1.22	0.82	1.97
	Per 10 years	PR	Whitcomb 2009		1.03	1.01	1.05
	Per 10 years	**OR**	**Pooled (3 studies)**	**0.00**	**1.34**	**1.23**	**1.47**
	≥30.4 vs. <30.4	PR	Nygaard2021		2.18	1.3	3.66
	52-55 vs. ≤ 51	OR	Parazzini 2000		1.5	1.1	2
	≥ 56 vs. ≤ 51	OR	Parazzini 2000		2.6	2	3.4
Ethnicity	Black vs. White	HR	Blomquist 2018		0.99	0.6	1.65
	Black vs. White	HR	Kudish 2011		0.53	0.4	0.71
	Black vs. White	OR	Swift 2005		1.2	0.44	3.26
	Black vs. White	OR	Whitcomb 2009		0.96	0.93	1.01
	Black vs. White	**OR**	**Pooled (2 studies)**	**0.0**	**0.96**	**0.92**	**1**
	Hispanic vs. White	HR	Kudish 2011		0.88	0.69	1.12
	Hispanic vs. White	OR	Swift 2005		4.29	1.8	10.2
	Other vs. White	OR	Swift 2005		2.4	0.47	12.1
	Asian vs. Black	OR	Whitcomb 2009		1.04	0.98	1.1
	Hispanic vs. Black	OR	Whitcomb 2009		1.03	0.98	1.08
	Hispanic vs. Non-Hispanic	PR	Nygaard 2021		0.96	0.45	2.03
Menopausal status	Yes vs. No	OR	Slieker 2009		1.29	0.86	1.94
	Yes vs. No	OR[a]	Swift 2005		1.61	0.93	2.78



For each study, the estimate, that is, odds ratio, hazard ratio, or prevalence ratio with the corresponding 95% confidence interval, and if appropriate, the pooled results of random-effects meta-analysis, are shown. The *superscript letter a* denotes data of univariable analysis.

I^2, the estimated between-study heterogeneity; *LL*, lower limit of 95% confidence interval; *POP*, pelvic organ prolapse; *UL*, upper limit of 95% confidence interval.

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inconsistency (because of high heterogeneity or effect estimates in contradicting directions and crossing the line of no effect). The evidence for cesarean delivery, levator defect, and age (for POP recurrence) were upgraded because of a large magnitude of effect (OR>3 or <0.3). Details about the GRADE assessment are provided in appendix 3.

Comment

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.

Comparison with existing literature

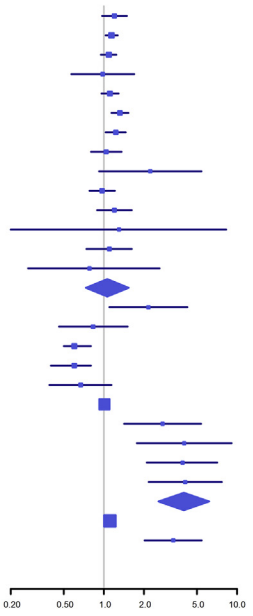
In the previous publication, risk factors were labeled as "confirmed risk factors" if the factors were significantly associated with POP or POP recurrence in a multivariable analysis in at least 2 studies.[4] In this current article, we supplemented the results by providing forest plots and meta-analyses. 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.

On the contrary, the forest plots also show inconsistencies between studies that used the same definitions for risk factors. This inconsistency is clearly present for the potential risk factor forceps delivery. In one study, it is significantly associated with developing primary POP, but in the other study, it is significantly protective against developing POP. Comparable inconsistencies were found in the meta-analysis by Leng et al[48] even though they analyzed vacuum and forceps delivery in a combined factor. The systematic review by Cattani et al[5] stated that forceps delivery is a risk factor for primary POP, but in contrast to our present review, they included studies that did not make a clear distinction between women with primary POP and women who already had a history of POP surgery. Although the results of our meta-analysis on forceps delivery were not conclusive in showing

