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Urogenital and pelvic complications in the Ehlers-Danlos syndromes and associated hypermobility spectrum disorders: A scoping review

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Abstract

The Ehlers-Danlos syndromes (EDS) and associated hypermobility spectrum disorders (HSD) are a heterogenous group of connective tissue disorders associated with significant morbidity. The urogenital aspects of these disorders are understudied and there is little guidance on the prevalence, types, or outcomes of urogenital complications in EDS/HSD. Our objective was to perform a scoping review to characterize and synthesize the literature reporting urogenital and pelvic complications in EDS/HSD patients. We performed a systematic search of three databases (Medline, CINAHL, Embase) to January 2019. English language, full-text articles reporting on urogenital or pelvic complications in EDS/HSD were included. A total of 105 studies were included (62 case reports/series, 43 observational) involving patients with hypermobile (23%), vascular (20%), classical (12%) EDS, and HSD (24%). Some studies looked at multiple subtypes (11%) or did not report subtype (33%). Reported complications included urinary (41%), gynecological (36%), obstetrical (25%), renal (9%), and men's health problems (7%), with some studies reporting on multiple areas. Urinary and gynecological complications were most prevalent in patients with HSD, while a broad range of complications were reported in EDS. While further research is required, results suggest a higher index of suspicion for urogenital problems is probably warranted in this population.

Keywords

Ehlers-Danlos syndrome; generalized joint hypermobility; joint hypermobility syndrome; urogenital abnormalities; urogenital system

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author (EG), upon reasonable request.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

1 | INTRODUCTION

The Ehlers-Danlos syndromes (EDS) are a heterogenous group of connective tissue disorders predominantly associated with defective collagen production. The heterogeneity of the syndromes is significant, with 19 genes and hundreds of mutations identified.[1] Clinically, EDS is characterized by degrees of connective tissue fragility, particularly in the skin, tendons, ligaments, blood vessels, and hollow organs.[1–3] EDS is associated with significant morbidity, including life threatening vessel and organ rupture, debilitating joint instability and pain, and prolonged, complicated wound healing.[1,2,4] Significant disability and reduced quality of life frequently occur[5–7] due to musculoskeletal problems,[8] severe chronic pain,[9] and persistent fatigue.[10] Overall, EDS remains understudied and there is a lack of data on prevalence, presentations, and natural history.[11,12]

The prevalence of EDS is reported to be approximately 1 in 5000 births,[13,14] however increasing awareness has been tied to increasing incidence.[14] A pair of surveys[15] involving 10,000 patients with 16 rare diseases found those with EDS experienced the longest delay in diagnosis, with more than half having received an initial misdiagnosis, and 70% of those received inappropriate treatment as a consequence. As EDS may be encountered clinically by a variety of providers, there is a need for broad awareness and increased understanding.

The complexity of EDS has led to several revisions in the recognized subtypes, as shown in Table 1, with the most recent in 2017.[1,16,17] This classification recognizes 13 distinct types, with the genetic basis of all known except for hypermobile EDS (hEDS). Hypermobility spectrum disorders (HSD) are a related set of diagnoses often studied in conjunction with hEDS due to phenotypic similarity and uncertainty if HSD represent distinct disorders or are part of a spectrum with hEDS.[19,20] In 2018, a 14th type of EDS was identified,[18] associated with pathogenic variants in the AEBP1 gene.

The urogenital system and pelvic region contain many collagen-rich tissues including the bladder, uterus, and pelvic ligaments, increasing the concern for related complications in those with EDS.[21–23] While there has been some recognition of this clinically, particularly in the field of obstetrics, little information is available on the prevalence, types, or outcomes associated with the urogenital complications of EDS more broadly.[1,21]

We were unable to identify any prior reviews on this topic, or sufficient studies suitable for a meta-analysis. We therefore undertook a scoping review, a methodology employing a broadly defined research area, systematic search, and primarily descriptive results.[24–26] Our goal was to broadly map the existing literature reporting urogenital and pelvic complications in people with EDS and summarize reported complications. We then present a discussion that provides context for findings with complication rates in the general population, as well as research and clinical implications.