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

Risk factor	Definition		Study	I^2	Est.	LL	UL
HRT	Current vs. Never	HR	Kudish 2011		1.2	0.97	1.49
	E+P vs. Placebo	HR	Kudish 2011		1.14	1.03	1.27
	Past vs. Never	HR	Kudish 2011		1.09	0.95	1.24
	Ever vs. Never	OR	Swift 2005		0.98	0.57	1.69
Urinary incontinence	Stress UI vs. Never	HR	Kudish 2011		1.11	0.96	1.29
	Urge UI vs. Never	HR	Kudish 2011		1.32	1.14	1.53
	Mixed UI vs. Never	HR	Kudish 2011		1.23	1.03	1.46
	Other UI vs. Never	HR	Kudish 2011		1.04	0.8	1.36
	UI surgery vs. No	OR	Slieker-Ten Hove 2009		2.23	0.92	5.41
Pulmonary disease	Astma vs. No	HR	Kudish 2011		0.97	0.78	1.21
	Emphysema vs. No	HR	Kudish 2011		1.2	0.89	1.62
	Chronic cough vs. No at 5-10 weeks postpartum	PR[a]	Nygaard 2021		1.3	0.2	8.29
Hysterectomy status	Yes vs. No	OR[a]	Swift 2005		1.1	0.74	1.62
	Yes vs. No	OR	Volloyhaug 2016		0.78	0.27	2.62
	Yes vs. No	**OR**	**Pooled (2 studies)**	**0.00**	**1.06**	**0.73**	**1.54**
Education	≤ High school vs. > High school	OR	Nygaard 2004		2.16	1.1	4.24
	Professional vs. ≤ College	PR	Nygaard 2021		0.83	0.46	1.51
	Intermediate vs. Elementary school	OR	Parazzini 2000		0.6	0.5	0.8
	High school/university vs. Elementary school	OR	Parazzini 2000		0.6	0.4	0.8
	Intermediate school vs. unknown	OR	Slieker-Ten Hove 2009		0.67	0.39	1.14
	≥ College vs. < College	PR	Whitcomb 2009		1.01	0.98	1.05
Levator defect	Unilateral avulsion vs. No avulsion	OR	Dietz 2012		2.76	1.42	5.37
	Bilateral avulsion vs. No avulsion	OR	Dietz 2012		4.01	1.77	9.1
	Avulsion vs. No avulsion	OR	Handa 2019		3.9	2.1	7.1
	Avulsion vs. No avulsion	OR	Volloyhaug 2016		4.08	2.17	7.69
	Avulsion vs. No avulsion	**OR**	**Pooled (2 studies)**	**0.00**	**3.99**	**2.57**	**6.18**
Levator hiatal area	Per cm²	OR	Dietz 2012		1.11	1.08	1.14
	> 40cm² vs. ≤ 40cm²	OR	Volloyhaug 2016		3.32	2.02	5.43



For each study, the estimate, that is, odds ratio, hazard ratio, or prevalence ratio with the corresponding 95% confidence interval, and if appropriate, the pooled results of random-effects meta-analysis, are shown. The *superscript letter a* denotes data of univariable analysis.

HRT, hormone replacement therapy; *I2*, the estimated between-study heterogeneity; *LL*, lower limit of 95% confidence interval; *POP*, pelvic organ prolapse; *UL*, upper limit of 95% confidence interval.

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a direct link between forceps delivery and POP, several studies outside the scope of this systematic review have identified forceps delivery as a risk factor for levator injury.[49] In turn, on the basis of our results, levator defect is identified as a risk factor for primary POP.

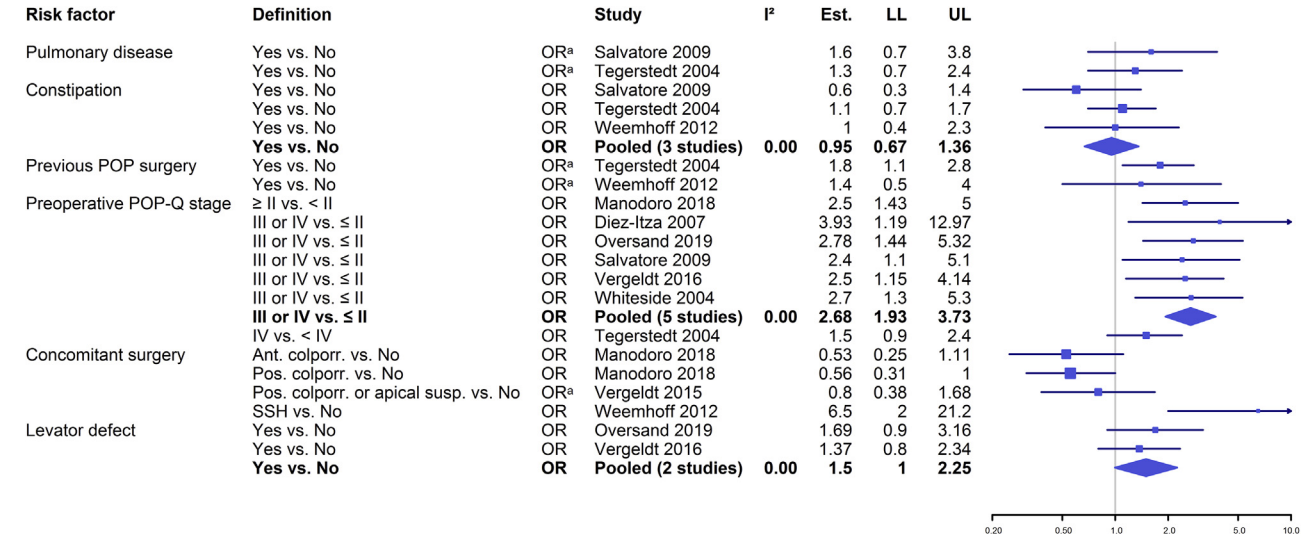
The results for BMI were also contradictory. For primary POP, it is a clear risk factor, but this could not be concluded for POP recurrence. The role of BMI on POP and POP recurrence has been investigated several times in the past decade. For primary POP, 2 studies reported BMI as a risk factor.[50,51] On the contrary, the systematic review by Zenebe et al[52] found no association between BMI and primary POP. This difference might be because of broader inclusion criteria for the definition of POP. For POP recurrence, Friedman et al[6] performed a systematic review and meta-analysis on BMI as a risk factor. They found that a higher BMI was not statistically significantly associated with POP recurrence, but a trend could be observed, which is in line with our results. In contrast, the large cohort study of Weltz et al[53] showed that BMI was a risk factor for reoperation in the anterior compartment. They found a trend for the apical and posterior compartment. We did not include studies with reoperation as an outcome measure, and therefore we cannot compare the results.

Obstetrical risk factors have been researched in multiple studies. Firstly, vaginal delivery seems to be an indisputable risk factor, which is confirmed by several reviews.[5,48,54–56] The literature on birthweight as a risk factor for POP has been contradictory so far. Our review shows that there is a significant association, which confirms the findings of the large study by Martinho et al.[57] 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.[6] 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

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



For each study, the estimate, that is, odds ratio or hazard ratio with the corresponding 95% confidence interval, and if appropriate, the pooled results of random-effects meta-analysis, are shown. The *superscript letter a* denotes data of univariable analysis.

I2, the estimated between-study heterogeneity; *LL*, lower limit of 95% confidence interval; *POP*, pelvic organ prolapse; *UL*, upper limit of 95% confidence interval.

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recurrences at a younger age as well. Two recent meta-analyses reported family history as a risk factor for primary POP and POP recurrence.[6,58] 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.

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.