2 | MATERIALS AND METHODS

2.1 | Search strategy

A systematic review of Medline (PubMed), CINAHL Plus (EBSCOhost), and Embase was conducted until January 2019. Medline was searched using with the following terms:

("Ehlers-Danlos Syndrome" OR "Ehlers Danlos" OR "Joint Instability" OR "Joint Hypermobility Syndrome" OR "Benign Joint Hypermobility Syndrome" OR "Generalized Joint Hypermobility") AND ("Sexual Health" OR "Reproductive Health" OR "Reproductive Medicine" OR "Urogenital System" OR "Urogenital Abnormalities" OR "Urogenital Surgical Procedures" OR "Male Urogenital Diseases" OR "Female Urogenital Diseases" OR "Pelvis" OR "Pelvic Floor" OR "Pelvic Floor Disorders" OR "Uterine Rupture").

Equivalent searches were used with each database. All databases included renal complications under urogenital terms. No filters were applied. Gray literature, including conference abstracts, was searched using ClinicalTrials.gov, CENTRAL, Greylit.org, and Opengrey.eu. References and citations of relevant articles were searched by hand. Full details of the search strategy, including the review protocol, can be found in the Appendix S1.

2.2 | Study selection

Study titles and abstracts were screened for the following inclusion criteria: (a) Study population diagnosed with any type of EDS included in the 2017 classification or equivalent type under older classifications, or any HSD, (b) study reported on urogenital, including renal, or pelvic complications, (c) English language, (d) full text available.

Venous or arterial complications related to the urogenital system were excluded as vascular in nature. Obstetrical complications relating to the fetus, including placental and fetal membrane problems, and miscarriage, were excluded, but maternal urogenital or pelvic complications such as uterine rupture were included. Opinion, basic science, animal, and review articles were excluded.

2.3 | Data collection and study assessment

The following information was extracted from included studies: (a) Study design (see Appendix S1 for details); (b) Type(s) of urogenital or pelvic complication reported; (c) For obstetric complications, whether they occurred in the ante-, intra-, or post-partum period; (d) EDS subtype(s) or HSD type(s) in the study population; (e) Sample size; (f) Publication date; (g) Country of origin. When available, participant age, gender, and method(s) of diagnosis were recorded.

3 | RESULTS

3.1 | Study selection

The selection process is summarized in Figure 1. Abstracts for 1103 unique records were screened and 966 were excluded. Of those excluded, 24 were considered potentially relevant but the full texts were unavailable in English. Following screening, 137 records underwent

full text review, with the exclusion of an additional 32; thus 105 unique studies were included in our review.

3.2 | Study characteristics

Table 2 summarizes the design and publication date characteristics of the 105 included studies.[27–131] Studies consisted of case reports/series (N = 62, 60%) and observational studies (N = 43, 40%), including cross sectional (N = 29), case-controlled (N = 12), and cohort (N = 2) designs. No clinical trials or treatment outcome studies were found. Publication dates ranged from 1956 to 2018, with 46% published between 2009 and 2018. Publications came from 28 countries, with 52% being from the United States or United Kingdom and 22% from other European and Scandinavia nations. In the observational studies, the mean sample size including controls was 246 (range 11–3475). The total number of patients with EDS or HSD included in all reviewed studies was 5282.

3.3 | Population characteristics

The majority (80% of all studies) reported on patients with EDS, including hEDS (23%), vEDS (20%), and cEDS (12%). Of the studies with EDS patients, 43% did not identify the subtype, 43% reported on one subtype, and 11% reported on two or more subtypes. Patients with HSD were included in 24% of reviewed studies. Occurrence of subtypes between observational studies and case reports/series were similar.

The most common primary methods of diagnosis were prior diagnosis from medical records (30%) and use of a standardized criteria, score, or scale (26%). There was significant overlap in the use of the Beighton, Brighton, and Villefranche scales or criteria for diagnosis of hEDS and HSD. Other methods were physical exam without specific criteria (16%), patient self-report (7.5%), genetic testing (7.5%), and skin biopsies (5%). In 8% of studies, diagnostic methodology was unclear or not reported.

The gender distribution of EDS or HSD patients in the studies skewed female, with 63% female only, 20% male only, and 18% both. Gender distribution was similar between study types, and when studies with hEDS or HSD patients were excluded.