We acknowledge some limitations of this review. First, we excluded studies that reported merely on composite outcome measures (ie, the combination of POP-Q, bothersome bulge, and/or retreatment) without reporting analyses for anatomic outcome measures separately.[20−22] Our review focused on anatomic outcomes, because we conformed to the previously set outcome measure. Subjective outcome measures may be confounded by spectrum bias.[52] In fact, approximately 8% of women report bothersome bulge symptoms without having an anatomic or objective prolapse.[59,60] It would be interesting to see whether the risk factors for subjective prolapse are applicable for anatomic prolapse also. Reoperation, on the other hand, is a reliable outcome measure that could have been included in the systematic review. Considering the extent of the systematic review, we decided to use the same outcome measures for primary POP and POP recurrence.

Another possible limitation of our review is that in contrast with other systematic reviews, we excluded the studies that reported on risk factors for recurrence after mesh surgeries. In our opinion, most cases in which mesh surgery is applied are complex and should not be compared with the group of women who undergo their first native tissue surgery. We also excluded studies from non-Western developed countries, because the population of women and exposition to risk factors in developing countries may not be comparable with those in Western developed countries. For example, a recent study reported that among others, anemia and carrying heavy objects for more than 5 hours a day are risk factors for developing POP[61]. Furthermore, we excluded case−control studies to select the studies with the best evidence and smaller risk of selection bias. Therefore, studies on

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,[35] 2000 Italy	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,[24] 2004 United States	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,[37] 2005 United States	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,[25] 2009 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, prolapse during pregnancy	Smoking, physical activity, education, parity, menopausal status, family history, UI, prolapse during pregnancy
Whitcomb et al,[29] 2009 United States	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,[36] 2011 United States	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,[23] 2012 Australia	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,[16] 2012 United States	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

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(continued)

TABLE 1
Included articles on primary pelvic organ prolapse *(continued)*

Reference	Study type	N/n	Inclusion criteria	Investigated risk factors	Adjustment variables
Glazener et al,[34] 2013 United Kingdom/ New Zealand	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,[28] 2015 Norway	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,[27] 2016 Norway	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,[30] 2018 United States	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
Handa et al,[31] 2019 United States	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,[32] 2019 United States	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,[26] 2019 Czech republic	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,[33] 2021 United States	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.

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TABLE 2
Included articles on pelvic organ prolapse recurrence

Reference	Study type	N/n	Inclusion criteria	Follow-up	Investigated risk factors	Adjustment variables
Tegerstedt and Hammarström,[42] 2004 Sweden	Retrospective cohort study	128/56	Women who had prolapse surgery (Manchester procedure, anterior colporrhaphy, posterior colporrhaphy, cervix amputation, vaginal hysterectomy, enterocele repair, abdominal vaginosacropexy or combinations)	10–12 y	Age, BMI, smoking, heavy lifting, complicated delivery, UI, incomplete emptying of bladder, pulmonary disease, constipation, fecal incontinence, preoperative stage, previous pelvic floor surgery, surgeon's experience	Age and BMI
Whiteside et al,[45] 2004 United States	Prospective cohort study	176/102	Women who underwent anterior colporrhaphy with or without hysterectomy, posterior colporrhaphy, bladder neck plication, vaginal vault suspension, enterocele repair, culdoplasty, bladder neck suspension, or retropubic paravaginal defect repair	1 y	Age, preoperative stage, hysterectomy status, number of sites involved, UI, previous prolapse surgery, menopausal status, diabetes, site of most advanced preoperative prolapse, previous incontinence surgery	Age, preoperative POP-Q stage
Diez-Itza et al,[38] 2007 Spain	Retrospective cohort study	134/42	Women who had vaginal hysterectomy, anterior colporrhaphy, or posterior colporrhaphy for prolapse	5 y	Age, BMI, weight, physical activity, parity, family history, pulmonary disease, constipation, preoperative POP-Q stage, surgeon's experience, abdominal hernias, and levator muscle contraction	Age, BMI, physical activity, parity, preoperative POP-Q stage, and pulmonary disease
Salvatore et al,[41] 2009 Italy	Prospective cohort study	360/36	Women who underwent prolapse surgery without using grafts (vaginal hysterectomy, and/or anterior colporrhaphy and/or posterior colporrhaphy)	26 mo	Age, BMI, parity, birthweight, menopausal status, preoperative stage, hysterectomy status, pulmonary disease, constipation, genital hiatus	Not described
Weemhoff et al,[17] 2012 The Netherlands	Prospective cohort study	156/80	Women who underwent anterior colporrhaphy with or without hysterectomy, posterior colporrhaphy, or sacrospinous fixation	2 y	Age, BMI, parity, family history, constipation, previous prolapse surgery, concomitant surgery	Family history, preoperative POP-Q stage, sacrospinous hysteropexy, levator defect
Wong et al,[46] 2014 United States	Retrospective cohort study	83/46	Women who underwent anterior colporrhaphy with and without mesh	4 y	Mesh and levator defect, mesh and no levator defect	Age, BMI, delivery mode, previous POP surgery, levator defect, and follow-up length

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(continued)

TABLE 2
Included articles on pelvic organ prolapse recurrence *(continued)*

Reference	Study type	N/n	Inclusion criteria	Follow-up	Investigated risk factors	Adjustment variables
Vergeldt et al,[43] 2015 The Netherlands	Prospective cohort study	139/76	Women planned for conventional anterior colporrhaphy for stage 2 or higher cystocele	12 mo	Age, BMI, parity, preoperative POP-Q, concomitant POP surgery, major levator defects at rest on 3D ultrasound, major levator defects on MRI, levator hiatal (LH) area at rest on 3D ultrasound, LH area during contraction on 3D ultrasound, LH area during Valsalva on 3D ultrasound, LH area at rest on MRI	Preoperative POP-Q stage and levator hiatal area
Vergeldt et al,[44] 2016 The Netherlands	Prospective cohort study	287/149	Women who had undergone anterior colporrhaphy without use of mesh	1 and 2 y	Age, BMI, parity, operative delivery, family history, preoperative POP-Q stage anterior compartment, number of compartments involved, major levator muscle defects, LH area during Valsalva	Operative delivery, preoperative POP-Q stage anterior compartment, number of compartments involved, major levator muscle defects, LH area during Valsalva
Manodoro et al,[39] 2018 Italy	Retrospective cohort study	519/71	Women with POP treated with native tissue repair involving vaginal hysterectomy followed by high uterosacral ligament suspension	32 mo	BMI, birthweight, operative delivery, premenopausal status, absence of anterior repair, absence of posterior repair, and preoperative POP-Q stage	BMI, birthweight, operative delivery, premenopausal status, absence of anterior repair, absence of posterior repair, and preoperative POP-Q stage
Oversand et al,[40] 2019 Norway	Prospective cohort study	189/90	Women with symptomatic primary concomitant anterior and midcompartment POP needing surgical treatment	12 mo	Local estrogen use, chronic disease, preoperative anterior POP-Q stage, levator defect	Local estrogen use, chronic disease, preoperative anterior POP-Q stage, and levator defect
Richter et al,[47] 2021 United States	Randomized trial, secondary analysis	117/24	Women with Stage 2–4 prolapse and SUI symptoms that plan vaginal surgery for treatment of prolapse of the vaginal apex (with or without a uterus)	2 y	POP-Q point D	Not described

BMI, body mass index in kg/m^2; *N/n*, number of women included in the study who underwent physical examination/number of women with POP recurrence; *LH*, levator hiatus; *POP*, pelvic organ prolapse; *POP-Q*, POP-Quantification system; *SUI*, stress urinary incontinence; *UI*, urinary incontinence.

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genetic risk factors, which are mostly case–control studies, were excluded.

Lastly, a limitation not only in this review but also in the whole field of risk factor research is heterogeneity in definitions, outcome measures, and correction for confounders. Because of this heterogeneity, studies cannot be easily compared or pooled, which makes it hard to draw solid conclusions. We tried to overcome this limitation by providing the forest plots.

Conclusions and implications

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. ■

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