There was heterogeneity in the reporting of subject age, including age at time of study participation, age of diagnosis, and age of first complication. Mean age was not reported in 16 studies (13 observational and 3 case reports/series). Of those with available data, the mean patient age was 36 years for observational studies, 25 years for case reports/series. Overall 38 studies included pediatric patients (≤18 years) and nine included geriatric patients (≥65 years).

3.4 | Urogenital and pelvic complications reported

Complications clustered into five interrelated domains, as shown in Table 3 (a) urinary (including the urinary system, other than the kidneys), (b) renal, (c) gynecological (including the female reproductive tract, genitalia, and sex hormones), (d) obstetric (related to or occurring during the ante-, intra-, or post-partum period), (e) Men’s health (including the

male internal or external genitalia, or sex hormones). Some studies reported on multiple domains.

3.4.1 | Urinary—Urinary complications were the most frequently reported overall, and were particularly common in studies of patients with HSD. Specific complications included stress, urge, intercourse, and nocturnal urinary incontinence (UI), vesicoureteral reflux (VUR), multiple and reoccurring bladder diverticula, recurrent urinary tract infections (UTIs), bladder outlet obstruction, bladder pain, dysuria, hematuria, megacystis, urinary retention, and voiding dysfunction.

Several studies found associations between VUR and HSD in pediatric populations. In a sample of 15 children with benign joint hypermobility syndrome (bJHS), a subtype of HSD, Beiraghdar et al[36] found 60% had VUR, and van Eerde et al[125] identified a significantly higher rate of generalized joint hypermobility (GJH), another subtype of HSD, in VUR patients compared to controls (24.0% vs 6.7%). In a study of 313 children with a history of UTI, Pournasiri et al[107] found that GJH was more common in children that also had VUR, and that the prevalence of GJH increased with VUR severity.

Bladder diverticula were reported in 44% of the studies mentioning urinary complications, although the majority (90%) was case reports/series.

Findings on UI were mixed, with 4[53,81,93,94] of 18 studies finding no association between either EDS or HSD and UI. Among the 14 studies reporting a positive correlation for EDS or HSD and UI, rates between 68% and 84% were reported for adult women.[31,45] A case-controlled study by Mastoroude et al[91] found the prevalence of UI in women with bJHS to be significantly greater than controls (73% vs 48%). In a prospective longitudinal cohort study of children with hEDS or joint hypermobility syndrome (JHS), Scheper et al[112] found UI in 23% overall and 40% among a subset more severely affected by EDS or JHS.

3.4.2 | Gynecological—The second most frequently reported domain was gynecologic complications. This included multiple types of pelvic organ prolapse (POP) including anterior, posterior, and apical; menstrual complications including irregular menses, intermenstrual bleeding, menorrhagia, and dysmenorrhea; ovarian and uterine abnormalities including premature pubarche, recurrent anovulation, primary ovarian failure, polycystic ovary syndrome, endometriosis, endometrial cysts, endometrial hyperplasia, uterine fibromas, and uterine polyps; pelvic or vulva varicose veins; and pelvic floor dysfunction.

Problems with the genital mucosa were also reported, including vaginal dryness, spontaneous genital skin fissures, genital edema, genital lacerations and bleeding after intercourse, perineal tearing during medical treatment, and recurrent vaginal infections. Berglund and Björck[38] found in a sample of 250 women with EDS, 67% reported genital mucosal problems, while Sorokin et al[118] reported 25% of women with EDS had vaginal dryness and 8.5% had post-coital bleeding. In two case reports,[70,124] such bleeding required emergency medical care.

Pain as a primary gynecological complaint was also reported with vulvodynia, vestibulodynia, dyspareunia, and generalized pelvic pain. In a retrospective cohort study of

386 women with hEDS, Hugon-Rodin et al[71] found that over 60% reported dyspareunia. Earlier cross sectional studies[43,44,93,118] reported rates in hEDS and other types of EDS of between 30% and 61%.

Women with EDS or HSD are thought to be at higher risk for POP due to the reliance on collagenous tissues for support of these structures. In this review, most (21/23) studies supported this correlation, reporting associations between hypermobility and POP[30,33,119] and higher rates or greater severity of POP in those with EDS or HSD as compared to controls.[90,101] Two studies reported negative findings. Knoepp et al[81] found no associated between bJHS and POP, while McIntosh et al[94] found no associated between degree of hypermobility and presence of POP in women with EDS.

3.4.3 | Obstetric—EDS is known to be associated with the potential for obstetric complications, particularly uterine rupture and post-partum hemorrhage, both of which were found in this review. Seven of the 26 studies reporting obstetric complications included uterine rupture. All patients had vEDS. Two studies reported similar rates, with 2.6% out of 76 pregnancies[97] and 2.7% of 183.[106]

Hemorrhage was reported in 14 studies, and included ante-, intra-, and post-partum hemorrhage. Lind and Wallenburg[87] found post-partum hemorrhage in 18.8% of births among EDS patients, vs 7% in a general population group. Several small[35,58,88,97] studies reported rates in EDS patients between 10% and 16.7%, with one[44] reporting a combined intra and post-partum hemorrhage rate of 19.4%. One retrospective cohort study[71] reported a rate of 4.8% from 747 pregnancies, however it was unclear how post-partum hemorrhage was defined and occurrence was self-reported by patients.

Additional obstetric complications included uterine torsion, cervical incompetence, preterm labor, severe perineal tearing, and failure of sutures for episiotomies and C-sections. Separation of the pubic symphysis and coccyx dislocation were also reported.

Several studies reported high rates of complications associated with peripartum joint laxity. Ainsworth and Aulicino[29] reported increased laxity during pregnancy in 60% to 79% of cEDS, hEDS, and vEDS patients, while Lind found over 70% of women with various types of EDS reported pelvic pain or instability during pregnancy. Karthikeyan and Venkat-Raman[79] found seven out of eight pregnant women with hEDS experienced significant laxity-associated pelvic girdle pain. Two case reports[32,66] also highlighted disabling pelvic girdle laxity during pregnancy.

3.4.4 | Renal—There were two reports each of renal failure and renal insufficiency. Other renal complaints appeared in one study each: anuria, infantile polycystic disease of kidney, kidney stones, medullary sponge kidney, polycystic kidneys, polyuria, renal cysts, renal ptosis, renal hypoplasia, renal tubular acidosis, renomegaly, and tubulointerstitial nephritis.

3.4.5 | Men's health—Complications specific to men's health were limited to case reports/series in patients with EDS, and included four reports of cryptorchidism, two reports

of hypogonadism, and one report each of testicular torsion, and tight foreskin requiring surgical correction.

4 | DISCUSSION

This review found that both male and female patients with EDS and HSD can experience a wide range of urogenital and pelvic complications throughout their lifespan.

Reports of urinary complications were most frequent, with over 40% of studies reporting one or more related problem. While we recognize that comparisons of rates across heterogeneous literature can be problematic, we include reported rates in the general population to provide greater context for our findings. In the general population, VUR is estimated to affect 25% to 40% of children,[132] while this review found rates of VUR in EDS and HSD up to 60%. Similarly, this review found higher rates of UI in EDS or HSD (68%-84% in adult women, 23%-40% in children) than has been reported in the general population (25%-45% in adult women,[133,134] 10% in children[133,135]). Nearly half of the studies which discussed urinary complications reported patients with bladder diverticulum, although most were case reports. Bladder diverticulum are uncommon in the general population, with one study[136] of incidental findings from abdominal CT scans reporting a rate of 0.22% out of over 3000 patients. In general, the literature on urinary complications was suggestive of an increased association with problems such as UI, bladder diverticula, and VUR, but many studies were small and were primarily in HSD. These results warrant further systematic investigations.

This review found significant breadth in the gynecological problems reported. In particular, the rate of dyspareunia (30%-61%) may be greater than in the general population. Dyspareunia in the general population has been reported[137] in 7.5% of sexually active women, with some geographic variation[138] (3.6% in Australia, 18.6% in Brazil) and higher rates among women post-partum[139] (24%). One prior review[140] of pain in EDS also noted the occurrence of vulvodynia and dyspareunia. Previous research[141] has found that less than a third of women with pelvic pain report it to a medical provider, thus the already high rates found in this review may underrepresent this problem.

Given the tissue fragility associated with EDS there is a plausible mechanism for mucosal complications and the results of this review suggest further research would be beneficial. As compared to the rates in EDS and HSD in this review (25%), rates of vaginal dryness in women among the general population are generally lower, from 5.8% to 19.7%.[138] The reported[142] general prevalence of post-coital bleeding in women varies widely, but is generally ≤9%, similar to what was found in EDS (8.5%) in this review. The severity of the bleeding reported in some of the EDS patients is notable.

Among the gynecological problems reported were some without a clear physiological, connective tissue explanation, such as ovarian and endometrial problems. Future research should examine the possibility of additional mechanistic pathways not currently recognized which may connect these problems to EDS.

Obstetric risks have long been associated with EDS, and specifically uterine rupture and post-partum hemorrhage. In this review, uterine rupture was only reported in vEDS patients, with a rate of ~3% per pregnancy, as compared to a general population rate of 0.035% out of 110 000 pregnancies.[143] Future research should confirm whether uterine rupture is a risk specific to vEDS. The included studies support a risk of hemorrhage for EDS patients, although there was variation in the rates reported (4.8%-18.8%). Rates of post-partum hemorrhage in the general population,[144] based on objective measurements of blood loss >500 mL, is reported as 10.6%, with rate based on subjective measurements being 6.09%. Further investigations might seek to identify the extent to which risk in EDS patients differs from the general population, and whether this risk differs between the subtypes of EDS or extends to those with HSD. Aside from rupture and hemorrhage, the reports of disabling increases in joint laxity during pregnancy (60%-87%) were of particular note. Pregnancy has been found to increase both local and generalized joint laxity in healthy subjects,[145,146] although specific rates were not available.[147] Primary care providers and obstetricians should be aware of this risk for women that have EDS or HSD and are or are planning to become pregnant.

Reports of renal and men's health complications were infrequent and diffuse. A link with EDS or HSD appears to be less likely.

Due to the genetic and phenotypic heterogeneity of EDS, research that evaluates complications on a subtype specific basis is particularly important for guiding clinical care. In this review, patients with hEDS or HSD most often reported gynecological or urinary complications, and those subtypes combined accounted for greater than 40% of the reports in those domains. The frequency of such complications among those with HSD is notable, as these disorders are commonly thought to involve primarily joint hypermobility and musculoskeletal problems, with few systemic effects. While reports involving HSD were almost exclusively limited to gynecological and urinary domains, complications in patients with hEDS were widely distributed. Similarly, vEDS patients reported a range of urogenital complications, in addition to prominent obstetric risks.

Interestingly, the literature to date has disproportionally reported on female patients, despite EDS being a possibly autosomal disorder. Previous research[3,4,148] has found a higher than expected prevalence of hEDS in women relative to men, with hormonal differences considered a possible factor. In this review, we found that a significant gender gap in the literature existed even when studies with hEDS and HSD patients were excluded. Further investigation into gender-specific prevalence and risks may be warranted.

4.1 | Research and clinical considerations

Nearly half of the research on urogenital and pelvic complications in EDS and HSD has been produced within the past decade, however the literature remains saturated with case reports and observational studies with inherently limited insight on prevalence and risk. This gap, in light of the numerous existing reports of complications, represents an important area for future investigation.

Because of the heterogeneity of EDS and the ongoing efforts to clarify and describe its subtypes, the application of consistent and valid diagnostic methodologies is essential. We suggest future studies utilize current, standardized diagnostic criteria specific to each subtype, evaluate patients to exclude related connective tissue disorders, and use genetic testing for diagnostic confirmation whenever available. Reporting data particular to subtypes in a mixed population would be informative. Additionally, because of the ongoing efforts to clarify whether hEDS and HSD are related, we suggest future studies include a comprehensive evaluation using the 2017 International criteria to either diagnose or exclude a diagnosis of hEDS. The most common diagnostic methods found in this review are not adequate to differentiate between hEDS and HSD.

Due to the variety of problems reported, patients in this review presented to emergency providers, urologists, nephrologists, gynecologists, obstetricians, and primary care physicians with both acute and chronic complications, highlighting the need for a broad awareness of EDS and HSD. Clinicians seeing patients with these disorders should be aware of the potential for increased risk of urogenital and pelvic complications. While the findings of this review cannot recommend specific screening or management strategies, results suggest an increased level of attention to related symptoms is appropriate. All providers should be alert to reports or complaints by patients of urogenital symptoms, and primary care or relevant specialists should consider proactively asking patient with EDS/HDS about urinary or gynecological symptoms. Specific areas of concern include urinary symptoms, such as recurrent UTIs or incontinence, and gynecological symptoms such as pain or prolapse. Further research is necessary to direct clinical practice, including identifying patients who may benefit from screening or preventative strategies, and assessing treatment outcomes to determine best practices in management.

5 | LIMITATIONS

The conclusions of this article are limited by the inherent preliminary nature of scoping reviews and the limitations of the included papers. Specific estimates of prevalence and risk cannot be drawn. Included studies did not undergo critical appraisal. Studies in the review included those examining urogenital or pelvic complications as the primary topic, and those reporting such problems as incidental findings. While results were presented by subtype when possible, many included studies did not identify the subtype or did not report results by subtype and so the findings of this review may not accurately represent subtype-specific risk or prevalence. Nearly two dozen potentially relevant non-English language articles were excluded. As the majority was case studies, we do not believe their exclusions significantly altered the findings of this review.

6 | CONCLUSION

While there has been a significant increase in reporting on urogenital and pelvic complications of EDS within the past decade, the literature remains saturated with case reports and series and observational studies in which statistical insights and generalizability are limited. While specific recommendations cannot be made based on the results of this review, the overall findings do suggest that clinicians should have an elevated index of

suspicion for urogenital complications in patients with EDS or HSD. The lack of rigorous studies on complication prevalence or risk represents a significant area of need and important opportunity for future research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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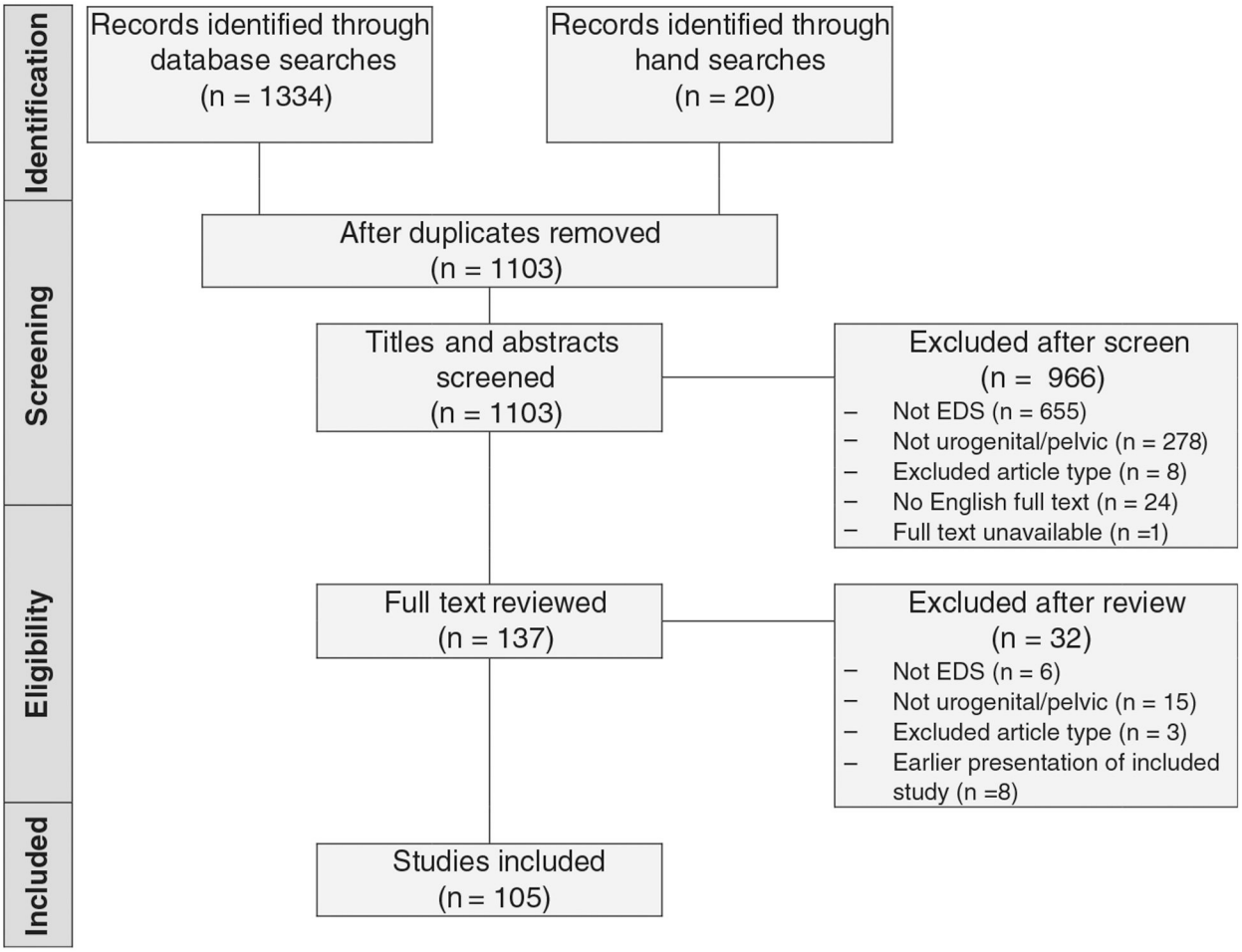

FIGURE 1.
Study selection flowchart

TABLE 1

Classification of EDS subtypes over time

1988, Berlin	1998, Villefranche[a]	2017, International
Type I, Gravis		
	Classical type	Classical EDS (cEDS)
Type II, Mitis		
Type III	Hypermobility type	Hypermobile EDS (hEDS) Hypermobility spectrum disorders[b] (HSD)
Type IV (A, B, C, D)	vascular type	Vascular EDS (vEDS)
Type VI	Kyphoscoliosis type	Kyphoscoliotic EDS (kEDS)
Type VII		
A	Arthrochalasia type	Arthrochalasia EDS (aEDS)
B		
C	Dermatospraxis type	Dermatospraxis EDS (dEDS)
Type VIII	Periodontitis type	Peridontal EDS (pEDS)
Type V	X-linked type	
Type IX	Occipital horn syndrome	
Type X	Fibronectin-deficient type	No longer part of EDS
Type XI	Familial hypermobility syndrome	
	Progeroid type	Spondylodysplastic EDS (spEDS) Brittle cornea syndrome (BCS) Cardiac-valvular EDS (cvEDS) Classical-like EDS (clEDS) Myopathic EDS (mEDS) Musculocontractural EDS (mcEDS) AEBP1 variant EDS[c]

Sources: References 1,16–18.

[a] Often referred to as Villefranche, 1997, however not published until 1998.

[b] HSD may include diagnoses such as Joint hypermobility (JH or JHM), Joint hypermobility syndrome (JHS), Benign joint hypermobility (bJHS), and generalized joint hypermobility (GJH).

[c] Not part of the 2017 International classification; was published separately[18] in 2018.

TABLE 2

Included studies by design and date of publication

	Total	Case report/series	Observational: cross sectional	Observational: case controlled	Observational: cohort
1988 or earlier	21 (20%)	19 (90%)	1 (5%)	1 (5%)	0
1989–1998	16 (15%)	10 (63%)	5 (31%)	1 (6%)	0
1999–2008	20 (19%)	11 (55%)	4 (20%)	5 (25%)	0
2009–2019	48 (46%)	22 (46%)	19 (40%)	5 (10%)	2 (4%)

TABLE 3

Number of studies reporting each complication domain, by disease subtype

	All types[a]	cEDS	hEDS	vEDS	Other/multiple EDS types	HSD	EDS and HSD	EDS type NR[b]
Urinary	43	2	4	1	6	13	2	15
Gynecological	38	0	8	3	7	10	1	9
Obstetric	26	3	4	9	2	0	1	7
Renal	10	0	1	1	1	1	0	6
Men's health	7	0	0	1	2	0	0	4

[a]Exceeds total number of studies in review (105) because some studies reported multiple complication domains.

[b]NR, not reported.